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High remission and low relapse with prolonged intensive DMARD therapy in rheumatoid arthritis (PRINT)

A multicenter randomized clinical trial

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Abstract

Objectives: To determine whether prolonged intensive disease-modifying antirheumatic drug (DMARD) treatment (PRINT) leads to high remission and low relapse rates in patients with severe rheumatoid arthritis (RA).

Methods: In this multicenter, randomized and parallel treatment trial, 346 patients with active RA (disease activity score (28 joints) [DAS28] (erythrocyte sedimentation rate [ESR]) > 5.1) were enrolled from 9 centers. In phase 1, patients received intensive treatment with methotrexate, leflunomide, and hydroxychloroquine, up to 36 weeks, until remission (DAS28 ≤ 2.6) or a low disease activity ($2.6 <$ DAS28 ≤ 3.2) was achieved. In phase 2, patients achieving remission or low disease activity were followed up with randomization to 1 of 2 step-down protocols: leflunomide plus hydroxychloroquine combination or leflunomide monotherapy. The primary endpoints were good European League Against Rheumatism (EULAR) response (DAS28 (ESR) < 3.2 and a decrease of DAS28 by at least 1.2) during the intensive treatment and the disease state retention rate during step-down maintenance treatment. Predictors of a good EULAR response in the intensive treatment period and disease flare in the maintenance period were sought.

Results: A good EULAR response was achieved in 18.7%, 36.9%, and 54.1% of patients at 12, 24, and 36 weeks, respectively. By 36 weeks, 75.4% of patients achieved good and moderate EULAR responses. Compared with those achieving low disease activity and a high health assessment questionnaire (HAQ > 0.5), patients achieving remission (DAS28 ≤ 2.6) and low HAQ (≤ 0.5) had a significantly higher retention rate when tapering the DMARDs treatment ($P=0.046$ and $P=0.01$, respectively). There was no advantage on tapering to combination rather than monotherapy.

Conclusions: Remission was achieved in a proportion of patients with RA receiving prolonged intensive DMARD therapy. Low disease activity at the start of disease taper leads to less subsequent flares. Leflunomide is a good maintenance treatment as single treatment.

Abbreviations: AE = adverse events, anti-CCP = anticyclic citrullinated peptide, CRP = C-reactive protein, DAS28 = disease activity score (28 joints), DMARD = disease-modifying antirheumatic drug, ESR = erythrocyte sedimentation rate, EULAR = European League Against Rheumatism, HCQ = hydroxychloroquine, LDA = low disease activity, LEF = leflunomide, MGA = medical

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global assessment, MTX = methotrexate, PGA = patient global assessment, RA = rheumatoid arthritis, RF = rheumatoid factor, SJC = swollen joint count, TJC = tender joint count, VAS = visual analog scale.

Keywords: DMARDs (synthetic), outcomes research, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovitis, cartilage damage, and bone erosion, leading to deformity and disability. Clinical remission or low disease activity (LDA) is the recommended treatment target in patients with RA.[1] Conventional disease-modifying antirheumatic drugs (DMARDs) remain the core medications employed in daily practice in many parts of the world.[2] Intensive treatment using combinations of DMARDs is proposed to be superior to routine step-up DMARD treatment.[3–6] However, in clinical practice, after patients achieve the treatment target, DMARDs are often tapered.[1,7] It has been reported that the risk of flare is higher in patients tapering DMARDs early than those continuing therapy.[8,9] Few studies have directly addressed the optimal approach to tapering. We hypothesized that prolonged intensive DMARD therapy will result in a high proportion of patients achieving remission and subsequently few patients relapsing upon DMARD tapering.

2. Methods

2.1. Trial design and participants

We performed a controlled randomized, single-blinded, parallel treatment trial of tapering protocols after initial intensive DMARD therapy. Nine hospitals in China collaborated and enrolled patients from July 2009 to June 2010. Follow-up was ended in March 2012. Key inclusion criteria were as follows: RA according to the 1987 revised American College of Rheumatology criteria[10]; disease activity score (28 joints) (DAS28) > 5.1 and age >18 years. Key exclusion criteria were previous use of prednisone >10 mg orally, chronic liver disease, cancer, excessive alcohol use, pregnancy (intended), or laboratory abnormalities: leucopenia ($<4.0 \times 10^9$/L), thrombocytopenia ($<100 \times 10^9$/L), elevated aspartate aminotransferase, alanine aminotransferase, and creatinine level.

The study was approved by Peking University People's Hospital's ethics committee. All patients gave written informed consent. This trial was registered in World Health Organization's International Clinical Trial Registry Platform with www.chictr.org (No. ChiCTR-TRC-09000469).

2.2. Randomization

Patients who achieved LDA during an open-label induction period were eligible for the step-down maintenance stage, and were randomly assigned by sealed opaque envelope containing computer-generated random allocations in a 1:1 ratio to 1 of 2 treatment groups. The statistician who generated the randomization sequence was not otherwise involved in the trial.

2.3. Interventions

There were 2 phases in the study. In phase 1, enrolled patients received DMARDs treatment comprising a combination of methotrexate (MTX), leflunomide (LEF), and hydroxychloroquine (HCQ). The starting dose of oral MTX was 7.5 mg/wk that could be increased to a maximum of 20 mg/wk. LEF (10–20 mg/d per rheumatologists' discretion) and HCQ (400 mg/d) were administrated in combination with MTX. Adverse events (AEs) and serious AEs were recorded throughout the study. Folic acid was administered to every patient (5 mg/wk, 1 single dose). Use of nonsteroidal anti-inflammatory drugs was allowed and the dose could be changed in the study. Intra-articular or intramuscular injection of glucocorticoids was allowed only once (no more than 40 mg Triamcinolone Acetonide or its equivalent) at the beginning of the study. Oral glucocorticoids (prednisone $\leq$ 10 mg/d) were allowed but were tapered to discontinuation before entering the step-down maintenance period. Disease activity was assessed every 12 weeks. Patients who achieved a DAS28 $\leq$ 3.2 entered the maintenance period.

In phase 2, patients who achieved a DAS28 $\leq$ 3.2 were randomized to 1 of 2 step-down maintenance regimens: LEF monotreatment group (10 mg/d) or LEF (10 mg/d) plus HCQ (400 mg/d) group. Disease activity was assessed every 12 weeks. Remission was defined as DAS28 $\leq$ 2.6.[11] Relapse of disease activity was defined as a DAS28 increase $\geq$ 0.6 from prior assessment.[12] Patients were followed for up to 48 weeks after randomization.

2.4. Outcome assessment

The primary endpoint was good European League Against Rheumatism (EULAR) response (i.e., a resulting DAS28 (erythrocyte sedimentation rate [ESR]) < 3.2 and a decrease of DAS28 by at least 1.2)[13] during the prolonged intensive treatment. The secondary endpoint was the disease retention (maintenance of good EULAR response) rate during step-down maintenance treatment. Clinically relevant predictive factors for good EULAR response in the prolonged intensive treatment period and predictive factors for disease flare in the randomized step-down maintenance period were assessed. Health assessment questionnaire disability index (HAQ, which had been translated and validated for the enrolled patients), swollen and tender joint counts (28 joints), concentration of C-reactive protein, erythrocyte sedimentation rate, physician and patient global assessments (0–10 cm visual analog scales), and patient assessed pain and fatigue (0–10 cm visual analog scales) were measured. Rheumatoid factor (RF) and anticyclic citrullinated peptide antibodies were performed by enzyme-linked immunosorbent assay twice at entry of the intensive and maintenance treatment phases, respectively. Extra-articular features were acquired, including rheumatoid nodules, vasculitis, secondary Sjogren syndrome, interstitial lung disease, and other extra-articular manifestations associated with RA.

2.5. Statistical analysis

A sample size of 344 patients was estimated for the intensive treatment period with the assumption that 80% of patients would achieve LDA or remission at the end of intensive treatment stage (on the basis of the TICORA trial).[14] A sample size of 110

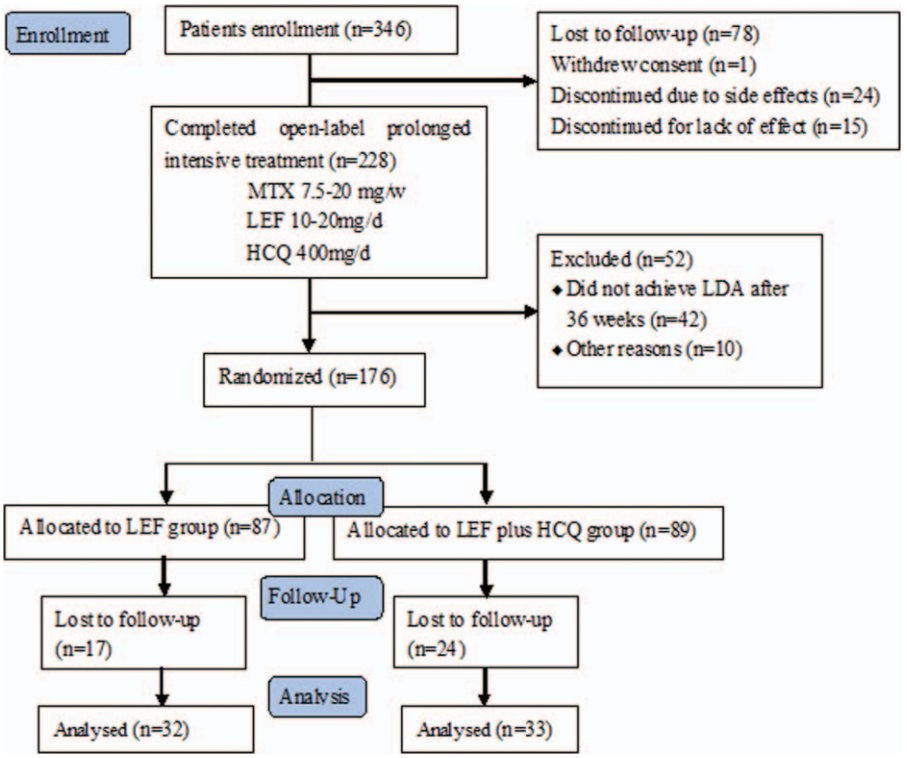

Figure 1. Trial profile. HCQ = hydroxychloroquine, LDA = low disease activity, LEF = leflunomide, MTX = methotrexate.

patients per maintenance treatment group was calculated to have 90% power to detect a 15% difference between the 2 groups with an α level of 0.05.

In the intensive treatment period, the intention-to-treat population included all patients who received at least 1 dose of study drug. Patients who were lost to follow-up, or withdrew from the trial were designated as nonresponders. In the randomized maintenance treatment period, the intention-to-treat population was made up of patients who had randomized and received at least 1 dose of assigned maintenance treatment. The safety population included all patients given at least 1 dose of study drug.

Descriptive statistics, nonparametric test, and χ^2 test were used as appropriate. Variables that were significant at $P < 0.20$ on the univariate analysis were entered into the multivariate model. Backward multivariate logistic regression analyses were conducted for the baseline predictors of good EULAR response at 12 weeks of the intensive treatment. Cox regression was performed to analyze the predictors for flare during the maintenance period. A 2-tailed P value < 0.05 was considered significant. Analyses were performed using the SPSS/PC program (version 16.0; Chicago, IL).

3. Results

3.1. Study population

Three hundred forty-six patients were recruited (Fig. 1), and their baseline metrics are shown in Table 1. The mean age of patients was 48.7 years with a mean duration of disease of 6.13 years. There were 35.3% (122/346) patients who did not received DMARDs treatment previously. The prevalence of patients who were receiving 1 or 2 DMARDs treatment at the enrollment was 16.8% (58/346). Furthermore, 16.2% (56/346) patients received oral glucocorticoids (prednisone $\leq$ 10 mg/d). The mean DAS28 at baseline was 6.17.

3.2. Response in intensive DMARDs treatment

In phase 1, the proportion of patients achieving a good EULAR response rose from 18.7% (64/343) to 36.9% (128/344) and 54.1% (187/346) at 12, 24, and 36 weeks. The total proportion

Table 1

Baseline characteristics of patients enrolled.

Patient characteristics	n = 346
Female (pt. mo.), n (%)	296 (85.55)
Age (y), mean (SD)	48.69 (12.90)
Initial treatment (pt. mo.), n (%)	122 (35.26)
Disease duration (y), mean (SD)	6.13 (7.33)
Morning stiffness $\geq$ 1 h, n (%)	198 (57.23)
Extra-articular manifest (pt. mo.), n (%)	110 (31.79)
Pain score (0–10), mean (SD)	6.89 (1.71)
DAS28 score, mean (SD)	6.17 (1.11)
Health assessment questionnaire score, mean (SD)	1.26 (0.67)
Swollen joint score (0–28), mean (SD)	8.40 (5.75)
Tender joint score (0–28), mean (SD)	12.36 (6.79)
Patient global health (0–10), mean (SD)	6.76 (1.51)
Physician global health (0–10), mean (SD)	6.44 (1.53)
Fatigue score (0–10), mean (SD)	5.66 (1.88)
Erythrocyte sedimentation rate (mm/h), mean (SD)	52.76 (30.27)
C-reactive protein (mg/L), mean (SD)	17.41 (25.31)
Anticycled citrullinated peptide antibody positive, n (%)	281 (81.21)
Rheumatoid factor positive, n (%)	274 (79.19)

DAS28 = disease activity score (28 joints), SD = standard deviation.

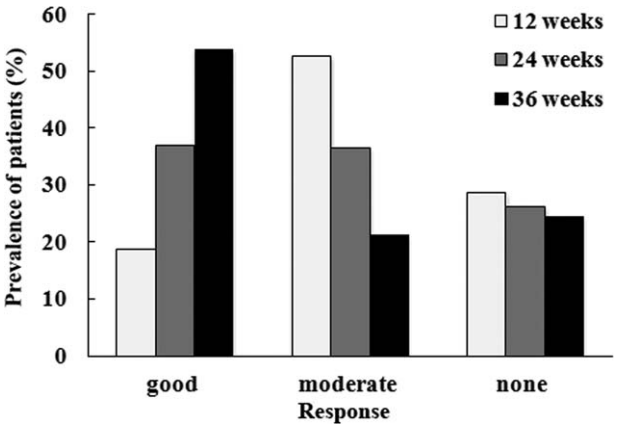

Figure 2. EULAR response for the modified intention-to-treat population of rheumatoid arthritis patients with intensive disease-modifying antirheumatic drug treatment. The prevalence of patients achieving good EULAR response increased 17% to 18% every 12 weeks. EULAR = European League Against Rheumatism.

of patients achieving EULAR response (good or moderate) was 75.4% (Fig. 2). The results demonstrate an approximate 18% increment of good EULAR response rate every 12 weeks, suggesting that the response continued to improve with prolonged intensive treatment.

3.3. Maintenance of LDA or remission in maintenance treatment

In phase 2, 176 patients achieving LDA or remission randomly entered into the step-down maintenance treatment phase of the study. By 48 weeks, 36.9% (65/176) patients maintained LDA or remission. Furthermore, we explored the impact of maintenance treatment regimens, disease, and functional activity on the maintenance of LDA.

In the LEF group, 36.8% (32/87) patients remained in LDA. In the LEF + HCQ group, the proportion of patients remaining LDA was 37.1% (33/89). For intent-to-treatment population, there was no difference in disease activity maintenance rate between the 2 groups (data not shown, $P=0.53$).

Patients achieving remission at initiation of the maintenance phase had a significantly higher retention rate of disease activity, compared with those achieving LDA by the point of taper ($P=0.046$). Similarly, a higher retention rate of the disease activity state was showed in patients with a low HAQ (≤ 0.5), in comparison with those with HAQ > 0.5 ($P=0.01$) at the start of phase 2. Additionally, patients achieving both remission and low HAQ had the highest retention rate during the maintenance period, compared with patients achieving only LDA or high HAQ (compared with $2.6 <$ DAS28 ≤ 3.2/LDA > 0.5, $P=0.02$; compared with DAS28 ≤ 2.6/LDA > 0.5, $P=0.04$, Fig. 3).

3.4. Predictor analysis

To identify baseline factors that predicted the early response for the intensive DMARD treatment, we evaluated clinical variables in patients achieving or failing to achieve a good EULAR response at 12 weeks. Those with a good EULAR response were younger (43.8 ± 13.6 years vs 47.9 ± 12.7 years, $P=0.03$), and had a lower baseline DAS28 score and ESR (DAS28: 5.98 ± 0.68 vs 6.32 ± 0.92, $P=0.001$; ESR: 43.08 ± 29.43 mm/h vs 56.63 ± 30.14 mm/h, $P=0.002$). Five variables with statistical significance at $P<0.20$ in the bivariate analysis were entered into the logistic regression analysis: age, number of tender joint, DAS28, HCQ, and ESR. Age and ESR were independent predictors for the good EULAR response of the intensive treatment arm ($P=0.03$ and $P=0.003$, Table 2).

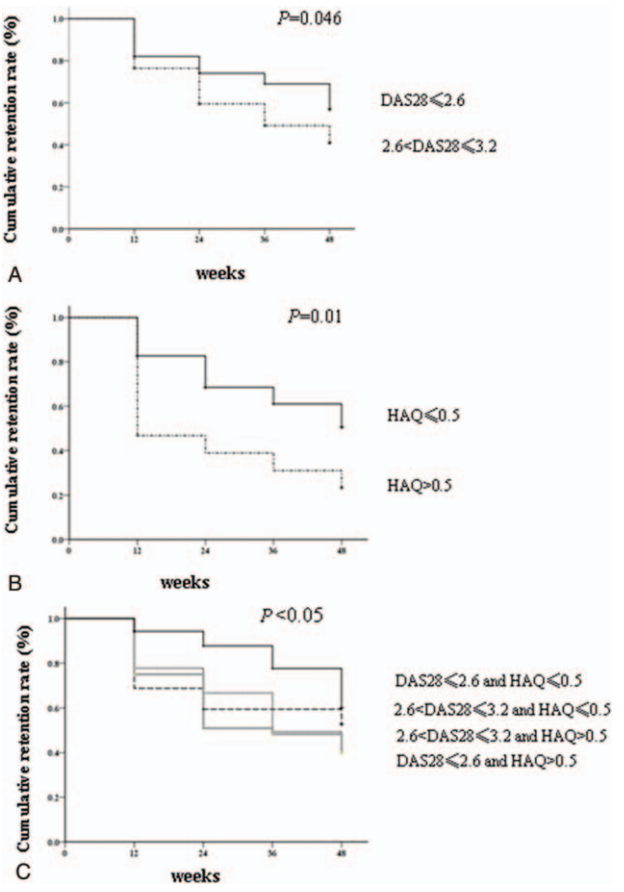

Figure 3. Kaplan–Meier curves for disease activity retention over the course of 48-week maintenance treatment. (A) Retention rate in patients with different disease activity. There were significantly higher disease retention rate in patients achieving remission (DAS28 $\leq$ 2.6) than those achieving LDA (2.6 $<$ DAS28 $\leq$ 3.2) ($P=0.046$). (B) Retention rate in patients with different functional activity. There were significantly higher disease retention rate in patients having low HAQ ($\leq$0.5) than those having HAQ $>$ 0.5 ($P=0.01$). (C) Retention rate in patients with different DAS28 and HAQ. It had been shown that patients achieving both remission and low HAQ had the highest disease retention rate during the maintenance period (DAS28 $\leq$ 2.6/HAQ $\leq$ 0.5 vs 2.6 $<$ DAS28 $\leq$ 3.2/HAQ $>$ 0.5, $P=0.02$; vs DAS28 $\leq$ 2.6/HAQ $>$ 0.5, $P=0.04$; vs 2.6 $<$ DAS28 $\leq$ 3.2/HAQ $\leq$ 0.5, $P=0.25$, respectively). DAS28 = disease activity score (28 joints), HAQ = health assessment questionnaire, LDA = low disease activity.

Univariate analysis of potential variables associated with a flare showed that achieving remission (DAS28 ≤ 2.6) ($P=0.07$), pain score ($P=0.05$), physician global health ($P=0.02$), fatigue score ($P=0.08$), patient global assessment ($P=0.09$), high HAQ (>0.5) ($P=0.02$), and C-reactive protein ($P=0.02$) at the entry of maintenance treatment were associated with disease relapse. Cox regression analysis demonstrated that high HAQ (OR: 2.16, 95% CI: 1.08–4.32, $P=0.03$) was an independent risk factor for the flare (Table 3). LDA or remission maintenance rate was not associated with the duration of prolonged intensive treatment, the maintenance treatment regimens, sex, age, and disease duration (data not shown).

Table 2

Potential baseline variables associated with achieving good EULAR response during 12 weeks of intensive treatment.

Variables	Univariate analysis			Multivariate analysis	
	Good EULAR response (n = 64)	Moderate or none response (n = 208)	*P*	OR	95% CI
Female, n (%)	52 (81.25)	176 (84.62)	0.47		
Age (y), mean (SD)	43.77 (13.58)	47.92 (12.74)	0.03*	0.98	0.96–1.00
Initial treatment, n (%)	22 (34.38)	76 (36.54)	0.75		
Disease duration (mo), mean (SD)	70.63 (102.96)	75.60 (84.69)	0.70		
TJC (0–28), mean (SD)	11.25 (5.20)	12.27 (6.93)	0.21		
SJC (0–28), mean (SD)	7.89 (4.88)	8.33 (5.83)	0.58		
Morning stiffness ≥ 1 h, n (%)	42 (65.63)	114 (54.81)	0.13		
Extra-articular manifest, n (%)	23 (35.94)	61 (29.33)	0.32		
Pain VAS (0–10 cm), mean (SD)	6.84 (1.79)	6.87 (1.68)	0.93		
PGA (0–10 cm), mean (SD)	6.73 (1.47)	6.79 (1.52)	0.79		
MGA (0–10 cm), mean (SD)	6.53 (1.53)	6.46 (1.57)	0.74		
Fatigue VAS (0–10 cm), mean (SD)	5.47 (2.31)	5.75 (1.80)	0.30		
DAS28, mean (SD)	5.98 (0.68)	6.32 (0.92)	0.001*		
HAQ, mean (SD)	1.13 (0.61)	1.28 (0.68)	0.10		
ESR (mm/h), mean (SD)	43.08 (29.44)	56.63 (30.14)	0.002*	0.98	0.97–0.99
CRP (mg/L), mean (SD)	23.50 (31.96)	28.80 (29.62)	0.23		
RF positive, n (%)	47 (75.81)	164 (80.79)	0.39		
Anti-CCP antibody positive, n (%)	50 (87.72)	166 (90.71)	0.51		

Anti-CCP = anticyclic citrullinated peptide, CI = confidence interval, CRP = C-reactive protein, DAS28 = disease activity score (28 joints), ESR = erythrocyte sedimentation rate, EULAR = European League Against Rheumatism, HAQ = health assessment questionnaire, MGA = medical global assessment, OR = odds ratio, PGA = patient global assessment, RF = rheumatoid factor, SD = standard deviation, SJC = swollen joint count, TJC = tender joint count, VAS = visual analog scale.

* Significant.

3.5. Adverse events

One hundred fifty AEs were reported in 346 patients representing a prevalence of 43.4% (150/346). The most common AEs were elevated transaminases (14.16%), and then upper abdominal illness (13.01%). Twenty-four patients discontinued the study because of the occurrence of AEs. Eight patients hospitalized for AEs: 2 upper abdominal illnesses, 2 pneumonia, 1 elevated transaminase, 1 pulmonary tuberculosis, 1 pneumatothorax, and 1 cerebral hemorrhage (Table 4).

4. Discussion

In 2010, Treat-to-Target (T2T) expert committee recommended that until the desired treatment target was reached, drug treatment should be adjusted.[1] New EULAR recommendation published in 2013 put forward to the idea the treatment target (remission or at least LDA) should be attained within 6 months and not necessarily within 3 months.[15] However, it is not known whether remission rate will increase if the intensive DMARDs therapy is prolonged. In this study, we found high response rate of RA with prolonged intensive DMARDs therapy. The proportion of patients with good EULAR response increased with time without shifting the treatment. There was around 18% increment of good response rate at 36 weeks. The result suggested that prolonged intensive treatment could be continued and steered though the treat goal was not reached at 6 months.

Several studies have analyzed the role of baseline characteristics as predictors of response, such as HAQ, disease duration,

Table 3

Potential variables associated with a flare at the entry of maintenance treatment.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Female	0.80 (0.43–1.49)	0.48		
Age, y	1.00 (0.99–1.02)	0.87		
Disease duration, mo	1.00 (0.99–1.00)	0.66		
Maintenance regimen (LEF + HCQ)	0.88 (0.56–1.38)	0.57		
Duration of intensive therapy, mo	1.04 (0.75–1.43)	0.83		
Pain VAS (0–10 cm)	1.17 (1.00–1.36)	0.05		
PGA (0–10 cm)	1.20 (0.97–1.47)	0.09		
MGA (0–10 cm)	1.30 (1.04–1.62)	0.02		
Fatigue VAS (0–10 cm)	1.13 (0.99–1.30)	0.08		
Achieving remission (DAS28 ≤ 2.6)	0.65 (0.40–1.04)	0.07		
High HAQ (>0.5)	2.22 (1.16–4.23)	0.02	2.16 (1.08–4.32)	0.03
ESR, mm/h	1.01 (0.99–1.03)	0.60		
CRP, mg/L	1.12 (1.02–1.23)	0.02		
RF positive	1.26 (0.75–2.11)	0.38		
Anti-CCP antibody positive	1.13 (0.48–2.67)	0.78		

Anti-CCP = anticyclic citrullinated peptide, CI = confidence interval, CRP = C-reactive protein, DAS28 = disease activity score (28 joints), ESR = erythrocyte sedimentation rate, HAQ = health assessment questionnaire, HCQ = hydroxychloroquine, LEF = leflunomide, MGA = medical global assessment, OR = odds ratio, PGA = patient global assessment, RF = rheumatoid factor, VAS = visual analog scale.

Table 4

Safety summary of 346 patients in prolonged intensive treatment.

	No. of patients	%
Total adverse events	150	43.35
Upper abdominal illness	45	13.01
Elevated transaminase	49	14.16
Leukopenia	34	9.82
Infection*	12	3.47
Alopecia	10	2.89
Skin rash	8	2.31
Diarrhea	6	1.73
Thrombocytopenia	6	1.73
Anemia	6	1.73
Proteinuria	6	1.73
Blurred vision	3	0.87
Dizziness	3	0.87
Finger numbness	3	0.87
Itch of skin	2	0.58
Oral ulcer	2	0.58
Cough	2	0.58
Headache	1	0.28
Elevated creatine kinase	1	0.28
Pneumatothorax	1	0.29
Cerebral hemorrhage	1	0.29

Twenty-four adverse events were followed by withdrawal of study drugs: upper abdominal illness 7, rash 4, elevated transaminase 3, pneumonia 2, herpes zoster 1, leukopenia 1, elevated creatine kinase 1, dizziness 1, alopecia 1, pneumatothorax 1, cerebral hemorrhage 1, and pulmonary tuberculosis 1. Eight severe adverse events causing hospitalization were upper abdominal illness 2, pneumonia 2, elevated transaminase 1, pulmonary tuberculosis 1, pneumatothorax, 1, and cerebral hemorrhage 1.

*Twelve infective events were upper respiratory tract infection 4, pneumonia 3, herpes zoster 2, urinary infection 1, acute bronchitis 1, and pulmonary tuberculosis 1.

and baseline disease activity.[16,17] Sex and age have also been related to the treatment response.[18–20] In our study, we found that age and ESR were the predictors for the outcome of intensive treatment, which was similar with the previous reports.[20] It seemed that young patients with low level of ESR were prone to respond to intensive treatment. Predicting clinical outcomes based upon baseline factors would be useful to help select the optimal management of RA.

Our study showed that patients achieving DAS28 remission and low functional activity (HAQ) had highest retention of their disease state and by corollary lowest relapse rates. HAQ was an independent predictor for disease relapse. Thus better control of disease activity (both clinical and functional) was important for sustaining the target during intensive treatment. Studies predicting flare of RA are rare. Scirè et al[21] showed that ultrasound power Doppler (PD)-positive synovial hypertrophy, even in a single joint, was the main predictor of relapse within 6 months. Saleem et al[22] reported that baseline PD activity, HAQ, and DAS28 predicted the flare after remission. Flare was associated with worse clinical and functional outcomes. Our results further confirmed the important impact of DAS28 and HAQ on the maintenance of the treatment target.

In this study, unique conventional DMARDs therapy using MTX in combination with LEF and HCQ was given to severely active RA patients. This combination therapy was thought to be toxic and rarely used in current clinical trials. In our study, good effect and safety of the triple intensive treatment were found during 36th week. MTX, as an anchor drug in RA, was the most common drug in RA treatment. In addition, a number of studies have shown that LEF has comparable efficacy to MTX.[23–26] In maintenance period, MTX and prednisone were withdrawn. We found that there was no advantage on tapering to combination rather than monotherapy, suggesting that LEF is a good maintenance treatment as single treatment. Though there were also some weakness of the study, such as the open label design and significant dropout, the study evaluated the induction and maintenance of remission of prolonged intensive DMARDs treatment at the first time.

In conclusion, the prolonged intensive DMARDs treatment was an effective treatment strategy for active RA, and a high remission could be continued and steered though the treat goal was not reached at 6 months. Higher remission and a lower HAQ lead to less flare when tapering the DMARDs.

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References

[1] Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631–7.
[2] O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med 2013;369:307–18.
[3] Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, 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;52:3381–90.
[4] Landewé RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347–56.
[5] Verstappen SM, Jacobs JW, van der Veen MJ, 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;66:1443–9.
[6] van Vollenhoven RF, Geborek P, Forslind K, 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;379:1712–20.
[7] Keystone EC, Smolen J, van Riel P. Developing an effective treatment algorithm for rheumatoid arthritis. Rheumatology (Oxford) 2012;51 (suppl 5):v48–54.
[8] ten Wolde S, Breedveld FC, Hermans J, et al. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. Lancet 1996;347:347–52.
[9] Klarenbeek NB, van der Kooij SM, Güler-Yüksel M, et al. Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. Ann Rheum Dis 2011;70:315–9.
[10] Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
[11] Fransen J, Creemers MC, van Riel PL. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatology (Oxford) 2000;43:1252–5.
[12] Smolen JS, Keystone EC, Emery P, et al. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:143–50.
[13] van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845–50.
[14] Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263–9.
[15] Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.

[16] Curtis JR, Yang S, Chen L, et al. Predicting low disease activity and remission using early treatment response to antitumour necrosis factor therapy in patients with rheumatoid arthritis: exploratory analyses from the TEMPO trial. Ann Rheum Dis 2012;71:206–12.
[17] Hyrich KL, Watson KD, Silman AJ, et al. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2006;45:1558–65.
[18] Anderson JJ, Wells G, Verhoeven AC, et al. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum 2000;43:22–9.
[19] Saevarsdottir S, Wallin H, Seddighzadeh M, et al. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis 2011;70:469–75.
[20] Curtis JR, McVie T, Mikuls TR, et al. Clinical response within 12 weeks as a predictor of future low disease activity in patients with early RA: results from the TEAR trial. J Rheumatol 2013;40:572–8.
[21] Scirè CA, Montecucco C, Codullo V, et al. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology (Oxford) 2009;48:1092–7.
[22] Saleem B, Brown AK, Quinn M, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis 2012;71:1316–21.
[23] Singer O, Gibofsky A. Methotrexate versus leflunomide in rheumatoid arthritis: what is new in 2011? Curr Opin Rheumatol 2011;23: 288–92.
[24] Narváez J, Díaz-Torné C, Ruiz JM, et al. Comparative effectiveness of rituximab in combination with either methotrexate or leflunomide in the treatment of rheumatoid arthritis. Semin Arthritis Rheum 2011;41: 401–5.
[25] Cohen S, Cannon GW, Schiff M, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. Arthritis Rheum 2001;44:1984–92.
[26] Donahue KE, Gartlehner G, Jonas DE, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med 2008;148:124–34.