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Efficacy, safety, and cost-effectiveness of triple therapy in preventing relapse in rheumatoid arthritis: A randomized controlled trial (ESCoRT study)

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Abstract

Background: Biological agents, such as tumor necrosis factor inhibitors (TNFi), have been widely used in rheumatoid arthritis (RA) patients and greatly improved goal achievement. The aim of this study was to investigate whether conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) combination was better in reducing relapse than methotrexate (MTX) monotherapy, and more cost-effective than continuing TNFi plus MTX in RA patients who achieved low disease activity (LDA) with TNFi and MTX therapy.

Methods: RA patients who failed to csDMARDs received an induction therapy of MTX plus TNFi for maximally 12 weeks. Those achieving LDA in 12 weeks were randomly assigned at a 1:1:1 ratio into three groups: (A) adding hydroxychloroquine and sulfasalazine for the first 12 weeks and then discontinuing TNFi for the following 48 weeks; (B) maintaining TNFi and MTX for 60 weeks; and (C) maintaining TNFi and MTX for the first 12 weeks and then discontinuing TNFi for the following 48 weeks. The primary outcome was relapse.

Results: A total of 117 patients were enrolled for induction therapy and 67 patients who achieved LDA within 12 weeks were randomized, with 24, 21, and 22 patients in groups A, B, and C, respectively. The relapse rates of groups A and B during the entire 60 weeks were comparable [10/22 (45.5%) *vs.* 7/20 (35.0%), $\chi^2 = 0.475$, $P = 0.491$], however, significantly lower than that of group C [10/22 (45.5%) *vs.* 17/20 (85.0%), $\chi^2 = 5.517$, $P = 0.019$; 7/20 (35.0%) *vs.* 17/20 (85.0%), $\chi^2 = 11.035$, $P = 0.004$, respectively]. Taking RMB 100,000 Yuan as the threshold of willingness to pay, compared to MTX monotherapy (group C), both TNFi maintenance and triple csDMARDs therapies were cost-effective, but triple csDMARDs therapy was better.

Conclusion: For RA patients who have achieved LDA with TNFi and MTX, csDMARDs triple therapy was a cost-effective option in favor of reducing relapse.

Trial registration: ClinicalTrials.gov, NCT02320630.

Keywords: Conventional synthetic disease-modifying anti-rheumatic drugs; Cost-effectiveness; Relapse; Rheumatoid arthritis; Tumor necrosis factor inhibitors

Introduction

Treat-to-target strategy with clinical remission or low disease activity (LDA) as a goal has been the core management of rheumatoid arthritis (RA) for over a decade.[1] Biological agents, such as tumor necrosis factor inhibitors (TNFi), have been widely used and greatly improved goal achievement. But how to maintain the patients in remission/LDA remains an open question.

Undoubtedly, the long-term use of biologics brings a heavy economic burden. For cost as well as safety reasons,

discontinuation of biologics is common in RA patients who have achieved remission or LDA, but meanwhile increases the risk of relapse. European League Against Rheumatism (EULAR) recommends that tapering or discontinuing biologics can be considered for patients in persistent remission,[2] but no detailed guidance on successful discontinuation was provided. Plenty of evidence showed that methotrexate (MTX) monotherapy could hardly maintain remission after TNFi discontinuation, with a relapse rate of 19–75%.[3-7] Flare after TNFi discontinuation was associated with joint damage progression, especially when elevated disease activity persisted.[8] Based on some researches showing the comparable power of

remission maintenance in patients receiving a half-dose and a full dose of TNFi, both regimens were better than stopping TNFi in RA patients who achieved remission with TNFi.[9] Dose reduction or increasing intervals of injection is preferred to sharp discontinuation.

Nevertheless, more cost-effective strategies also need to be considered. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) are much cheaper,[10] with <10% of the annual cost of biologics in China. In RA patients who failed to MTX, adding hydroxychloroquine (HCQ) and sulfasalazine (SSZ) to MTX (called triple therapy thereafter) was shown the same efficacy and safety as adding a biological agent to MTX.[11,12] Past evidence has shown the superior efficacy of csDMARDs in combination with monotherapy.[13] The efficacy and safety of the triple therapy have also been proved in lots of global trials.[14-17]

In the Swedish Farmacotherapy (SWEFOT) trial, early RA patients with insufficient response to MTX were randomly allocated to receive infliximab plus MTX or triple therapy. At the end of 2 years, a small but statistically significant difference in radiographic outcomes favored the infliximab group, while disease activity, quality of life, and work loss were improved similarly in both groups, and no statistically significant differences in utility or quality-adjusted life years (QALY) gain were detected.[18-21] But whether the triple therapy is as effective as biologics in preventing relapse in RA patients who have achieved remission or LDA remains unclear.

This 1:1:1 randomized enrollment parallel-group superiority study aimed to investigate whether the triple therapy was better in reducing RA relapse than MTX monotherapy, and meanwhile more cost-effective than continuing TNFi plus MTX in patients who have achieved LDA with TNFi and MTX. We tried to find out a more reasonable biologic-free strategy to maintain remission/LDA than MTX monotherapy. In this study, a biosimilar of Etanercept, a recombinant human tumor necrosis factor α receptor II: IgG Fc fusion protein (rhTNFR-Fc) was used. Its excellent efficacy in reducing disease activity and slowing radiographic progression has been shown in RA patients.[22]

Methods

Ethical approval

This trial was approved by the Peking University Ethics Committee (No. IRB00001052-13058). Written informed consent was obtained from each participant.

Study design

This was a prospective, two-stage, multiple-center study. The first stage was an induction phase with rhTNFR-Fc 50 mg/week plus MTX 10–20 mg/week for no more than 12 weeks. Titration dose of MTX from 10 mg/week to 20 mg/week was allowed. Patients who achieved LDA, defined as disease activity score based on 28-joint count

and C-reactive protein (DAS28-CRP) ≤3.2 at this stage, were qualified for enrollment into the second stage, which was a randomized, evaluators blinded controlled trial of 60 weeks. At the second stage, all eligible patients were randomized into one of the three arms at a ratio of 1:1:1. For patients in group A, HCQ 200 mg twice daily and SSZ 1000 mg twice daily were added for the first 12 weeks and then rhTNFR-Fc was stopped, but all other medications were continued for the following 48 weeks (intervention group). Patients in group B maintained rhTNFR-Fc and MTX for 60 weeks (control group 1). Patients in group C maintained rhTNFR-Fc and MTX for the first 12 weeks and then stopped TNFi but continued MTX for the following 48 weeks (control group 2). During the entire 60 weeks of the second stage, the dosages of all active medications remained unchanged.

All the patients were followed up for 60 weeks, or when RA relapsed. The study flow chart is shown in Supplementary Figure 1, http://links.lww.com/CM9/B226. This trial was registered on the *ClinicalTrials.gov* (NCT02320630).

Participants

Patients were recruited from seven rheumatology centers. The major inclusion criteria were as follows: (1) fulfilled the 2010 EULAR/ACR classification criteria of RA; (2) between 18 and 70 years old; (3) disease durations >6 months; (4) DAS28-CRP >3.2 after treatment with MTX alone or in combination with other csDMARDs for >3 months. Exclusion criteria included patients with insufficient response or contraindications to MTX, HCQ, or SSZ (including pregnancy); with contraindication to TNFi treatment; with grade IV changes on X-ray of hands. The detailed inclusion and exclusion criteria are listed in Table 1.

Randomization

The randomization was performed by a central random system, an electronic interactive network answering system (IWRS), provided by Peking University Clinical Research Centre. Randomization information produced by IWRS using the static block random method was under the responsibility of designated staff in each study center. The blocked randomization, stratified by study center and gender of patients, was performed centrally at the visit when a patient reached LDA (V0, week 0).

Concomitant medications

Prednisolone >10 mg/day or equivalent, other csDMARDs (leflunomide, azathioprine, cyclosporine, cyclophosphamide, and tripterygium), and other biological agents were not permitted.

Non-steroidal anti-inflammatory drugs were permitted, but the name, dosage, and treatment duration were recorded. Anti-hypertension medications, antidiabetic agents, nitrates, low dose aspirin, and β-blocker were permitted if necessary.

Table 1: The inclusion and exclusion criteria of the study.

Inclusion criteria
1. Fulfill the 2010 EULAR/ACR classification criteria for RA
2. Disease duration >6 months
3. Age ≥18 years and ≤70 years
4. Use MTX alone or in combination with other csDMARDs for >3 months
5. DAS28-CRP >3.2

Exclusion criteria
1. Received any of the below therapies
   A. Large surgical operations within 8 weeks
   B. Ever use of any cell elimination therapy
   C. Intravenous injection of rituximab or IL-6 inhibitor within 6 months
   D. Intra-articular injection of glucocorticoid within 4 weeks
   E. Live vaccines or live attenuated vaccines within 4 weeks
2. Having diseases or organ/tissue damages as any of the below
   A. Autoimmune diseases other than RA. Patients combined with Sjogren Syndrome were permitted
   B. Severe or uncontrolled cardiac disease, nervous system disease, pulmonary disease, renal disease, liver disease, endocrine disease (including diabetes mellitus), and gastrointestinal disease
   C. Current or relapsing bacterial/viral/fungal/mycobacterium/other infections (include but not limited to tuberculosis or atypical mycobacterium disease, granuloma in chest X-ray, type B or type C hepatitis, HIV, Zoster)
   D. Malignant disease
   E. Nerve damage or other painful diseases which may affect pain evaluation
3. Laboratory abnormalities
   A. Serum creatinine >130 μmol/L
   B. ALT or AST >2 upper normal limitations, or total bilirubin > upper normal limitation
   C. Platelet <100 × 10^9/L, or WBC <3 × 10^9/L
4. Hands X-ray shows IV grade RA according to ACR imaging staging
5. Previous severe adverse reaction with any experimental drugs
6. Pregnant or plan to be pregnant in 2 years, or lactating women

ACR: American College of Rheumatology; ALT: Alanine aminotransferase; AST: Aspartate transaminase; csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs; DAS28-CRP: 28-joint disease activity score based on C-reactive protein; EULAR: European League Against Rheumatism; HIV: Human immunodeficiency virus; MTX: Methotrexate; RA: Rheumatoid Arthritis; WBC: White blood cell.

Follow-up schedules and data to be collected

A total of 14 visits were scheduled. Data collected at each visit are summarized in Supplementary Table 1, http://links.lww.com/CM9/B226. Subjects who relapsed or experienced intolerant adverse events before the end of the trial could exit the trial. The subsequent therapeutic regimen was at the discretion of the treating rheumatologist with no specification. All patients who exited early were continuously followed up for safety and cost-effectiveness analysis.

Outcomes

The primary outcome was RA relapse, defined as DAS28-CRP >3.2 with an increase of ≥0.6.

The secondary outcomes were as follows: the incremental cost-effectiveness ratio (ICER, incremental cost per reducing 1 case of relapse) during 60 weeks after randomization; change in disease activity at week 60 from baseline, assessed by DAS28-CRP, DAS28 based on erythrocyte sedimentation rate (DAS28-ESR), clinical disease activity index (CDAI) and simplified disease activity index (SDAI); duration of maintaining LDA or clinical remission after randomization; change of modified Sharp score at week 60 from baseline; ultrasonic remission

at week 60; mean health assessment questionnaire-disability index (HAQ-DI)[23] and EuroQol-5 dimension (EQ-5D)[24] at week 60; and adverse events.

Ultrasound assessment

An ultrasound scan was performed by two rheumatologists who were experienced in ultrasonography and blinded to the patients' clinical data. Twenty-two joints (bilateral wrists, metacarpophalangeal joints, and proximal inter-phalangeal joints) were scanned for each patient, including longitudinal, transverse, and special sectional views. A LOGIQ E9 machine (GE, Germany) with a linear probe ML 6–15 was applied, using both grayscale (GS) and Power Doppler (PD) modes. Doppler setting: 7.5–10 MHz, low wall filtering, pulse repetition frequency 700–1000 Hz. The maximum gain was considered proper when the Doppler signal was not detected beneath the cortical bone. Five RA patients were randomly selected to test the inter-observer reliability of ultrasound evaluation between the two operators. Weighted kappa analysis showed excellent inter-observer reliability of 0.893 (95% confidence interval [CI]: 0.844–0.942) for GS and 0.923 (95% CI: 0.857–0.988) for PD.

The interpretation of lesions was based on the definitions from Outcome Measures in Rheumatoid Arthritis Clinical

Trials (OMERACT).[25] The GS and PD synovitis were assessed by semi-quantitative scoring systems (0–3) proposed by Szkudlarek *et al*.[26] GS synovitis was classified as: 0 = absent; 1 = mild (slight hypoechoic or anechoic image in joint capsule); 2 = moderate (presence of elevation of articular capsule); and 3 = marked (important distension of articular capsule). The PD synovitis was classified as follows: 0 = absent; 1 = mild (one PD signal); 2 = moderate (two or more PD signals, <50% of intraarticular flow); and 3 = marked (>50% of intraarticular flow). The total GS/PD score was the sum of the GS/PD score for all 22 joints in each patient. The physical examination and ultrasound scan of joints were blindly performed on the same visiting day.

Blinding

An independent assessment committee blinded to grouping was established for disease activity and clinical outcomes assessment. The operators of ultrasound were also blinded. The members of the assessment committee, the ultrasound operators, and the investigators worked independently. In the case of a serious adverse event (SAE) during the study, non-blinding was permitted, and the relevant institutional review board (IRB) and principal study site (Peking University First Hospital) would be informed and decide to continue or terminate the trial.

Sample size calculation

The sample size was calculated by PASS 11.0 (Power Analysis and Sample Size, NCSS, Kaysville, Utah, USA). Our hypothesis was that the relapse rate of group A (triple therapy group) was lower than that of group C (MTX monotherapy group) 60 weeks after randomization. Based on the previous study, the relapse rate of group C (MTX monotherapy) was 38% within 1 year, and presumably 16% after adding SSZ and HCQ (group A). At a power of 0.8 and a significance level of 0.05 (two sides), using a 1:1:1 treatment allocation of enrollment, the estimated sample size was 61 for each group to detect the difference in relapse rate between the two arms. Based on an assumption of a 10% dropout rate, the target sample size for recruitment was 204 (68 for each group).

Statistical analysis

All statistical analyses were performed using SPSS 22.0 (IBM Corp, Armonk, NY, USA).

The compatibility between the study groups at baseline was checked. The Student's *t*-test or Wilcoxon rank-sum test was used for quantitative variables. The chi-squared test or Fisher's exact test was used for categorical variables. The Cochran–Mantel–Haenszel test or the Wilcoxon rank-sum test was used for ordinal variables.

In the analysis of comparing the relapse rate between groups A and C, the intent-to-treat principle was followed. The estimation of the treatment effect with its CI was analyzed by the Mantel–Haenszel method stratified by study centers in consideration of its potential influence. Kaplan–Meier curves were used to show the difference in

relapse among groups. The changes in disease activity, Sharp score, PD/GS synovitis score on ultrasound, and HAQ score were compared among the three groups using the covariance analysis model. Per-protocol analysis was conducted as the sensitivity analysis.

Analysis of pharmaceutical economics was performed parallelly to the clinical analysis. A decision tree based on a per-protocol set was built to perform base case analysis and sensitivity analysis [Supplementary Figure 2, http://links.lww.com/CM9/B226]. We also conducted a series of one-way deterministic sensitivity analysis. In the cost-effectiveness analysis, the rate of non-relapse was taken as effectiveness. The direct cost, total cost, and average cost/effectiveness ratio of each treatment strategy were calculated. The incremental cost-effectiveness ratio (ICER) of groups A and B against group C were calculated. A cost-utility analysis was performed using EQ-5D as the index of utility. The costs and average cost/utility ratio of each treatment strategy were calculated. The incremental cost-utility ratio (ICUR) of groups A and B against group C was also calculated. The treatment strategy was considered as having cost-utility if the ICUR was below three times of per capita gross domestic product (GDP) of China in the past year (RMB 100,000 Yuan).

The cost included medical expenses and productivity lost (direct cost and indirect cost). Bootstrap was used to calculate the 95% CI of ICER and draw the cost-effectiveness acceptability curve. The factors which may affect the analysis were evaluated by one-way and probability sensitivity analysis. All the analyses were performed by TreeAgePro11.0 software (TreeAge Software Inc., Williamstown, USA).

Safety analysis was performed based on the safety set. The incidence of adverse events, SAE, and adverse reactions related to the study medications were described. Crosstabs were constructed to map the changes in laboratory indexes.

Considering the multiple comparisons among three groups (A *vs*. B and A *vs*. C) will increase the type I error, we used Bonferroni-adjusted significance tests to adjust the *P*-value required for significance to 0.025.

Results

Demographics and baseline clinical features of enrolled patients

Among the 123 RA patients screened, 117 entered the induction stage with a median age of 58.4 years, and 81.2% were female. Sixty-seven (57.3%) patients achieved DAS28-CRP <3.2 within 12 weeks after initiating MTX and TNFi treatment and then were randomized. There were 24, 21, and 22 patients in groups A, B, and C in the randomization stage, respectively [Figure 1]. Fifty patients failed in entering the randomization stage due to adverse events (4 patients), lost to follow-up (1 patient), protocol violation (1 patient), and no achievement of DAS28-CRP <3.2 (44 patients). During the 60-week follow-up in the randomization stage, there were five patients who dropped out [Figure 1].
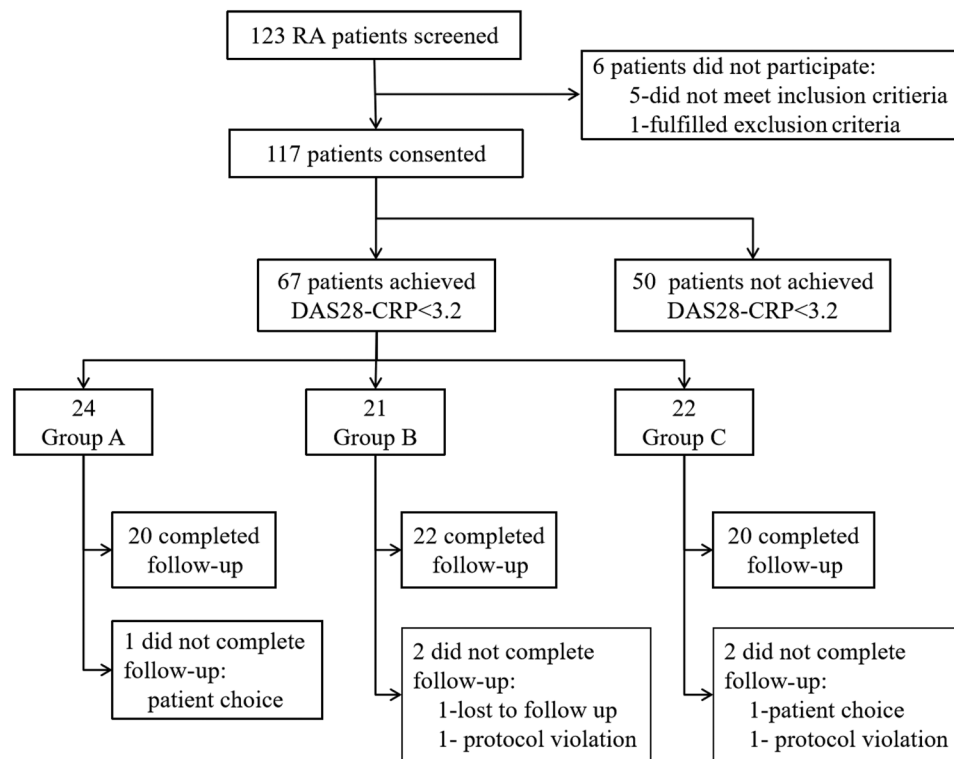
Figure 1: Consort diagram of patient progress throughout the study. CRP: C-reactive protein; DAS: Disease activity score; RA: Rheumatoid arthritis.

The baseline demographics and clinical features of 67 enrolled patients are given in Table 2.

Predictive factors for achievement of LDA with TNFi and MTX treatment within 12 weeks

A total of 67 out of 117 (57.3%) patients achieved LDA after initiating TNFi plus MTX treatment within 12 weeks. Compared with 44 patients who did not achieve LDA, the patients who achieved LDA had a lower proportion of female, shorter disease duration, fewer baseline tender joint counts, lower baseline disease activity, and lower baseline HAQ-DI [Table 3]. Multiple logistic regression analysis showed that male gender and few tender joint counts were predictive factors for the achievement of LDA with TNFi and MTX treatment within 12 weeks [Supplementary Table 2, http://links.lww.com/CM9/B226].

Clinical features of patients at randomization and their clinical outcomes in three groups

Eventually, 67 patients entered the randomization stage, with a median age of 59 years and 71.6% were female. At randomization, their clinical features were similar among the three groups, except for a bit higher PD score in group B. During follow-up of 60 weeks, relapse was observed in 10/22 (45.5%), 7/20 (35.0%), and 17/20 (85.0%) patients in three groups, respectively [Figure 2]. The relapse rates in group A and group B were comparable ($\chi^2 = 0.475$, $P = 0.491$), however, both higher than that in group C ($\chi^2 = 5.517$, $P = 0.019$; $\chi^2 = 11.035$, $P = 0.004$, respectively). Interestingly, the LDA maintenance duration before relapse was shorter in group B than that in groups A

and C (10.4 [4.0–47.0] vs. 20.0 [4.0–44.0] weeks, $Z = -2.070$, $P = 0.038$; 10.4 [4.0–47.0] vs. 16.0 [3.0–36.0] weeks, $Z = -2.221$, $P = 0.026$), and similar between group A and group C ($Z = -0.736$, $P = 0.462$).

For those patients who did not relapse, the disease activity assessed by DAS28-CRP, DAS28-ESR, CDAI, and SDAI, as well as HAQ-DI and EQ-5D was all comparable among three groups at week 60 [Supplementary Table 3, http://links.lww.com/CM9/B226].

Radiological outcomes of patients in three groups

The modified sharp score was evaluated by an X-ray of bilateral wrists and hands. The bone erosion (BE) score, joint space narrowing score, and total score were comparable among the three groups at baseline. There were 13, 12, and 3 patients who completed all the 60 weeks of follow-up in each group, respectively. The BE scores at week 60 were significantly higher in group A than that in groups B and C (0 (0–2) vs. 2 (2–83), $Z = -2.577$, $P = 0.010$; 0 (0–2) vs. 4.5 (2–7), $Z = -2.729$, $P = 0.010$, respectively), although no difference was found between groups B and C ($Z = -1.849$, $P = 0.078$). The joint space narrow (JSN) scores and modified total sharp scores (mTSS) at week 60 and change in sharp scores at the end of week 60 against baseline were similar among the three groups [Table 2].

A total of 48 out of 67 patients received ultrasound examination at randomization and 20 non-flared patients received repeated ultrasound scans at week 60. Overall, the proportion of patients with PD synovitis significantly decreased ($\chi^2 = 6.557$, $P = 0.010$), but not with GS synovitis ($\chi^2 = 0.483$, $P = 0.487$). Further analysis showed

Table 2: Comparison of baseline characteristics and outcomes among patients of the three groups in the randomization stage.

Items	Group A (n = 24)	Group B (n = 21)	Group C (n = 22)	$F^*/\chi^{2\dagger}$	P values
Age (years)	59.0 (22.0–72.0)	59.3 (31.0–70.0)	52.6 (29.0–72.0)	2.117*	0.347
Female	18 (75.0)	17 (81.0)	13 (59.1)	2.695†	0.260
BMI (kg/m²)	23.2 ± 3.1	23.7 ± 3.2	23.9 ± 4.4	0.252*	0.778
Disease duration (months)	42 (6–253)	66 (12–300)	84 (7–336)	4.553*	0.103
TJC	2 (0–5)	2 (0–6)	1 (0–5)	1.456*	0.483
SJC	1 (0–4)	1 (0–2)	0 (0–3)	4.162*	0.125
PGA	20 (10–45)	30 (5–70)	20 (0–50)	3.977*	0.137
EGA	20 (10–45)	30 (10–70)	20 (0–50)	3.720*	0.156
ESR	18 (2–100)	18 (4–46)	15 (2–45)	0.017*	0.991
CRP	3.01 (1.22–30.7)	3.36 (1.59–34.28)	3.52 (1.14–60.1)	0.127*	0.938
RF (IU/mL)	175.5 (0–1930.0)	31.2 (0–1010.0)	61.5 (0–3410)	3.440*	0.179
Anti-CCP	20 (90.9)	17 (85.0)	18 (90.0)	0.468†	0.791
DAS28-CRP	2.88 (1.71–3.19)	3.00 (2.22–3.09)	2.74 (1.34–3.19)	1.144*	0.564
DAS28-ESR	3.15 ± 0.54	3.10 ± 0.64	2.80 ± 0.90	1.557*	0.219
SDAI	8.71 (2.45–12.55)	9.36 (3.23–16.16)	7.51 (0.18–14.14)	4.361*	0.113
CDAI	8.5 (2–12)	8.5 (3–16)	6 (0–14)	4.782*	0.092
HAQ	0.18 (0–2.75)	0.35 (0.05–1.05)	0.05 (0–0.80)	5.789*	0.081
EQ-5D	0.869 (0.505–0.961)	0.783 (0.505–0.961)	0.918 (0.591–0.961)	3.381*	0.147
PD	0 (0–4)	1.5 (0–27)	1 (0–5)	6.002*	0.049
GS	4 (0–15)	45 (2–40)	2 (0–23)	3.251*	0.197
Modified sharp score at baseline					
BE	0 (0–30)	1 (0–81)	1.5 (1–29)	4.157*	0.125
JSN	7 (1–28)	6 (1–67)	8 (1–32)	0.341*	0.843
mTSS	9 (1–58)	8 (1–148)	9.5 (2–61)	0.192*	0.908
MTX dosage (mg/week)	12.5 (10–15)	10 (10–15)	10 (10–15)	0.356*	0.837
Relapse	10 (45)	7 (35)	17 (85)	11.422†	0.001
Duration of LDA/remission before relapse (weeks)	20.0 (4.0–44.0)	10.4 (4.0–47.0)	16.0 (3.0–36.0)	6.148*	0.046
Sharp Score at week 60					
BE	0 (0–2)	2 (0–83)	4.5 (2–7)	7.753*	0.021
JSN	8 (1–17)	6 (1–74)	10 (9–11)	0.501*	0.778
mTSS	9.5 (1.0–17.0)	9.0 (3.0–157.0)	14.5 (13.0–16.0)	1.104*	0.576
Sharp score progression					
BE	0 (0–0)	0 (0–3)	3 (0–6)	5.207*	0.074
JSN	1 (0–3)	1 (−1–7)	4.5 (1–8)	1.902*	0.386
mTSS	1 (0–3)	1 (−1–9)	7.5 (1–14)	1.460*	0.482

Data are expressed as mean ± standard deviation, median (Q1–Q3) or *n* (%). * *F*. † χ^2. Anti-CCP: Anti-cyclic citrullinated protein; BE: Bone erosion; BMI: Body mass index; CDAI: Clinical disease activity index; CRP: C-reactive protein; DAS: Disease activity score; EGA: Evaluator global assessment; EQ-5D: Euro Qol five-dimension questionnaire; ESR: Erythrocyte sedimentation rate; GS: Gray scale; HAQ-DI: Health Assessment Questionnaire-Disability Index; JSN: Joint space narrow; LDA: Low disease activity; mTSS: Modified total sharp score; PD: Power Doppler; PGA: Patient global assessment; RF: Rheumatoid factor; SDAI: Simplified disease activity index; SJC: Swollen joint count; TJC: Tender joint count.

that the proportion of patients with PD synovitis was only significantly decreased in group B (χ^2 = 17.895, *P* < 0.001) [Supplementary Table 4, http://links.lww.com/CM9/B226]. Both total PD score and GS score significantly decreased in patients of group B (*Z* = −3.452, *P* = 0.001; *Z* = −3.275, *P* = 0.001, respectively) [Supplementary Table 5, http://links.lww.com/CM9/B226]. In patients of group A, only GS score decreased (*P* = 0.009, *Z* = −2.587), whereas neither PD nor GS synovitis improved in patients of group C [Supplementary Table 5, http://links.lww.com/CM9/B226].

Cost-effectiveness and cost-utility analysis among three groups

Direct cost-effectiveness analysis and total cost-effectiveness analysis are shown in Supplementary Figure 3, http://

links.lww.com/CM9/B226. The cost-effectiveness and cost-utility analysis for the three therapeutic strategies are present in Supplementary Tables 6 and 7, http://links.lww.com/CM9/B226. The triple therapy showed the lowest average direct cost-effectiveness ratio, total cost-effectiveness ratio, direct cost-utility ratio, and total cost-utility ratio. Compared to MTX monotherapy, triple therapy had cost-effectiveness, and cost-utility, when RMB 100,000 Yuan was taken as the threshold of willingness to pay (WTP). Compared to triple therapy, TNFi maintenance therapy had neither cost-effectiveness nor cost-utility.

The tornado analysis indicated that the most influential parameter was the cost of rhTNFR-Fc. For the triple therapy group, the ICUR was decreased from RMB 3.0 million Yuan per QALY to RMB 0.278 million Yuan per

Table 3: Comparison of baseline characteristics between patients achieved and not achieved DAS28-CRP <3.2 in the induction stage.

Items	Total patients enrolled in the induction stage ($n=111$)	Patients achieved DAS28-CRP<3.2 ($n=67$)	Patients not achieved DAS28-CRP<3.2 ($n=44$)	$T^*/\chi^{2\dagger}/Z^\ddagger$	P values
Age (years)	58.4 (22.0–72.0)	59.0 (22.0–72.0)	56.6 (24.0–72.0)	−1.018‡	0.309
Female	91 (81.2)	48 (71.6)	43 (97.7)	10.818†	0.001
BMI (kg/m^2)	23.8 ± 3.8	23.6 ± 3.6	23.9 ± 4.0	−0.450*	0.653
Disease duration (months)	76 (6–408)	66 (6–336)	108 (6–408)	−1.806‡	0.071
TJC	10 (1–28)	8 (2–28)	13 (1–28)	−3.154‡	0.002
SJC	4 (0–21)	4 (0–21)	5 (0–18)	−1.765‡	0.078
PGA	60 (20–90)	60 (20–90)	70 (20–90)	−0.835‡	0.404
EGA	60 (10–90)	50 (10–90)	60 (20–90)	−1.743‡	0.081
ESR	33 (2–170)	33 (2–105)	34 (6–170)	−0.950‡	0.342
CRP	14.3 (1.3–138.0)	15.2 (1.3–104.0)	14.8 (1.4–138.0)	−0.220‡	0.826
RF positive	81 (73.0)	48 (71.6)	33 (75.0)	0.210†	0.647
Anti-CCP positive	96 (86.5)	60 (89.6)	36 (81.8)	0.719†	0.397
HAQ-DI	1.03 ± 0.61	0.90 ± 0.57	1.25 ± 0.60	−2.847*	0.005
PD	2 (0–38)	2 (0–38)	2 (0–20)	−0.372‡	0.710
GS	6 (0–56)	5 (0–56)	6 (0–37)	−1.011‡	0.312

Data are expressed as mean ± standard deviation, median (Q1–Q3) or n (%). * T. † χ^2. ‡ Z. Anti-CCP: Anti-cyclic citrullinated protein; BMI: Body mass index; CDAI: Clinical disease activity index; CRP: C-reactive protein; DAS: Disease activity score; ESR: Erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; RF: Rheumatoid factor; SDAI: Simplified disease activity index; SJC: Swollen joint count; TJC: Tender joint count.
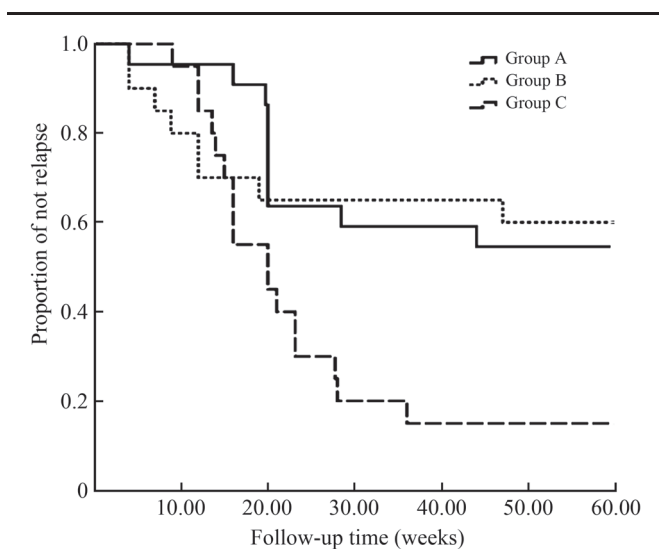

Figure 2: The Kaplan–Meier Curve of disease relapse of the three groups. The relapse rates in group A and group B were comparable ($\chi^2 = 0.475$, $P = 0.491$), however, both higher than that in group C ($\chi^2 = 5.517$, $P = 0.019$; $\chi^2 = 11.035$, $P = 0.004$, respectively).

QALY if the cost of rhTNFR-Fc was reduced from RMB 1300 Yuan to RMB 100 Yuan per week [Supplementary Figure 4, http://links.lww.com/CM9/B226].

TNFi maintenance therapy would gain the better net monetary benefit of utility if the cost of rhTNFR-Fc was RMB 130.54 Yuan per week or less [Supplementary Figure 5, http://links.lww.com/CM9/B226], and better net monetary benefit of effectiveness (evaluated by relapse-free rate) when the weekly cost was RMB 399.16 Yuan or less [Supplementary Figure 6, http://links.lww.com/CM9/B226].

Considering the possibility of data imprecision due to the small sample size, we performed a one-way sensitivity

analysis by varying the relapse rate difference by 30% of the base case among the three groups [Supplementary Figure 7, http://links.lww.com/CM9/B226].

Adverse effects

All 117 patients were included in the safety analysis. Sixty-two (55.6%) patients experienced adverse events, including elevated aminotransferase (27, 23.1%), upper respiratory tract infection (18, 15.4%), rash (14, 12.0%), gastrointestinal symptoms (10, 8.5%), leukocytopenia (8, 6.8%), pruritus (6, 5.1%), urinary tract infection (2, 1.7%), pneumonia (2, 1.7%), and hyperlipidemia, periodontitis, edema of lower extremities, herpes zoster, anemia, and new-onset hypertension (1, 0.9% each), respectively. In the induction stage, four patients withdrew from the study due to adverse events (one each with pneumonia, severe skin allergy, herpes zoster, and hepatic impairment with leukocytopenia). No SAE was observed.

Among the 67 patients enrolled in the randomization stage, adverse reactions were observed in 37 (55.2%) patients, which was similar to that in the total safety set. Most adverse effects were comparable among the three groups, except for more frequent gastrointestinal symptoms in patients of groups A and C ($\chi^2 = 11.955$, $P = 0.001$) [Table 4]. No dropout due to adverse events occurred in the randomization stage.

Discussion

In the current study, we evaluated the cost-effectiveness, safety, and efficacy in preventing relapse of triple csDMARDs therapy (MTX + HCQ + SSZ) in comparison with MTX monotherapy and continuation of TNFi plus MTX among RA patients achieving LDA or remission. We found triple therapy was superior to MTX monotherapy

Table 4: Adverse events among the three groups, n (%).

Items	Group A (n = 24)	Group B (n = 21)	Group C (n = 22)	χ^2	P values
Total adverse events	12 (50.0)	12 (57.2)	13 (59.1)	0.429	0.807
Liver damage	5 (20.8)	7 (33.3)	6 (27.3)	0.893	0.640
Upper respiratory tract infection	3 (12.5)	7 (33.3)	6 (27.3)	3.059	0.217
Rash	1 (4.2)	1 (4.8)	2 (9.1)	0.545	0.761
Gastrointestinal involvement	8 (33.3)	1 (4.8)	0	14.274	0.001
Pruritus	1 (4.2)	1 (4.8)	1 (4.5)	0.010	0.995
Leukocytopenia	3 (12.5)	2 (9.5)	1 (4.5)	0.972	0.615
Urinary tract infection	0	1 (4.8)	1 (4.5)	1.809	0.405
Anemia	1 (4.2)	0	0	2.081	0.353
Hyperlipidemia	0	0	1 (4.5)	1.513	0.219
Periodontitis	0	0	1 (4.5)	1.513	0.219

in preventing relapse and meanwhile more cost-effective than TNFi maintenance therapy.

With the wide application of biological agents, more RA patients have been able to achieve remission or LDA. But the great "unmet need" currently lies in the appropriate strategy to maintain remission or LDA after the reduction or discontinuation of biologics. Previous studies showed that 19–75% of patients relapsed in 12 months after discontinuation of TNFi (3–5). In our trial, the relapse rate was as high as 85%, although TNFi and MTX were continued for additional 12 weeks before cessation. MTX monotherapy for maintenance after discontinuing TNFi has been proved inappropriate. Some studies showed that discontinuation of biologics was associated with an increased risk of losing remission whereas tapering was not.[27,28] EULAR also recommends that tapering biologics can be considered for RA patients in sustained remission.[8] Nevertheless, biological therapy with a taping dose remains expensive indeed and whether tapering can contribute to final withdrawal is unknown.

The efficacy and safety of MTX, HCQ, and SSZ triple therapy have been proven for decades.[14-17] Several randomized controlled trials also demonstrated similar efficacy to TNFi in combination with MTX in RA.[14,29] For instance, the TEAR study showed equivalent mean DAS28 during weeks 48–102 in patients receiving MTX plus etanercept and triple therapy.[12] Given the similar outcomes, however, huge difference in cost, triple therapy was found to be more durable than MTX-etanercept therapy in patients with inadequate response to MTX.[30] Moreover, triple therapy showed almost the same safety profiles to TNFi plus MTX therapy, except for slightly higher non-serious gastrointestinal symptoms and lower infectious events reported in some studies.[31,32]

Whether the triple therapy is as effective as biologics in preventing RA relapse in patients who have achieved remission or LDA remains unclear. A previous study showed that combination therapy of MTX and cyclosporin did not prevent RA relapse in 58% of patients with LDA after discontinuation of TNFi.[4] We noticed that TNFi was stopped exactly at the initiation of combination therapy, which we think may explain the high frequency of flare in the study, as cyclosporin usually takes several weeks to take effect. Therefore, in the current study, adding HCQ and SSZ was required for 12 weeks before TNFi cessation. Importantly, we found relapse rates were pretty similar in patients receiving triple therapy and TNFi maintenance therapy, indicating that triple therapy can be an alternative to biologics on the premise of 12-week overlap therapy. To be noted, this conclusion derived from RA patients who have achieved LDA with MTX and TNFi therapy for no more than 12 weeks may be inappropriate for other clinical situations.

Plenty of studies have demonstrated better cost-effectiveness of triple therapy than biologics. RACAT study showed that etanercept-MTX was superior in efficacy however with a higher ICER compared with triple therapy for active RA patients with inadequate response to MTX.[33] A Swedish study reported that infliximab cost €20916 more than triple therapy over a period of 21 months while providing only 0.01 additional QALY, resulting in an ICER of €2404197 per QALY.[29] A UK study showed adalimumab, etanercept, or infliximab cost $8586 more than csDMARDs combinations over a period of 12 months, however, no difference in EQ-5D.[34] Choi et al[35] reported that compared with MTX monotherapy, etanercept plus MTX as well as MTX plus CsA regimens, triple therapy was the most cost-effective option for MTX-resistant RA patients. A Chinese study also reported similar results.[36]

It is noteworthy that we do not mean biologics should be abandoned from csDMARDs resistant RA patients who have achieved remission by TNFi plus MTX, rather triple therapy should be recommended in preference to biologics for the sake of cost savings. The TNFi we used in this trial was a cheaper biosimilar to etanercept. The cost of biosimilars has been continuously decreasing in China in recent years. Moreover, the reimbursement policy of biologics will make the cost-effective margin between triple therapy and TNFi smaller.

There are a couple of novelties of our trial. We designed an overlap of triple csDMARDs with TNFi for 12 weeks as a bridging therapy for the consideration of reducing relapse. Besides, the cost-effective and cost-utility analyses were conducted in RA patients who have achieved the therapy target. Most previous studies compared the pharmacoeconomics of triple therapy and biologics in improving the

disease activity of RA patients, but few studies focused on the efficacy of maintenance of remission.

We are aware of the limitations of this study. First, both patients and investigators were not blinded based on the open-labeled design. But clinical evaluators and ultrasound operators were blinded to grouping and treatment, which maximally guaranteed the objectivity of the study. Second, the study was terminated early due to a high relapse rate especially in group C. There were no precise data available for reference when we designed the study. But a greater difference in flare rate among groups makes a smaller sample size required. We understand although the primary endpoint has been achieved, the significant difference may be by chance or not real due to the small sample size. A study with an expanded scale is warranted in the future to confirm the conclusion. Third, the potential long-term cost-effective analysis cannot be performed because of the inherent shortcomings in the observation period of the trial. Finally, the achievement of LDA was low at the first stage of the study. This may be attributable to the short duration of MTX plus TNFi treatment, low dose of MTX (median 10–12.5 mg/week), and enrolled established RA patients (median disease duration 37–81 months).

In conclusion, for RA patients who have achieved the clinical target with TNFi and MTX, the MTX, HCQ, and SSZ triple therapy is as effective as TNFi maintenance therapy in reducing relapse, but more cost-effective. Triple therapy can be used as an alternative to TNFi for maintenance.

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Conflicts of interest

None.

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