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Cost-effectiveness analysis of etanercept plus methotrexate vs triple therapy in treating Chinese rheumatoid arthritis patients

Zhi-Chao Shi, MB[a], Hong-Ping Fei, PhD[b,*], Zhi-Liang Wang, MM[b]

Abstract

Objective: This study aimed to explore the cost-effectiveness of etanercept plus methotrexate (ETN+MTX) compared to triple disease-modifying anti-rheumatic drugs (DMARDs) in treating Chinese rheumatoid arthritis (RA) patients.

Methods: The 134 Chinese RA patients who were about to initiate ETN+MTX or triple DMARDs therapy based on treat-to-target strategy were consecutively recruited and categorized into ETN+MTX group (N = 49) or triple DMARDs group (N = 85). Treatment efficacy was assessed at month 3 (M3)/M6/M9/M12 after initiation of treatment. Also, 1-year treatment cost was evaluated, and cost-effectiveness analysis and sensitivity analysis were conducted.

Results: RA patients in ETN+MTX group exhibited similar disease activity and quality of life at each time point while elevated 28-joint disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) change (M0-M12) and low disease activity rate compared with triple DMARDs group. For 1-year treatment cost, ETN+MTX required increased drug cost, decreased other medical cost, and finally elevated total cost compared with triple DMARDs. Meanwhile, compared to triple DMARDs, ETN+MTX produced an additional quality-adjusted life year (QALY) of 0.015, resulting in an incremental cost-effectiveness ratio (ICER) of ¥2,939,506.7 per QALY that was 53.1 folds of gross domestic product (GDP) per capita in China. More interestingly, sensitivity analysis revealed that the ETN price had to be reduced at least by 71.3% before ETN+MTX became cost-effectiveness compared to triple DMARDs.

Conclusion: ETN+MTX is less cost-effective in treating Chinese RA patients compared with triple DMARDs.

Abbreviations: ACPA = anti-citrullinated protein antibodies, BMI = body mass index, CEA = cost-effectiveness analysis, CRP = C-reactive protein, DAS28-ESR = 28-joint disease activity score based on erythrocyte sedimentation rate, DMARDs = disease-modifying anti-rheumatic drugs, ETN = etanercept, ETN+MTX = etanercept plus methotrexate, GDP = gross domestic product, HCQ = hydroxychloroquine, ICER = incremental cost-effectiveness ratio, ICER = incremental cost-effectiveness ratio, LDA = low disease activity, MTX = methotrexate, NSAIDs = non-steroidal anti-inflammatory drugs, QALY = quality-adjusted life year, RA = rheumatoid arthritis, SJC = swollen joint count, SSZ = sulfasalazine, TJC = tender joint count, ULN = upper limit of normal.

Keywords: etanercept, incremental cost-effectiveness ratio, quality-adjusted life year, rheumatoid arthritis, triple therapy

1. Introduction

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease presenting with tendering/swelling joints, pain and various extra-articular manifestations (such as cardiovascular diseases, lung diseases and renal diseases).[1,2] Currently, RA has been reported to be a global health problem which affects approximately 1% of the world population and over 0.4% of the Chinese population.[2–4] In order to solve this problem, a variety of disease management approaches have been applied in RA patients, and drug therapy is the main therapeutic approach, including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoid, disease-modifying anti-rheumatic drugs (DMARDs) and biologics.[2,5,6] Among these 4 treatment agents, DMARDs are considered as first-line treatment agents for RA patients which obviously decrease disease activity and inflammation level, whereas there are still parts of RA patients who are not responsive to DMARDs or intolerable to adverse events.[2,7] For biologics, they provide favorable anti-RA efficacy in reducing disease activity and suppressing radiographic progression for aggressive RA patients.[5–7] As the most common biologics, tumor necrosis factor (TNF)-α inhibitors (such as etanercept (ETN) and infliximab) are widely applied in clinical practices for RA patients due to their great treatment efficacy. However, the extremely high cost of these TNF-α inhibitors brings in substantial burdens to individuals and families, and they have been reported to provide narrow benefits for RA patients compared with triple DMARDs therapy (methotrexate (MTX) plus sulfasalazine (SSZ) and hydroxychloroquine (HCQ)).[8–12]

Editor: Raouf Hajji.

The authors have no funding and conflicts of interest to disclose.

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How to cite this article: Shi ZC, Fei HP, Wang ZL. Cost-effectiveness analysis of etanercept plus methotrexate versus triple therapy in treating Chinese rheumatoid arthritis patients. Medicine 2020;99:3(e16635).

Received: 1 February 2019 / Received in final form: 24 June 2019 / Accepted: 5 July 2019

http://dx.doi.org/10.1097/MD.0000000000016635

Therefore, pharmacoeconomic analyses about the cost-effectiveness of TNF-α inhibitors are necessary to balance the limit budgets and the best possible treatment outcomes.

Recently, several pharmacoeconomic studies have been performed regarding the cost-effectiveness of TNF-α inhibitors in RA patients, and they illuminate that ETN plus MTX (ETN +MTX) might not be cost-effective in treating RA patients compared with triple DMARDs.[13,14] However, most of these pharmacoeconomic studies have been conducted in developed countries, and information about the cost-effectiveness of TNF-α inhibitors in treating Chinese RA patients is still limited. Therefore, the aim of the current study was to explore the treatment efficacy and the cost-effectiveness of ETN+MTX compared to triple DMARDs in treating Chinese RA patients.

2. Methods

2.1. Patients

Between Jan 2016 and Dec 2016, 134 RA patients from Lishui People's Hospital about to initiate ETN+MTX combination therapy or triple DMARDs therapy were consecutively recruited in this study. The inclusion criteria were:

(1) diagnosed RA according to 1987 American College of Rheumatology (ACR) classification criteria for RA;[15]
(2) age over 18 years;
(3) failed to respond to monotherapy of DMARDs;
(4) At active disease condition with a 28-joint disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) more than 3.2;
(5) scheduled to receive treat-to-target strategy with ETN+MTX or treat-to-target strategy with triple DMARDs therapy (MTX+HCQ+SSZ) based on the disease status and personal willingness.

The exclusion criteria included:

(1) other immune rheumatism diseases;
(2) suffering from active tuberculosis, hepatitis, infections or cancers;
(3) contraindications to any study drugs;
(4) serious liver or renal dysfunction (serum transaminase level >2 times upper limit of normal (ULN) or creatinine > 2 times ULN);
(5) New York Heart Association Class III or IV congestive heart failure;
(6) prior treatment with any TNF-α inhibitors within 4 weeks before enrollment;
(7) any significant unstable medical condition considered a contraindication by investigators;
(8) pregnant or nursing women. This study was approved by Institutional Review Boards of the Hospital and was conducted in accordance with the Guidelines for Good Clinical Practice and the *Declaration of Helsinki*. All the enrolled participants provided written informed consents.

2.2. Data collection

After enrollment, baseline characteristics of enrolled patients were recorded, including age, gender, body mass index (BMI), disease duration, rheumatoid factor status, anti-citrullinated protein antibodies (ACPA), history of biologics.

2.3. Treatment

According to the disease status and personal willingness, 49 patients planning to receive treat-to-target strategy with ETN +MTX were assigned to the ETN+MTX group, and 85 patients scheduling to receive treat-to-target strategy with triple DMARDs therapy were assigned to the triple DMARDs therapy group. For patients in the ETN+MTX group, treat-to-target strategy was performed for 12 months as follows (Fig. 1): initial regimen: ETN 50 mg once a week subcutaneously for 3 months; MTX 10 to 20 mg once a week orally for 3 months. Patients' DAS28-ESR score was assessed every 3 months, and at the assessed time points, patients with DAS28-ESR score ≤3.2 (low disease activity) were prescribed reduction regimen (ETN 25 mg once a week subcutaneously and MTX 10–20 mg once a week orally) for subsequent therapy; as for patients with DAS28-ESR score > 3.2, the initial regimen was maintained for the following therapy. In the triple DMARDs therapy group, treat-to-target strategy was carried out for 12 months as follows (Fig. 1): initial regimen: MTX 10 mg once a week orally, then escalated each month in 2.5 to 5.0 mg increments to a maximum of 20 mg/week by month 3; SSZ 500 mg twice a day orally for 3 months, and HCQ 200 mg daily orally for 3 months. Patients' DAS28-ESR score was assessed every 3 months as well, and for patients with DAS28-ESR score ≤3.2 (low disease activity) at the assessed time points, the initial regimen was maintained for the following therapy; as for patients with DAS28-ESR score > 3.2, they were prescribed the increased regimen (MTX 10 to 20 mg once a week orally, SSZ 1000 mg twice a day orally, and HCQ 400 mg daily) for subsequent therapy. Besides, all patients in both groups who received NSAIDs or glucocorticoids treatment during the study, the dosage and duration of NSAIDs and glucocorticoids were required to record in detail.

2.4. Evaluation of efficacy

Patients were followed up every 3 months after the initiation of therapy. Tender joint count (TJC), swollen joint count (SJC), ESR, C-reactive protein (CRP) and Health Assessment Questionnaire Disability Index (HAQ-DI) were measured or assessed at baseline (M0), month 3 after initiation of therapy (M3), M6, M9, M9, and M12. And the DAS28-ESR score was calculated at each follow-up point by TJC, SJC, and ESR (DAS28-ESR = $[0.56*\sqrt{}(TJC) + 0.28*\sqrt{}(SJC) + 0.70*\ln(ESR)]*1.08 + 0.16$). Moreover, the clinical remission was defined as the DAS28-ESR score < 2.6, and the low disease activity (LDA) was defined as the DAS28-ESR score≤3.2.[16]

2.5. Assessment of cost

For assessment of 12-month economic cost in the present study, all required data were collected routinely in the case report form, which included medication use, outpatient service, emergency service and hospital stays. Total cost consisted of drug cost and other medical cost, and both drug cost and other medical cost were obtained from the receipts for medical expenses of patients.

2.6. Cost-effectiveness analysis (CEA)

Cumulative cost (total cost) and quality-adjusted life year (QALY) were calculated for each treatment strategy in the CEA. QALYs were estimated by the area under utility curves. A

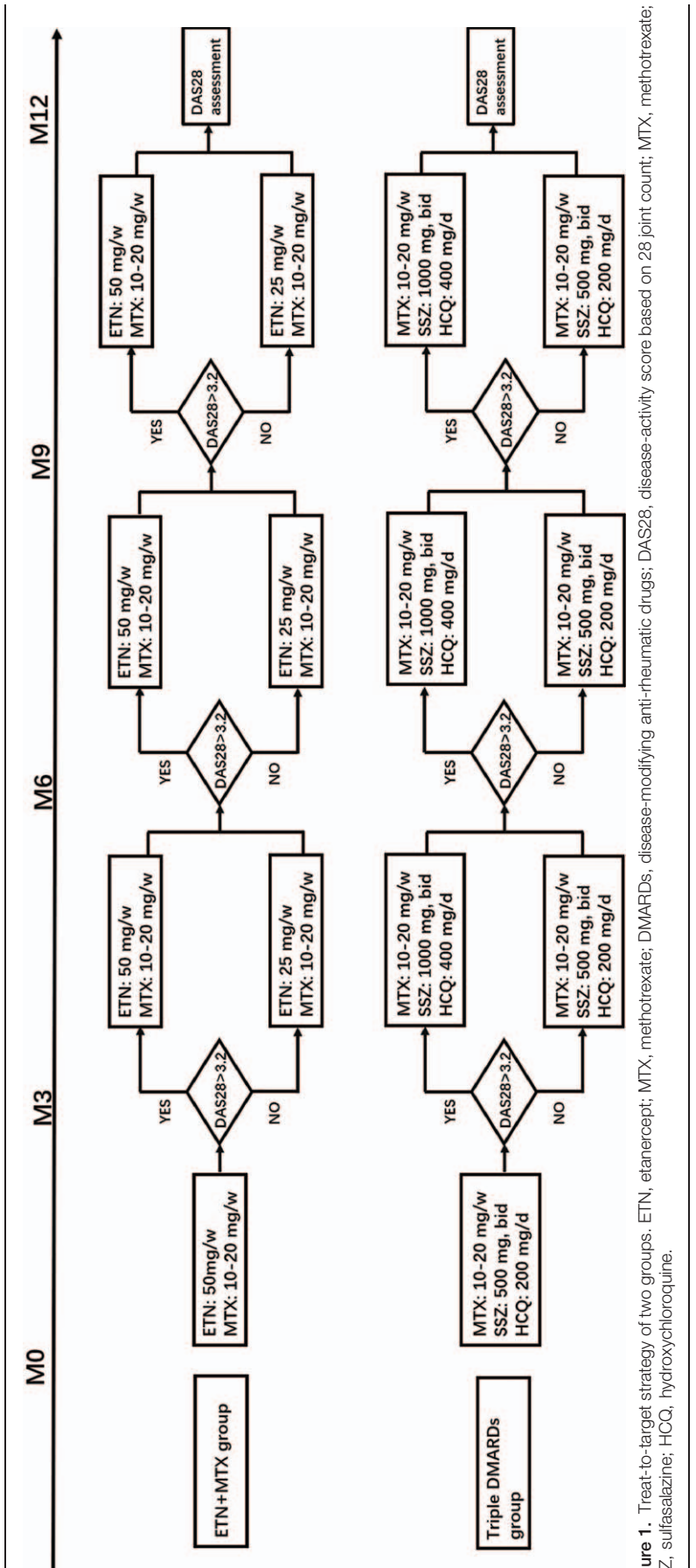

Figure 1. Treat-to-target strategy of two groups. ETN, etanercept; MTX, methotrexate; DMARDs, disease-modifying anti-rheumatic drugs; DAS28, disease-activity score based on 28 joint count; MTX, methotrexate; SSZ, sulfasalazine; HCQ, hydroxychloroquine.

utility value indicates the weight that the general population or patients with a specific disease gives to a specific health state, which could be assessed using direct methods (e.g., time trade-off [TTO] or standard gamble [SG]) or indirect methods based on preference or utility values assigned to health states defined by generic health-related quality of life (HRQoL) questionnaires (the Europe Quality of Life five-dimension (EQ-5D) and Health Utilities Index–3 [HUI-3]). In the current study, direct methods and indirect methods were not included due to resource restrictions, patients' burden and complexity of these methods. And the utility values were obtained from a relation function between HAQ-DI scores and EQ-5D utility values reported in the previous study[17]: EQ-5D = 0.9567–0.309×HAQ-DI. For the CEA, an incremental cost-effectiveness ratio (ICER) was calculated, which was the ratio of incremental cost to incremental benefits (QALY) between treatment groups. Further, the ICER below the 3 times of annual gross domestic product (GDP) per capita was defined as cost-effective according to the recommendations of the World Health Organization's (WHO) Choosing Interventions that are Cost-Effective (CHOICE) program.[18] In case of China, GDP per capita was 53,980.0 RMB (¥) in 2016 and ¥59,660.0 in 2017, and the average of GDP per capita between 2016 and 2017 was ¥55,320.0.

2.7. Sensitivity analysis

Considering for the introduction of other biosimilars and other market effects on TNF inhibitors drug pricing, one-way sensitivity analyses were performed with two different drug prices, namely −30% and −50% of the current ETN-related cost. Besides, the reduction proportions of ETN price meeting the "cost-effective" threshold were calculated as well.

2.8. Statistical analysis

Data were presented as mean value ± standard deviation or count (percentage). Comparison between 2 groups was determined by *t* test or Chi-square test. SPSS 22.0 statistical software (SPSS Inc., Chicago, IL) was used for statistical analysis, and GraphPad Prism 7.01 software (GraphPad Software Inc., San Diego, CA) was used for figure making. *P* value $<.05$ was interpreted as statistically significant.

3. Results

3.1. Study flow

The 270 RA patients were invited to the current study, whereas 47 patients were excluded because of the following reasons: 37 patients refused the invitation and 10 patients missed the invitation. Then the remaining 223 patients were screened, among whom 28 patients did not meet the criteria and 7 patients refused to sign the informed consents. Subsequently, 188 eligible patients were enrolled and categorized into ETN+MTX group (N = 69) or triple DMARDs group (N = 119) based on their treatment schedules. In ETN+MTX group, 20 patients were excluded because of the following reasons: 8 patients stopped therapy due to personal reasons, 7 patients missed the follow-up, 3 patients withdrew the informed consents and 2 patients stopped therapy due to adverse events (including 1 patient who occurred liver abnormality and 1 patient who occurred tuberculosis). In triple DMARDs group, 34 patients were excluded due to the following reasons: 10 patients stopped therapy due to personal reasons, 12 patients missed the follow-up, 6 patients withdrew the informed consents and 6 patients stopped therapy due to adverse events (including 3 patients who occurred liver abnormality, 1 patient who occurred kidney abnormality, 1 patient who occurred pulmonary infection and 1 patient who occurred unknown fever). At last, 49 (71%) patients in ETN +MTX group and 85 (71%) patients in triple DMARDs group completed the study and were included in the final analysis (Fig. 2).

3.2. Baseline characteristics of RA patients

The mean ages in ETN+MTX group and triple DMARDs group were 57.2 ± 13.2 years and 57.7 ± 11.9 years respectively, and the numbers of female and male patients were 44 (89.8%) and 5 (10.2%) in ETN+MTX group, and were 66 (77.6%) and 19 (22.4%) in triple DMARDs group (Table 1). Besides, the mean values of TJC, SJC, DAS28-ESR score and HAQ-DI score were 7.3 ± 3.4, 6.9 ± 3.6, 5.4 ± 0.6 and 1.8 ± 0.3 in ETN+MTX group, and were 7.0 ± 3.4, 6.2 ± 3.2, 5.3 ± 0.7 and 1.8 ± 0.3 in triple DMARDs group. There was no difference in baseline characteristics between ETN+MTX group and triple DMARDs group (all $P > .05$, Table 1).

3.3. Comparison of disease activity and quality of life between ETN+MTX group and triple DMARDs group

The TJC (Fig. 3A), SJC (Fig. 3C), ESR (Fig. 3E), CRP (Fig. 3G), DAS28-ESR (Fig. 3I) and HAQ-DI (Fig. 3K) were similar between ETN+MTX group and triple DMARDs group at each time point (all $P > .05$). Also, TJC change (M0-M12) (Fig. 3B), SJC change (M0-M12) (Fig. 3D), ESR change (M0-M12) (Fig. 3F), CRP change (M0-M12) (Fig. 3H) and HAQ-DI change (M0-M12) (Fig. 3L) were also similar between 2 groups (all $P > .05$). However, DAS28-ESR change (M0-M12) was higher in ETN+MTX group compared with triple DMARDs group ($P = .007$, Fig. 3J).

3.4. Comparison of remission rate and LDA rate between ETN+MTX group and triple DMARDs group at M12

In ETN+MTX group, 14 (28.6%) patients achieved remission and 34 (69.4%) patients achieved LDA. In triple DMARDs group, 14 (16.5%) patients achieved remission and 43 (50.6%) patients achieved LDA (Table 2). The LDA rate was higher in ETN+MTX group compared with triple DMARDs group ($P = .034$), while the remission rate was similar between the two groups ($P = .097$).

3.5. Comparison of 1-year cost between ETN+MTX group and triple DMARDs group

The drug cost was ¥58,323.3 ± 68,811.9 in ETN+MTX group and was ¥10,156.7 ± 1,382.7 in triple DMARDs group. Other medical costs in ETN+MTX group and triple DMARDs group were ¥7,406.4 ± 2,870.1 and ¥11,480.4 ± 3,505.5, respectively. As for total cost, it was ¥65,729.7 ± 7,059.7 in ETN+MTX group and was ¥21,637.1 ± 4,077.2 in triple DMARDs group. In brief, compared to triple DMARDs group, ETN+MTX group presented with increased drug cost ($P < .001$) and total cost

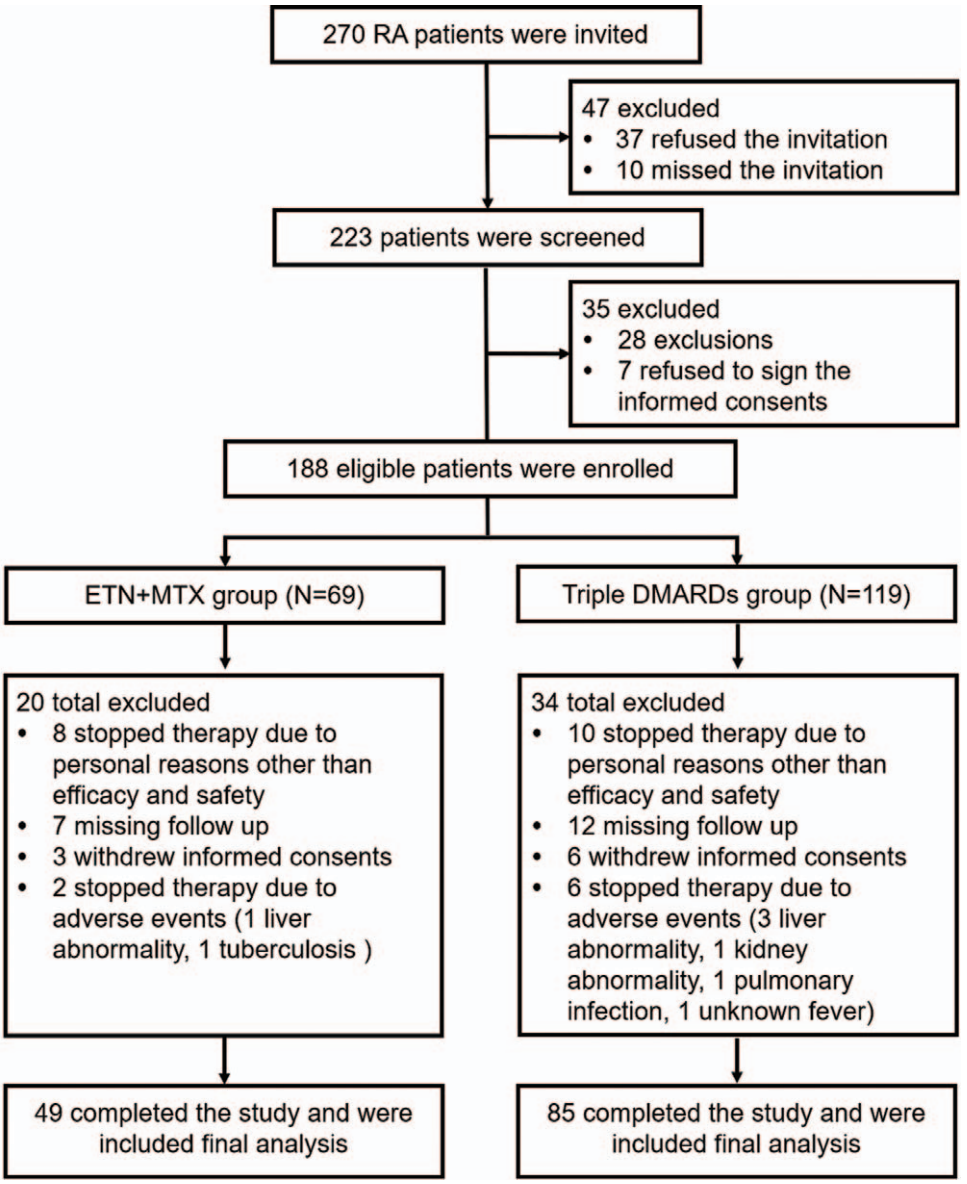

Figure 2. Study flow. RA, rheumatoid arthritis; ETN, etanercept; MTX, methotrexate; DMARDs, disease-modifying anti-rheumatic drugs.

($P < 0.001$) whereas decreased other medial cost ($P < .001$) (Table 3).

3.6. Cost-effectiveness analysis of RA patients

The QALY was 0.572 year in ETN+MTX group and was 0.557 year in triple DMARDs group, thus ETN+MTX provided an extra QALY of 0.015 year compared with triple DMARDs. Meanwhile, ETN+MTX group required an additional cost of ¥44,092.6 compared to triple DMARDs group, resulting in an ICER of ¥2,939,506.7 per QALY, that was 53.1 folds of GDP per capita in China. Therefore, ETN+MTX was extremely less cost-effective in treating Chinese RA patients compared to triple DMARDs when the willingness-to-pay threshold was 3 times of average GDP per capita between 2016 and 2017 (¥165,960.0) (Table 4).

3.7. Sensitivity analyses of price

Decreasing the price of ETN by 30.0% resulted in an ICER of ¥1,773,040.0 per QALY (32.1 folds of GDP per capita in China), and decreasing the price of ETN by 50.0% produced an ICER of ¥995,400.0 per QALY (18.0 folds of GDP per capita in China), both of which still made ETN+MTX less cost-effective compared to triple DMARDs (Table 5). Besides, decreasing the price of ETN by 71.3% realized an ICER of ¥165,960.0 per QALY (3.0 folds of GDP per capita in China); and decreasing the price of ETN by 74.2% yielded an ICER of ¥55,320.0 per QALY (1.0 fold of GDP per capita in China). These data revealed that the price of ETN should be reduced at least by 71.3% before ETN +MTX became cost-effective in treating Chinese RA patients compared with triple DMARDs (willingness-to-pay threshold was 3 times of average GDP per capita between 2016 and 2017).

Table 1

Baseline characteristics of patients with RA.

Characteristics	ETN+MTX group (N = 49)	Triple DMARDs group (N = 85)	*P* value
Age (year), mean ± SD	57.2 ± 13.2	57.7 ± 11.9	.823
Gender, No. (%)			.077
Female	44 (89.8)	66 (77.6)	
Male	5 (10.2)	19 (22.4)	
BMI (kg/m^2), mean ± SD	22.3 ± 3.4	21.7 ± 3.0	.308
Disease duration (year), mean±SD	3.9 ± 3.3	4.7 ± 3.1	.119
Rheumatoid factor, No. (%)			.897
Positive	34 (69.4)	61 (71.8)	
Negative	12 (24.5)	18 (21.1)	
Undetected	3 (6.1)	6 (7.1)	
ACPA, No. (%)			.118
Positive	34 (69.4)	64 (75.3)	
Negative	9 (18.4)	6 (7.1)	
Undetected	6 (12.2)	15 (17.6)	
History of biologics, No. (%)	7 (14.3)	17 (20.0)	.406
TJC, mean ± SD	7.3 ± 3.4	7.0 ± 3.4	.692
SJC, mean ± SD	6.9 ± 3.6	6.2 ± 3.2	.257
ESR (mm/h), mean ± SD	51.3 ± 28.9	53.5 ± 28.9	.672
CRP (mg/L), mean ± SD	46.2 ± 38.8	45.3 ± 46.4	.911
DAS28-ESR score, mean ± SD	5.4 ± 0.6	5.3 ± 0.7	.778
HAQ-DI score, mean ± SD	1.8 ± 0.3	1.8 ± 0.3	.957

Comparison between 2 groups was determined by *t* test or Chi-square test. *P* value < .05 was considered significant.

ACPA = anti-citrullinated protein antibodies; BMI = body mass index; CRP = C-reactive protein; DAS28-ESR = disease-activity score based on 28 joint count (DAS28) based on erythrocyte sedimentation rate; DMARDs = disease-modifying antirheumatic drugs; ESR = erythrocyte sedimentation rate; ETN = etanercept; HAQ-DI = Assessment Questionnaire Disability Index; MTX = methotrexate; RA = rheumatoid arthritis; SD = standard deviation; SJC = swollen joint count; TJC = tender joint count.

4. Discussion

In the present study, we had some interesting discoveries:

(1) ETN+MTX group patients exhibited similar disease activity and quality of life at each visit, but higher DAS28-ESR change (M0-M12) and LDA rate at M12 compared with triple DMARDs group patients.
(2) ETN+MTX increased drug cost and total cost compared to triple DMARDs.
(3) ETN+MTX was extremely less cost-effective in treating Chinese RA patients compared with triple DMARDs, unless the price of ETN was reduced at least by 71.3%.

TNF-α inhibitors (such as ETN, infliximab and adalimumab) are the most popular biologics for treating RA patients.[5,19] Among various TNF-α inhibitors, ETN is most common in clinical practices which functions as a decoy receptor binding to TNF-α and blocking its activities, thereby reducing the disease activity in RA patients.[5,20,21] Several previous studies have been performed to compare the treatment efficacy of ETN+MTX with triple DMARDs in treating moderate to severe RA patients.[8–10,22] For example, a recent clinical trial discovers that the disease activity is similar after RA patients being treated with ETN+MTX or treated with triple DMARDs for 48 weeks.[10] In another clinical trial, RA patients treated with ETN+MTX present with similar disease activity but slower radiographic progression compared with patients treated with triple DMARDs after a 2-year follow-up.[8] These previous studies illustrate that ETN +MTX exhibits similar or slightly better treatment efficacy compared with triple DMARDs. However, most of these previous studies are conducted in developed countries, and little was known about the treatment efficacy of ETN+MTX or triple DMARDs in Chinese RA patients. Besides, the majority of previous studies are randomized control trials, whose results may be not comparable to the study of real-world data from clinical practice. In the present real-world study, we enrolled 134 Chinese RA patients and investigated the treatment efficacy between ETN +MTX and triple DMARDs, which revealed that RA patients who were treated with ETN+MTX exhibited similar disease activity and quality of life at each visit, but higher DAS28-ESR change (M0-M12) and LDA rate at M12 compared with RA patients who were treated with triple DMARDs. The possible reasons for our results might be that:

(1) ETN directly inhibited the activities and functions of TNF-α, leading to a quick decrease in disease activity and inflammation level in RA patients.
(2) Triple DMARDs (which consisted of MTX, SSZ and HCQ) also provided great efficacy in decreasing disease activity and inflammation level for RA patients, which was similar compared to ETN. Therefore, ETN+MTX presented with slightly better treatment efficacy compared with triple DMARDs.

Limited information regarding the cost of ETN+MTX and triple DMARDs in treating RA patients is found, there are only 2 clinical studies reporting.[13,14] One of the 2 studies which is conducted in America reveals that the total cost of triple DMARDs in treating RA patients is $13,100 for a year, $23,800 for 2 years and $52,600 for 5 years, while the total cost of ETN +MTX in treating RA patients is much higher than that of triple DMARDs, with a cost of $39,000 for a year, $74,200 for 2 years and $148,800 for 5 years.[14] Another study which is conducted in Canada illustrates that the total cost of triple DMARDs and ETN+MTX in treating RA patients is $6,328 and $21,611 respectively for a year, suggesting that the cost of ETN+MTX is much higher compared to triple DMARDs in RA patients.[13] In order to evaluate the cost of ETN+MTX and triple DMARDs in treating Chinese RA patients, we conducted the current study and found the similar results that the 1-year drug cost (¥58,323.3 vs ¥10,156.7) and total cost (¥65,729.7 vs ¥21,637.1) were elevated while other medical cost (¥7,406.4 vs ¥11,480.4) was decreased for ETN+MTX compared to triple DMARDs. The possible explanations for the results might be that:

(1) The price of ETN was much higher compared to DMARDs, therefore the drug cost of ETN+MTX was increased compared with triple DMARDs.
(2) ETN might decrease disease activity of RA patients a little more effectively and rapidly compared with triple DMARDs, which caused fewer hospital stays, thereby reducing other medical cost.
(3) The increment of drug cost exceeded the decrement of other medical cost in ETN+MTX group compared with triple DMARDs group. Therefore, the total cost of ETN+MTX was higher than that of triple DMARDs.

Currently, they are more than 5 million RA patients in China, and a large percentage of them are lived in underdeveloped areas.[4] For these RA patients, decreasing the disease activity is the dominating treatment objective, while treatment cost is also a concerned issue. Therefore, further pharmacoeconomic analyses

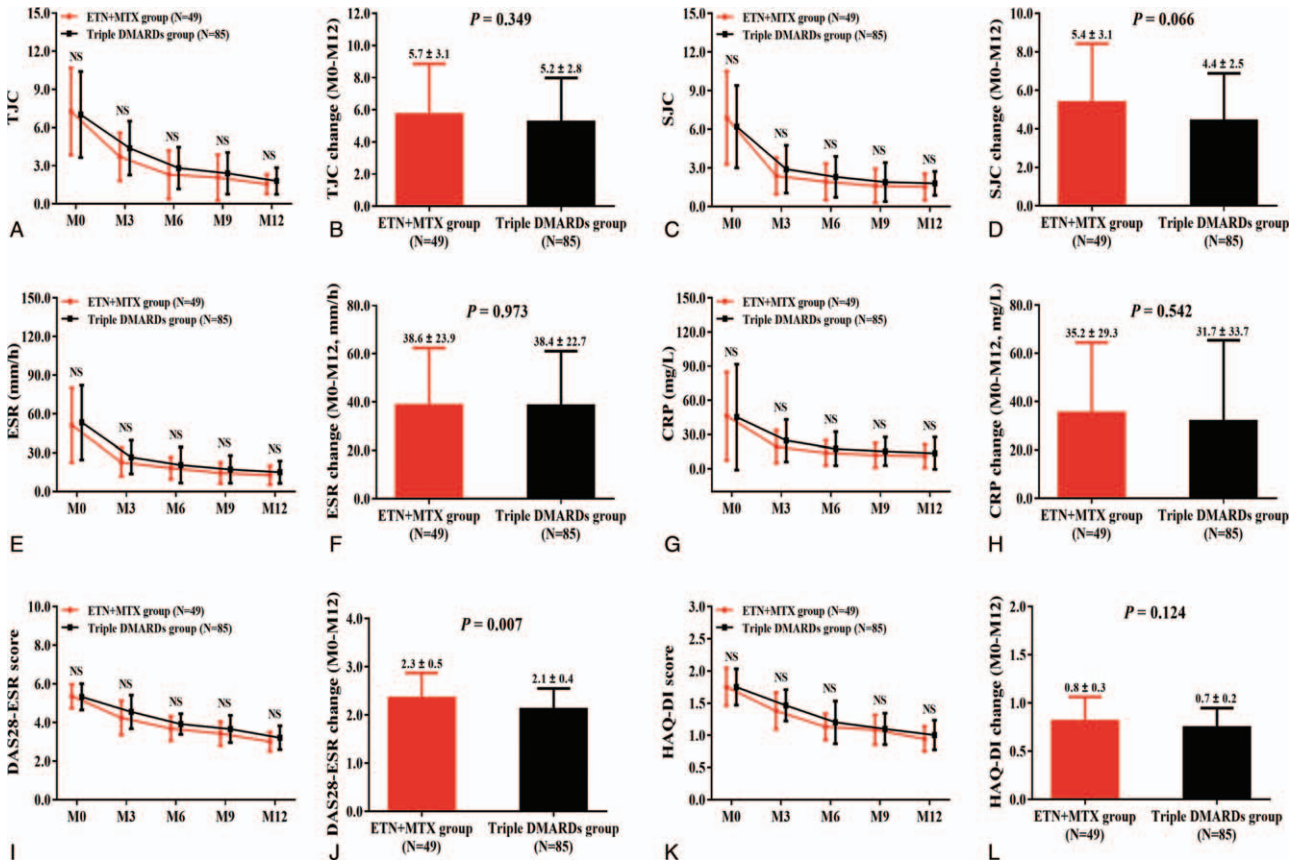

Figure 3. Disease activity and quality of life in ETN+MTX group and triple DMARDs group. The TJC (A), SJC (C), ESR (E), CRP (G), DAS28-ESR (I) or HAQ-DI (K) was of no difference between ETN+MTX group and triple DMARDs group at each time point. Besides, TJC change (M0-M12) (B), SJC change (M0-M12) (D), ESR change (M0-M12) (F), CRP change (M0-M12) (H) and HAQ-DI change (M0-M12) (L) were also similar between two groups. However, DAS28-ESR change (M0-M12) was elevated in ETN+MTX group compared with triple DMARDs group (J). Comparison between two groups was determined by t test. $P < 0.05$ was interpreted as statistically significant. ETN, etanercept; MTX, methotrexate; DMARDs, disease-modifying anti-rheumatic drugs; TJC, tender joint count; SJC, swollen joint count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, disease-activity score based on 28 joint count; HAQ-DI, Health Assessment Questionnaire Disability Index; NS, no significance.

focusing on TNF-α inhibitors and triple DMARDs are urgent and pivotal in China. Hence, we compared the cost-effectiveness of ETN+MTX with triple DMARDs in RA patients, and discovered that the incremental QALY of ETN+MTX over triple DMARDs was 0.015 year, indicating the slightly better treatment efficacy of ETN+MTX compared with triple DMARDs. And ETN+MTX yielded an ICER of ¥2,939,506.7 per QALY, which was 53.1 folds of GDP per capita in China, suggesting that ETN+MTX was extremely less cost-effective in treating Chinese RA patients compared with triple DMARDs when the willingness-to-pay threshold was 3 times of average GDP per capita between 2016 and 2017 (¥165,960.0). These findings were in line with two previous studies, which show that the ETN+MTX is not cost-effective in treating American RA patients (when the willingness-to-pay threshold is $1,000,000 per QALY) or Finnish RA patients (at any conceivable willingness-to-pay threshold).[14,22] Besides, we also discovered that the price of ETN had to be reduced at least by 71.3% before ETN+MTX became cost-effectiveness in treating Chinese RA patients compared with triple DMARDs. Considering that the price of ETN biosimilar is strikingly lower than that of ETN (about 1/4), while its efficacy is similar to ETN, we speculated that ETN biosimilar might be cost-effective in treating moderate to severe RA patients in comparison with triple DMARDs, while it needs further investigation. As far as we know, this study was the first pharmacoeconomic study of TNF-α inhibitors in Chinese RA patients, which might provide novel insights in optimizing treatment strategies and balancing the limited budget with the optimal possible health outcomes for Chinese RA patients.

There were a few limitations in this study. Firstly, the willingness-to-pay threshold in the current study was 3 times of GDP per capita during the same period in China, whereas it was not accurate enough due to that the GDP per capita between rural areas and urban areas of China varied. Secondly, the

Table 2

Comparison of remission and LDA rate at M12 between 2 groups.

Items	ETN+MTX group (N = 49)	Triple DMARDs group (N = 85)	*P* value
Remission rate, No. (%)	14 (28.6)	14 (16.5)	.097
LDA rate, No. (%)	34 (69.4)	43 (50.6)	.034

Comparison between 2 groups was determined by Chi-square test. *P* value < .05 was considered significant.

DMARDs = disease-modifying antirheumatic drugs; ETN = etanercept; LDA = low disease activity; M12 = 12th month after treatment; MTX = methotrexate.

Table 3

Comparison of costs during 12 months between 2 groups.

Groups	Drug cost (¥)		Other medical cost (¥)		Total cost (¥)	
	Mean	SD	Mean	SD	Mean	SD
ETN+MTX	58,323.3	68,811.9	7406.4	2870.1	65,729.7	7059.7
Triple DMARDs	10,156.7	1382.7	11,480.4	3505.5	21,637.1	4077.2
P value	<.001		<.001		<.001	

Comparison between 2 groups was determined by *t* test. *P* value <.05 was considered significant.
¥ = RMB; DMARDs = disease-modifying antirheumatic drugs; ETN = etanercept; MTX = methotrexate; SD = standard deviation.

Table 4

Cost-effectiveness analysis.

Groups	QALY	Incremental QALY	Total cost (¥)	Incremental cost (¥)	ICER (¥/QALY)	GDP per capita* (¥)	ICER/ GDP per capita (folds)
ETN+MTX	0.572	0.015	65,729.7	44,092.6	2,939,506.7	55,320.0	53.1
Triple DMARDs	0.557	–	21,637.1	–	–	–	–

¥ = RMB; DMARDs = disease-modifying antirheumatic drugs; ETN = etanercept; GDP = gross domestic product; ICER = incremental cost-effectiveness ratio; MTX = methotrexate; QALY = quality-adjusted life years.
* the average of GDP per capita of China between 2016 and 2017 was ¥55,320.

Table 5

Sensitivity analyses.

Items	QALY	Incremental QALY	Total cost (¥)	Incremental cost (¥)	ICER (¥/QALY)	GDP per capita* (¥)	ICER/GDP per capita (folds)
Price of ETN down by 30.0%							
ETN+MTX group	0.572	0.015	48,232.7	26,595.6	1,773,040.0	55,320.0	32.1
Triple DMARDs group	0.557	–	21,637.1	–	–		
Price of ETN down by 50.0%							
ETN+MTX group	0.572	0.015	36,568.1	14,931.0	995,400.0	55,320.0	18.0
Triple DMARDs group	0.557	–	21,637.1	–	–		
Price of ETN down by 71.3%							
ETN+MTX group	0.572	0.015	24,126.5	2489.4	165,960.0	55,320.0	3.0
Triple DMARDs group	0.557	–	21,637.1	–	–		
Price of ETN down by 74.2%							
ETN+MTX group	0.572	0.015	22,466.9	829.8	55,320.0	55,320.0	1.0
Triple DMARDs group	0.557	–	21,637.1	–	–		

¥ = RMB; DMARDs = disease-modifying antirheumatic drugs; ETN = etanercept; GDP = gross domestic product; ICER = incremental cost-effectiveness ratio; MTX = methotrexate; QALY = quality-adjusted life years.
* the average of GDP per capita of China between 2016 and 2017 was ¥55,320.0.

comparison of the efficacy and the cost between ETN+MTX and triple DMARDs was performed within 12 months, while their efficacy and cost in a longer period still remained unclear. Thirdly, the sample size was relatively small, which might decrease statistic power. Fourthly, there might be some confounding biases from unmeasured differences between the two groups; therefore, randomized control trials are needed in further study. At last, a lot of patients lost to follow up during the experiment, which might also bring in biases.

In conclusion, ETN+MTX produces an ICER higher than the acceptable willingness-to-pay threshold, suggesting that ETN +MTX is less cost-effective in treating Chinese RA patients compared with triple DMARDs.

Author contributions

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