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A novel etanercept biosimilar Anbainuo plus methotrexate exhibits increased cost-effectiveness compared to conventional disease-modifying anti-rheumatic drugs in treating rheumatoid arthritis patients

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Abstract

The aim of this study was to evaluate the cost-effectiveness of Anbainuo (ABN) plus methotrexate (MTX) (ABN + MTX) versus conventional disease-modifying anti-rheumatic drugs (cDMARDs) in rheumatoid arthritis (RA) patients.

Forty-eight moderate to severe RA patients underwent ABN + MTX or cDMARDs treatment were consecutively enrolled and assigned to ABN + MTX group (n = 26) and control group (n = 22). Patients were followed up and their disease activity and quality of life (QoL) were evaluated at 3rd month, 6th month and 12th month after initiation of treatment. Treatment costs of 2 groups were calculated, then pharmacoeconomic analysis was performed.

ABN + MTX increased drug cost and total cost while decreased indirect cost compared with cDMARDs after 12-month treatment. ABN + MTX group gained additional 0.22 quality-adjusted life years (QALY) and yielded an incremental cost-effectiveness ratio (ICER) of ¥104,293.6 per QALY after treatment. Sensitivity analysis reveals that rising ABN price by 20% produced an ICER of ¥130,403.6 per QALY, which was still lower than 3 times of the mean gross domestic product (GDP) per capita during the same period in China (¥165,960). Besides, ABN + MTX was more cost-effective in severe RA patients compared to moderate RA patients.

ABN + MTX is cost-effective in treating moderate to severe RA patients compared with cDMARDs, although the total cost of ABN + MTX is relatively higher.

Abbreviations: ABN = anbainuo, cDMARDs = conventional disease-modifying anti-rheumatic drugs, GDP = gross domestic product, MTX = methotrexate, QALY = quality-adjusted life years, RA = rheumatoid arthritis.

Keywords: anbainuo, conventional disease modifying antirheumatic drugs, cost-effectiveness, price, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA), a chronic autoimmune disease that is characterized by persistent synovitis and various extra-articular manifestations such as rheumatoid nodules, pulmonary diseases as well as cardiovascular diseases, occurs in approximately 1% of world population and 0.42% of Chinese population.[1–3] RA commonly erodes bone and destroys cartilage, which greatly decreases patients' quality of life (QoL), and they may cause disability if RA patients are treated inappropriately.[4–6] Among the various therapeutics, conventional disease modifying anti-rheumatic drugs (cDMARDs) such as methotrexate (MTX) and sulfasalazine are considered as first choices for RA treatment, whereas a number of RA patients fail to response or are intolerant to these drugs; and newly developed biologic therapies such as etanercept (Enbrel) significantly decrease disease activity, alleviate bone erosion and improve QoL of RA patients compared to cDMARDs.[3,4,7] However, the medical cost of etanercept is multiple folds more than that of cDMARDs, which brings in great economic burdens to RA patients.[8–10] According to a recent study conducted in America, etanercept + MTX is not cost-effective in treating early aggressive RA patients compared to cDMARDs; another study conducted in Canada also reveals that etanercept + MTX only provides marginally more quality-adjusted life years (QALYs) while needs substantially more costs compared with cDMARDs in treating active RA patients.[11,12]

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Considering the high priced etanercept and the less developed economy in China, etanercept might be also not cost-effective in treating Chinese RA patients compared to cDMARDs, which could be proved by the truth that etanercept is rarely used in Chinese hospitals especially in hospitals from rural areas, despite that there are 5 million RA patients in China.

Anbainuo (ABN), a novel bio-similar etanercept product that is independently developed by local Chinese pharmaceutical company (Hisun Pharmaceutical), is launched in 2015 by China Food and Drug Administration.[13,14] ABN is observed to exhibit good efficiency and tolerance in treating moderate to severe RA patients, and more importantly, it is much cheaper than etanercept in China (almost 1/3 price of etanercept), which means that it could alleviate RA patients' economic burdens greatly.[13,14] However, the cost-effectiveness of ABN in treating RA patients has not been reported in China until now. Therefore, the objective of the current study was to evaluate the cost-effectiveness of ABN + MTX versus cDMARDs in RA patients.

2. Materials and methods

2.1. Patients

Fifty-nine RA patients with moderate to severe disease activity underwent ABN + MTX or conventional disease-modifying anti-rheumatic drugs (cDMADRs) treatment at ZhuZhou Central Hospital between March 2015 and October 2016 were consecutively enrolled in this study. The inclusion criteria included: (1) diagnosed as RA according to the 2010 American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR) classification criteria;(2) aged 18 to 70 years old;(3) with moderate to severe disease activity, which was defined as Disease Activity Score (DAS) 28 score $\geq$ 3.2 and the level of C-reactive protein (CRP) >1.5 mL or the level of erythrocyte sedimentation rate (ESR) elevated (>30 mm/h for female, >20 mm/h for male); (4) disease duration $\geq$ 3 months; (5) if patients received Non-Steroidal Anti-inflammatory Drugs (NSAIDs) therapy before enrollment, the duration of stable dosage of NSAIDs should be more than 2 weeks; and as for patients treated with glucocorticoids previously, the duration of stable dosage of glucocorticoids should be more than 4 weeks; (6) swollen joint count (SJC) or tender joint count (TJC) of hands, wrist, podarthrum or ankle was more than 3.

The exclusion criteria were as follows: (1) patients with contraindications to ABN therapy; (2) patients who were treated with biologicals within 3 months; (3) Patients complicated with uncontrolled diseases of the heart and lung systems, liver and kidney dysfunction or severe gastrointestinal system diseases; (4) patients had a history of active or recurrent bacterial, viral, fungal, mycobacterium, mycobacterium or other severe infection; (5) patients with a history of active tuberculosis; (6) patients with a history of tumor; (7) pregnant women or planned to get pregnant within 12 months.

This study was approved by the Ethics Committee of ZhuZhou Central Hospital (Approved No. 2015-K-05010). All patients signed the written informed consents before enrollment.

2.2. Grouping and treatment

A total of 59 RA patients were recruited at the beginning of the study, among which 31 patients about to undergo ABN + MTX therapy were assigned to ABN + MTX group, and 28 patients who scheduled to receive cDMADRs treatment were allocated to control group accordingly. In the ABN + MTX group, ABN and MTX were administrated to the patients as follows: ABN 25 mg twice a week subcutaneously for 24 weeks or ABN 50 mg once a week subcutaneously for 24 weeks, and MTX 10 to 20 mg once a week orally for 24 weeks. Besides, in the ABN + MTX group, 1 patient previously received NSAIDs therapy with stable dosage for more than 2 weeks, and 3 patients previously received glucocorticoids therapy with stable dosage for more than 4 weeks. In the control group, depending on the clinical requirements and patients' willingness, cDMADRs were administrated alone or in combination to the patients for 24 weeks: 11 patients received MTX (10–20 mg once a week orally) + leflunomide (10 mg qd), and 17 patients received MTX (10–20 mg once a week orally) + sulfasalazine (1 g tid orally), +hydroxychloroquine (400 mg qd). Moreover, 5 patients in the control group previously received NSAIDs therapy with stable dosage for more than 2 weeks. For the 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. After the 24-week intervention period, switching therapy between TNF inhibitors and cDMADRs due to lack of efficacy was allowed, and the dosage and duration of drugs would be recorded as well. Finally, one patient switched therapy from TNF inhibitors to cDMADRs, and 2 patients switched therapy from cDMADRs to TNF inhibitors. These 3 patients who switched therapy were still included in the analysis based on intention-to-treat (ITT) principle, while there were 11 patients being excluded from analysis due to lost follow up without any assessment or withdrawing the informed consents. Therefore, 48 patients were included in the final analysis: 26 cases in the ABN + MTX group and 22 cases in the control group.

2.3. Baseline assessment

Baseline assessments (M0) included TJC, SJC, CRP, ESR, pain Visual Analogue Scale (VAS) score, patient global assessment (PGA) score, physician global assessment (PhGA) score, and Health Assessment Questionnaire Disability Index (HAQ-DI). DAS28 (CRP) and DAS28 (ESR) were used to assess disease activity of patients, which were calculated as follows: DAS28 (CRP) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.014* PGA + 0.36*ln(CRP + 1) + 0.96; DAS28 (ESR) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.014*PGA + 0.70*ln(ESR).

2.4. Follow-up assessment

All patients were followed up at 3rd month (M3), 6th month (M6) and 12th month (M12) after initiation of treatment, and the TJC, SJC, ESR, CRP, pain VAS score, PGA score, PhGA score, and HAQ-DI were evaluated at each visit. The primary outcome of efficacy was DAS28-ESR remission rate at M12, and the secondary outcomes of efficacy included DAS28-ESR response rate at M6 and M12, DAS28-ESR low disease activity (LDA) rate at M6 and M12, the changes of TJC, SJC, CRP, ESR, pain VAS score, DAS28-CRP, PGA score, PhGA score and HAQ-DI from M0 to M6/M12. The DAS28-ESR remission rate was defined as the percentage of patients with DAS28-ESR$\leq$2.6 after treatment; the DAS28-ESR LDA rate was defined as the percentage of patients with DAS28-ESR$\leq$3.2 after treatment; and the DAS28-ESR response rate was defined as the percentage of patients with an improvement of DAS28-ESR > 1.2 after treatment.

2.5. Direct, indirect and total costs calculation

During the study, data were collected routinely on medication use, outpatient service, emergency service, hospital stays and working days loss of patients and caregivers. Direct costs consisted of drug costs and other medical costs, and indirect costs included lost productivity costs of patients and caregivers due to working days lost. Drug costs were calculated on the basis of unit cost and the dosages recorded in the case report form (CRF), and other medical costs were calculated by using the unit costs, the times of outpatient and emergency and the duration of hospitalization. All unit costs of medication, outpatient, emergency and hospitalization were derived from the electronic medical records of ZhuZhou Central Hospital. Indirect costs were calculated by the losing working days multiplied by local average daily wage. Accordingly, total costs were obtained by the sum of drug costs, other medical costs and indirect costs.

2.6. Pharmacoeconomic assessment

Pharmacoeconomic assessment was performed by the cost-effectiveness analysis. Differences in costs and quality adjusted life-year (QALY) between ABN + MTX group and control group were analyzed, and an incremental cost-effectiveness ratio (ICER) was calculated by incremental cost divided by incremental QALY.[12] In order to assess the cost-effectiveness between 2 groups, we defined thresholds for the assessment of cost-effectiveness as follows:

(1) cost-effectiveness: ICER was lower than three times of the annual GDP per capita;
(2) not cost-effectiveness: ICER was higher than three times of the annual GDP per capita.

The threshold of acceptable cost-effectiveness was defined referring to the willingness-to-pay (WTP) recommended by the World Health Organization's (WHO) Choosing Interventions that are Cost-Effective (CHOICE) program.[15] In case of China, GDP per capita was 53980 RMB (¥) in 2016 and ¥59,660 in 2017, and the average of GDP per capita between 2016 and 2017 was ¥55320.

2.7. QALY calculation

QALY as an outcome measure that expressed both the duration and quality of life was widely used in cost-effectiveness analysis, which was measured on a scale of 0 to 1, where 0 and 1 correspond to the worst and best possible health outcomes, respectively. We estimated the QALYs for various health states by using the mean health utility of each health state and the time spent in the health state, and the Europe Quality of Life five-dimension (EQ-5D) utility values were used as health utility values, which were estimated form a relation function between HAQ-DI scores and EQ-5D questionnaire utility values [16]: EQ-5D = 0.9567 − 0.309*HAQ-DI. In summary, QALY was calculated as [17]: QALY = (mean health utility of each health state)* (each time interval in the health state).

2.8. Sensitivity analyses

To evaluate the uncertainty of market effects on drug pricing, sensitivity analyses were performed. In the sensitivity analyses, drug price of ABN was varied as follows:

(1) fell by 20% and 50% of its base-case price;
(2) rose by 20% and 50% of its base-case price, and then the ICER for QALY was calculated again to assess cost-effectiveness between 2 groups.

2.9. Statistical analysis

SPSS 21.0 statistical software (IBM, USA) and GraphPad Prism 6.01 software (GraphPad Software Inc, USA) were used for statistical analysis and chart making. Data were presented as mean value ± standard deviation or count (percentage). Comparison between 2 groups was determined by *t* test or Chi-square test; comparison at paired time point was determined by paired *t* test. All tests were 2-sided and $P < .05$ indicated a significant difference.

3. Results

3.1. Study flow

The 124 RA patients were invited for screening while 28 RA patients were excluded due to that: 13 patients missed invitation, 9 patients disagreed to participate, 6 patients were unable to participate due to the distance. The remaining 96 patients were screened for eligibility, while 37 patients were excluded: including 12 patients were without moderate to severe disease activity, 8 patients were treated with biologicals within three months, 8 patients disagreed with the informed consents, 6 patients were with history of severe infection, 2 patients were with disease duration <3 months, 1 patient was pregnant, and 8 patients disagreed with the informed consents. Hence totally 59 patients were enrolled into the study, among whom 31 patients about to receive ABN + MTX were allocated to ABN + MTX group while 28 patients about to receive cDMARDs were allocated to control group (Fig. 1). In ABN + MTX group, after treatment with ABN + MTX for 24 weeks, there were 4 patients who lost follow up without any assessment and 1 patient who withdrew the informed consent. In control group, after treatment with cDMADRs for 24 weeks, there were 4 patients who lost follow up without any assessment and 2 patients who withdrew the informed consent. As a result, 26 RA patients in ABN + MTX group and 22 patients in control group were included into efficacy and pharmacoeconomic analyses (Fig. 1).

3.2. Baseline characteristics

In ABN + MTX group, mean age was 57.6 ± 14.3 years, number of female patients was 22 (84.6%), while in control group, mean age was 59.0 ± 7.9 years, number of female patients was 16 (72.7%), there was no difference of age ($P = .478$) or gender ($P = .676$) between two groups (Table 1). The disease duration in ABN + MTX group was 4.4 ± 3.3 years and in control group was 4.2 ± 3.3 years. As for the history of treatment, the number of patients received with cDMADRs, Chinese herb, Glucocorticoid and NSAIDs was 15 (57.7%), 8 (30.7%), 4 (15.4%) and 4 (15.4%) respectively in ABN + MTX group, while 12 (54.5%), 6 (27.3%), 2 (9.1%) and 5 (22.7%) respectively in control group. TJC was higher in ABN + MTX group compared with the control group ($P = .032$), while other baseline characteristics of RA patients were similar between 2 groups (all $P > .05$, Table 1).

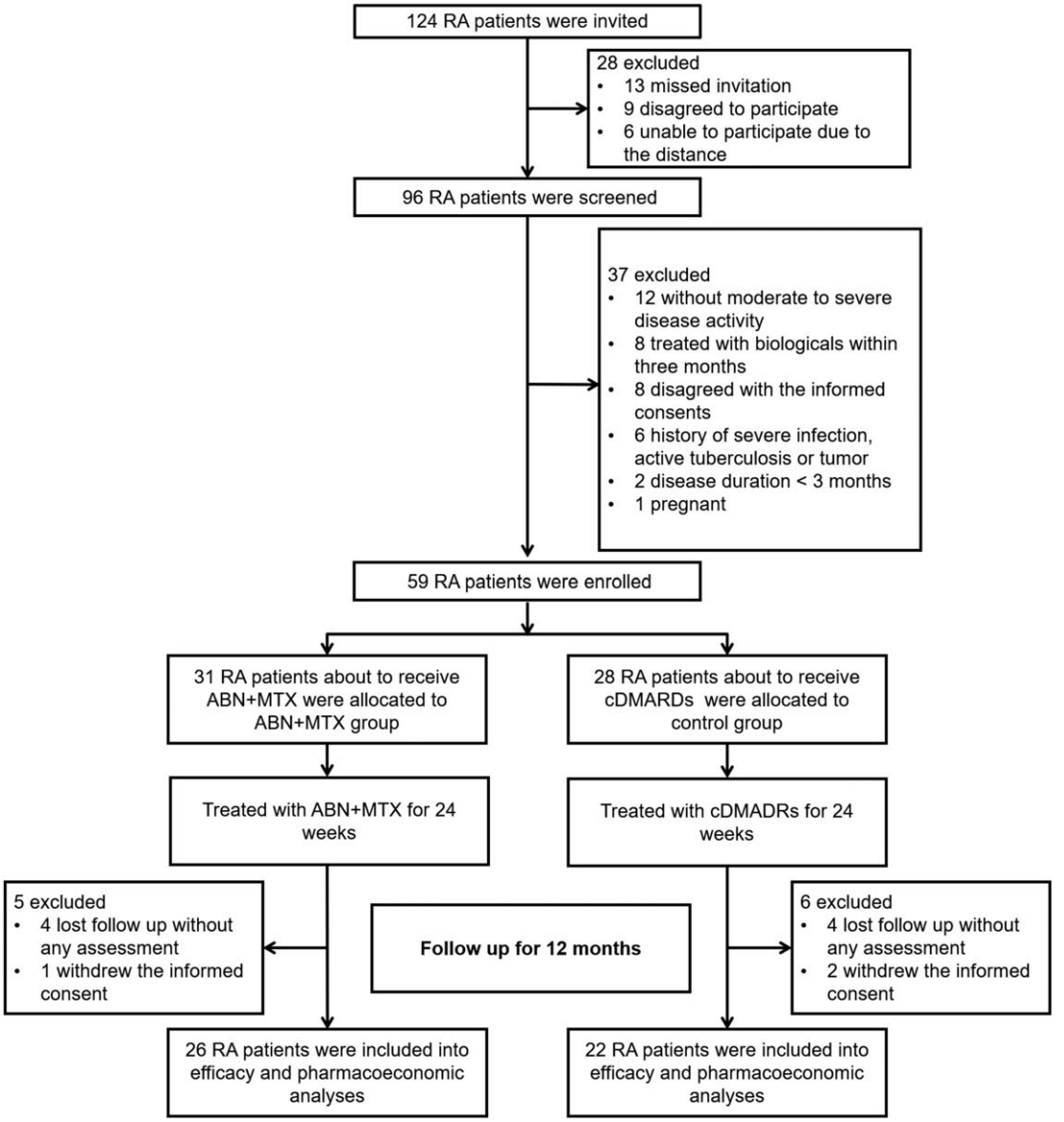

Figure 1. Study flow.

3.3. Comparison of disease activity reduction and QoL improvement between two groups at each visit

From M0, the improvement of DAS28-ESR (Fig. 2A), DAS28-CRP (Fig. 2B), TJC (Fig. 2C), SJC (Fig. 2D) and pain VAS (Fig. 2G) were more obvious in ABN + MTX group compared to control group at M3, M6 and M12 (all $P < .05$); besides, the improvement of PGA (Fig. 2H) were more obvious at M3 ($P < .05$) and M12 ($P < .05$), the improvement of PhGA (Fig. 2I) was more obvious at M6 ($P < .01$) and the improvement of HAQ-DI (Fig. 2J) were more obvious at M3 ($P < 0.05$) as well as M6 ($P < .05$) in ABN + MTX group compared to control group; As for the improvement of ESR (Fig. 2E) or CRP (Fig. 2F), no difference was observed between 2 groups at each visit (all $P > .05$). These data indicated that ABN + MTX is superior to cDMARDs in decreasing RA activity and improving quality of life.

3.4. Comparison of DAS28-ESR response rate, remission rate and LDA rate between two groups

No difference of DAS28-ESR response rate was discovered between ABN + MTX group and control group at M6 ($P = .516$) or M12 ($P = 0.221$) (Fig. 3A); in addition, DAS28-ESR remission rate ($P = .055$, Fig. 3B) and DASS28-ESR LDA rate ($P = .977$, Fig. 3C) were also similar between 2 groups at M6, whereas both of them were obviously increased in ABN + MTX group compared with control group at M12 (all $P < .05$), which further implied that ABN + MTX presented with better treatment efficacy compared with cDMARDs.

3.5. Comparison of cost between ABN + MTX group and control group

Drug cost, other medical cost, indirect cost and total cost of RA patients at M6 and M12 were compared between ABN

Table 1

Baseline characteristics of patients with RA.

Parameters	ABN + MTX group (N = 26)	Control group (N = 22)	*P* value
Age (years)	57.6 ± 14.3	59.0 ± 7.9	.676
Gender-Female (n/%)	22 (84.6)	16 (72.7)	.478
Disease duration (years)	4.4 ± 3.3	4.2 ± 3.3	.744
Disease Activity (n/%)			1.000
Moderate	5 (19.2)	4 (18.2)	
Severe	21 (80.8)	18 (81.8)	
TJC	10.6 ± 4.7	7.6 ± 4.0	.023
SJC	8.2 ± 5.0	6.0 ± 4.2	.107
ESR (mm/h)	61.0 ± 42.0	57.6 ± 36.0	.769
CRP (mg/L)	42.2 ± 41.4	43.2 ± 30.8	.928
Pain VAS	6.5 ± 1.8	6.5 ± 1.4	.861
PGA	6.5 ± 1.9	6.8 ± 1.2	.552
PhGA	6.4 ± 1.9	6.7 ± 1.2	.490
HAQ-DI	1.9 ± 0.4	1.8 ± 0.2	.280
DAS28 (ESR)	6.1 ± 1.4	5.8 ± 0.9	.307
DAS28 (CRP)	5.4 ± 1.0	5.3 ± 0.8	.491
History of treatment (n/%)			
cDMADRs	15 (57.7)	12 (54.5)	.827
Chinese herb	8 (30.7)	6 (27.3)	.791
Glucocorticoid	4 (15.4)	2 (9.1)	.511
NSAIDs	4 (15.4)	5 (22.7)	.516

Data were presented as mean value ± standard deviation or count (percentage). Comparison between 2 groups was determined by *t* test or Chi-square test. *P* value < .05 was considered significant. ABN = anbainuo, ESR = erythrocyte sedimentation rate, cDMADRs = conventional disease modifying antirheumatic drugs, CRP = C-reactive protein, DAS28 = disease activity score in 28 joint, HAQ-DI = Health Assessment Questionnaire Disability Index, MTX = methotrexate, NSAIDs = non-steroidal anti-inflammatory drugs, PGA = patient global assessment, PhGA = physician global assessment, RA = rheumatoid arthritis, SJC = swollen Joint Count, TJC = tender Joint Count, VAS = visual analogue scale.

+MTX group and control group, which revealed that (Table 2):

(1) at M6, drug cost (27,970.5 ± 1,116.5 vs 3,723.6 ± 2,023.6, $P < .001$) and total cost (45,482.0 ± 15,294.3 vs 21,595.6 ± 2,678.6, $P < .001$) were elevated in ABN + MTX group compared with control group;
(2) at M12, drug cost (39,433.9 ± 20,301.7 vs 7126.6 ± 4022.0, $P < .001$) and total cost (58,208.2 ± 23,433.9 vs 35,263.6 ± 4150.2, $P < .001$) were increased whereas indirect cost (8389.0 ± 10,511.8 vs 14,952.0 ± 1779.2, $P = .004$) was decreased in ABN + MTX group compared to control group;
(3) as for other medical cost, no difference was discovered between 2 groups either at M6 (9,893.1 ± 9,462.8 vs 9,188.6 ± 1,521.3, $P = .711$) or at M12 (10,385.4 ± 9,393.6 vs 13,185.0 ± 1644.0, $P = .147$).

These data suggested that ABN + MTX decreased indirect cost while increased drug cost and total cost compared with cDMARDs.

3.6. Cost-effectiveness of ABN + MTX vs cDMARDs in RA patients

Patients in ABN + MTX group and control group achieved 0.66 QALY and 0.44 QALY at M12 respectively, thus ABN + MTX group gained additional 0.22 QALY compared to control group; on the other hand, ABN + MTX group cost extra ¥22,944.6 compared with control group; resulting in an ICER of ¥104,293.6 per QALY, which was lower than 2 times of the mean GDP per capita during the same period in China. Therefore, ABN + MTX was cost-effective in increasing the QALY of RA patients (Table 3).

3.7. Cost-effectiveness of ABN + MTX vs cDMARDs in subgroups

RA patients were further divided into moderate RA patients and severe RA patients according to disease activity (criteria were depicted in Method Section), then cost-effectiveness analysis was conducted respectively (Table 4). In moderate RA patients, ABN + MTX group yielded 0.69 QALY at M12 while control group yielded 0.44 QALY at the same time, thus ABN + MTX group gained additional 0.25 QALY compared with control group; besides, ABN + MTX group cost additional ¥27,052.6 compared with control group, leading to an ICER of ¥108,210.4 per QALY in moderate RA patients. In severe RA patients, QALY was 0.66 and 0.45 in ABN + MTX group and control group, ABN + MTX group achieved extra 0.21 QALY accordingly, and ABN + MTX group cost more ¥22,053.7 than that of control group, resulting an ICER of ¥105,017.6 per QALY in severe RA patients (Table 4). Both the abovementioned ICERs were below 2 times of the mean GDP per capita during the same period in China. These data indicated that ABN + MTX is cost-effective in increasing QALY than control in both moderate RA patients and severe RA patients, and ABN + MTX vs cDMARDs exhibited increased cost-effectiveness in severe RA patients than in moderate RA patients.

3.8. Sensitivity analyses of price

Rising ABN price by 20% produced an ICER of ¥130,403.6 per QALY, which was less than 3 times of the mean GDP per capita during the same period in China; rising ABN price by 50% resulted in an ICER of ¥169,474.5 per QALY, which was higher than 3 times of the mean GDP per capita during the same period in China; besides, reducing ABN price by 20% or 50% leaded to a lower ICER than the 2 times of mean GDP per capita during the same period in China (Table 5). These data indicated that ABN + MTX would be cost effective till the price was increased 20% as if price was increased more, the ICER might increase a lot offsetting it over mean GDP per capita. In addition, the comparison of secondary outcomes between two groups at each visit was shown in Supplementary Table 1, http://links.lww.com/MD/D393.

4. Discussion

In the current study, we described that:

(1) ABN decreased disease activity and increased QoL for RA patients more effectively compared with cDMARDs;
(2) ABN + MTX decreased indirect cost while increased drug cost and total cost for RA patients compared with cDMARDs.
(3) ABN + MTX was cost-effective in treating moderate to severe RA patients compared to cDMARDs, and it was still cost-effective when rising the price of ABN by 20%; besides, ABN + MTX was more cost-effective in treating severe RA patients compared to moderate RA patients.

According to the latest report, there is approximately 5 million of RA patients in China, and a large proportion of RA patients are lived in less developed cities or rural areas, at which they are unable to receive adequate biologic agent treatments due to the

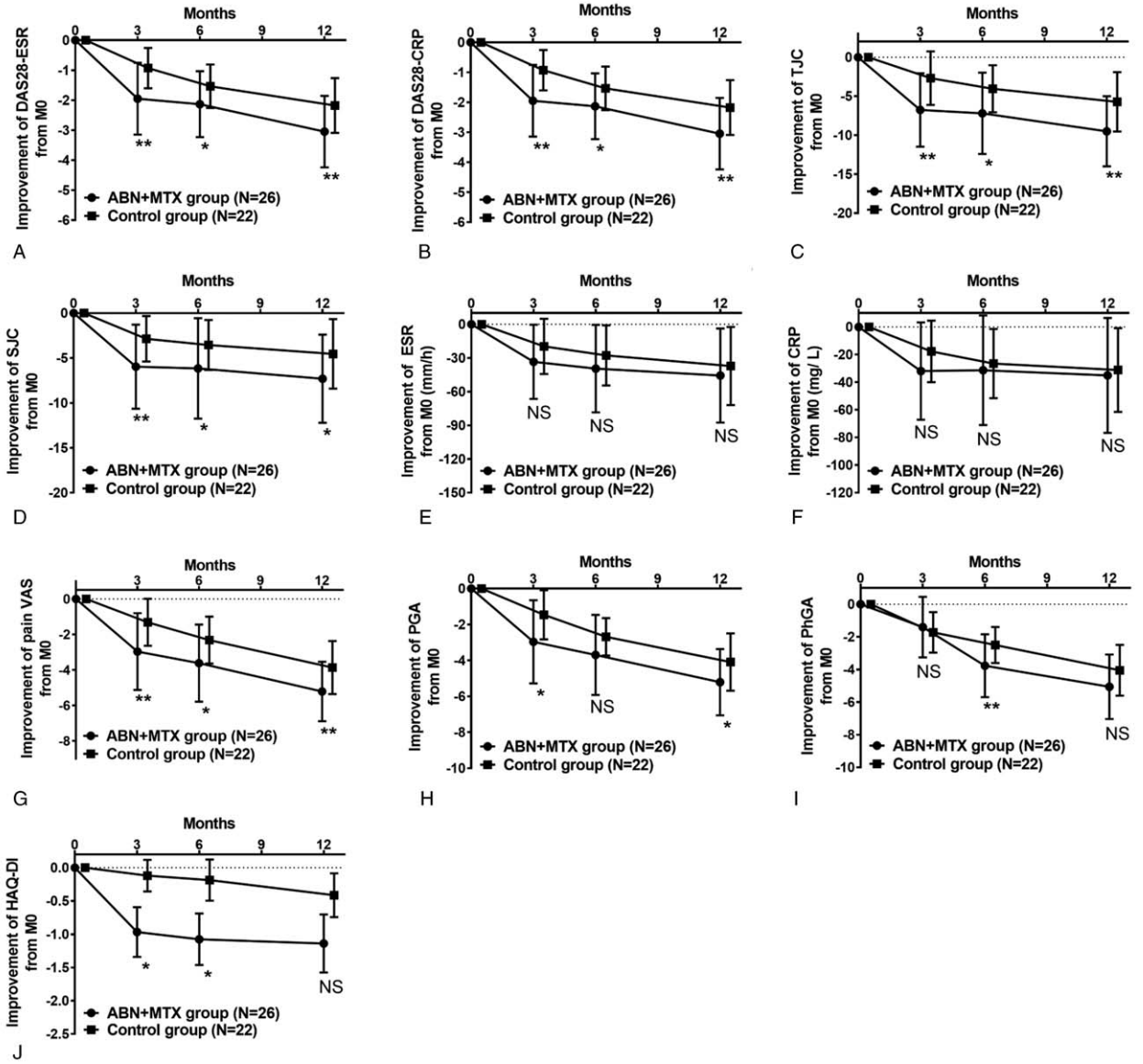

Figure 2. Disease activity reduction and QoL improvement between two groups at each visit. From M0, the improvement of DAS28-ESR (A), DAS28-CRP (B), TJC (C), SJC (D) and pain VAS (G) in ABN + MTX group were increased compared to control group at M3, M6 and M12; meanwhile, the improvement of PGA (H) were elevated at M3 and M12, the improvement of PhGA (I) was increased at M6 and the improvement of HAQ-DI (J) were increased at M3 as well as M6 in ABN + MTX group compared to control group; As for the improvement of ESR (E) and CRP (F), they were similar between two groups at each visit. Comparison between 2 groups was determined by *t* test. $P < .05$ was considered significant. $^{*}P < .05$, $^{**}P < .01$. DAS28 = disease activity score in 28 joints, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, TJC = tender Joint Count, SJC = swollen Joint Count, VAS = Visual Analogue Scale, ABN = Anbainuo, MTX = methotrexate, PGA = patient global assessment, PhGA = physician global assessment, HAQ-DI = Health Assessment Questionnaire Disability Index.

extremely high medical cost even though they are eligible to these biologic agents.[1] ABN, a bio-similar of etanercept that is independently developed by local Chinese pharmaceutical company and launched in 2015, might become a prior alternative in RA treatment for its much lower cost compared with other imported biologic agents such as infliximab (IFX), adalimumab (ADA) and etanercept.[13,14] ABN exhibits favorable treatment efficacy in decreasing disease activity of RA patients, which is confirmed by 2 recent clinical studies.[13,14] For instance, in a multicentral, randomized, double-blind clinical trial (phase II), the treatment efficacy in 396 RA patients was compared between ABN + MTX and MTX, which reveals that ABN + MTX is more effective compared to MTX monotherapy in controlling disease activity and radiographic progression.[14] In another phase III clinical trial, 600 RA patients who are poorly responding to MTX are enrolled and randomized as ABN group and control group; in the first 12-week double-blind period, ABN group receives ABN while control group receives placebo, in the later 12-week open-label period, both groups receive ABN; ABN group achieves lower DAS28-ESR, HAQ-DI and PGA scores while higher ACR20, ACR50 and ACR70 response rates compared with control group.[13] However, no study compares the treatment efficacy of ABN + MTX with cDMARDs. Partly in line with these previous studies, our study revealed that RA

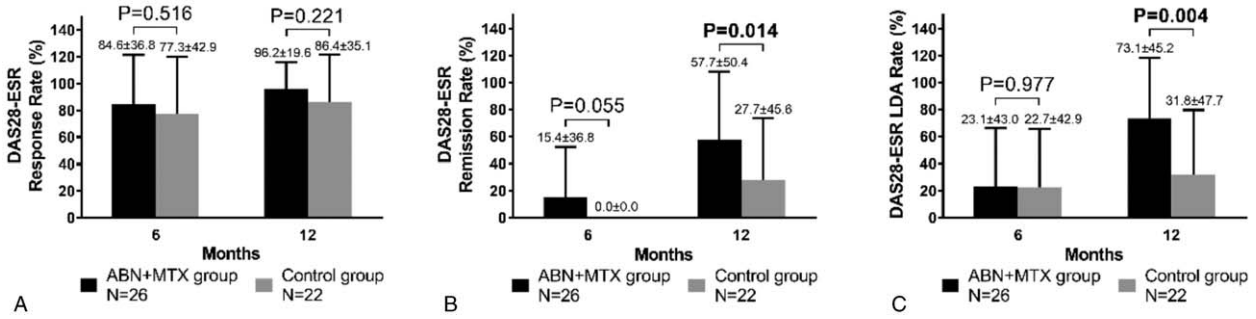

Figure 3. DAS28-ESR response rate, remission rate and LDA rate between 2 groups. No difference of DAS28-ESR response rate was found between ABN + MTX group and control group at M6 or M12 (A), DAS28-ESR remission rate (B) and DASS28-ESR LDA rate (C) were also similar between two groups at M6, while both of them were increased in ABN + MTX group compared with control group at M12. Comparison between two groups was determined by Chi-square test. $P < .05$ was considered significant, which were shown as bold. DAS28 = disease activity score in 28 joints; ESR = erythrocyte sedimentation rate, ABN = Anbainuo, MTX = methotrexate, LDA = low disease activity.

Table 2

Comparison of cost between 2 groups.

	6 months			12 months		
	ABN + MTX group	**Control group**	***P* value**	**ABN + MTX group**	**Control group**	***P* value**
Drug cost (¥)	27,970.5 ± 1,116.5	3,723.6 ± 2,023.6	<.001	39,433.9 ± 20,301.7	7,126.6 ± 4,022.0	<.001
Other medical cost (¥)	9,893.1 ± 9,462.8	9,188.6 ± 1,521.3	.711	10,385.4 ± 9,393.6	13,185.0 ± 1,644.0	.147
Indirect cost (¥)	7,618.5 ± 10,425.7	8,683.3 ± 1,516.4	.611	8,389.0 ± 10,511.8	14,952.0 ± 1,779.2	.004
Total cost (¥)	45,482.0 ± 15,294.3	21,595.6 ± 2,678.6	<.001	58,208.2 ± 23,433.9	35,263.6 ± 4,150.2	<.001

Data were presented as mean value ± standard deviation. Comparison between two groups was determined by *t* test. *P* value < .05 was considered significant. ABN = Anbainuo; MTX = methotrexate.

Table 3

Cost-effectiveness analysis.

Group	QALY	Incremental QALY (¥)	Total cost (¥)	Incremental cost (¥)	ICER (¥/QALY)
ABN + MTX	0.66	0.22	58,208.2	22,944.6	104,293.6*
Control	0.44	–	35,263.6	–	–

Data were presented as mean value or mean value ± standard deviation. * The average of GDP per capita in China between 2016 and 2017 was ¥55,320, and the ICER was less than 2 times of the mean GDP per capita. ABN = anbainuo, CER = cost-effectiveness ratio, GDP = gross domestic product, ICER = incremental cost-effectiveness ratio, MTX = methotrexate, QALY = quality-adjusted life years.

Table 4

Cost-effectiveness analysis of subgroup.

Disease activity	Group	QALY	Incremental QALY	Total cost (¥)	Incremental cost (¥)	ICER (¥/QALY)
Moderate	ABN + MTX	0.69	0.25	56,823.2	27,052.6	108,210.4*
	Control	0.44	-	29,770.6	-	-
Severe	ABN + MTX	0.66	0.21	58,538.0	22,053.7	105,017.6*
	Control	0.45		36,484.3	-	-

Data were presented as mean value or mean value ± standard deviation. * The average of GDP per capita in China between 2016 and 2017 was ¥55,320, and the ICER was less than 2 times of the mean GDP per capita. ABN = etanercept, CER = cost-effectiveness ratio, GDP = gross domestic product, ICER = incremental cost-effectiveness ratio, MTX = methotrexate, QALY = quality-adjusted life years.

patients who received ABN + MTX treatment achieved larger disease activity decrement and QoL improvement compared with cDMARDs. The superb efficacy of ABN was mainly due to that: ABN is a recombinant human TNF-II:Fc fusion protein which is able to inhibit dysregulated activity of TNF-α directly in RA patients through acting as a decoy TNF receptor, whereas cDMARDs inhibit dysregulated activity of TNF-α through regulating activities of immune cells, which is less effective compared with ABN; therefore, ABN decreases disease activity of RA patients more obviously than that of cDMARDs, and more obvious disease activity decrement means more alleviated symptoms and higher QoL improvement. In brief, ABN is a promising treatment option for RA patients.

In the present study, indirect cost (¥8,389.0 ± 10,511.8 vs ¥14,952.0 ± 1779.2) was lower while drug cost (¥39,433.9 ± 20,301.7 vs ¥7126.6 ± 4022.0) and total cost (¥58,208.2 ± 23,433.9 vs ¥35,263.6 ± 4150.2) were much higher in ABN + MTX group than that in cDMARDs group after 12-month

Table 5

Sensitivity analyses.

	QALY	Incremental QALY	Total cost (¥)	Incremental cost (¥)	ICER (¥/QALY)
Price of ENT up by 20%					
ABN + MTX group	0.66	0.22	63,952.4	28,688.8	130,403.6*
Control group	0.44	–	35,263.6	–	–
Price of ENT up by 50%					
ABN + MTX group	0.66	0.22	72,548.0	37,284.4	169,474.5
Control group	0.44	–	35,263.6	–	–
Price of ENT down by 20%					
ABN + MTX group	0.66	0.22	50,000.1	14,736.5	66,984.1*
Control group	0.44	–	35,263.6	–	–
Price of ENT down by 50%					
ABN + MTX group	0.66	0.22	37,702.2	2,438.6	11,084.5*
Control group	0.44	–	35,263.6	–	–

Data were presented as mean value. The average of GDP per capita in China between 2016 and 2017 was ¥55,320, and the ICER was less than 3 times of the mean GDP per capita. ABN = Anbainuo, ICER = incremental cost-effectiveness ratio, MTX = methotrexate, QALY = quality-adjusted life years.

treatment, indicating that ABN + MTX was more costly in treating RA patients than that of cDMARDs. Our result was in line with several previous studies. For example, a study conducted in 2007 reveals that the productivity costs (indirect costs) of IFX + MTX, ADA + MTX and ADA + etanercept are lower than cDMARDs, whereas the their drug costs and total costs are higher than that of cDMARDs in 6 months.[18] Another study which is conducted in 2006 also shows that the total cost of etanercept is larger compared with cDMARDs in RA treatment for 1 year, 2 years, and 5 years, respectively. The possible explanation for our results was that: the price of ABN is higher than cDMARDs, leading to a much higher drug costs in ABN + MTX group compared with cDMARDs; meanwhile, ABN + MTX exhibits better treatment efficacy than that of cDMARDs, which might contribute to fewer hospital stays and indirect cost; however, the significantly increased drug cost in ABN + MTX group offsets its decreased indirect cost, causing an elevated total cost in ABN + MTX group compared with cDMARDs group.

Previously, the cost-effectiveness analysis of etanercept has been conducted in different countries. In a cost-effective analysis conducted in 2006 of America, etanercept + MTX only gains additional 0.007 QALY while produces extra $96,200 compared with cDMARDs in 5 years of early aggressive RA patients, leading to an ICER of $12.5 million per QALY, indicating that etanercept + MTX is not cost-effective in treating American RA patients compared with cDMARDs when acceptable ICER threshold is $1 million.[12] In another study conducted in 2014 of Canada, cost-effectiveness of etanercept + MTX in active RA patients has also been analyzed, which reveals that etanercept + MTX provides an extra 0.15 QALYs while it cost extra $77,290 compared with cDMARDs, leading to an ICER of $521,520 per QALY, implying that ABN + MTX is not cost effective compared with cDMARDs in treating Canadian RA patients when acceptable ICER threshold is $100,000 per QALY.[11] These studies illuminate that etanercept + MTX is not cost-effective in treating RA patients compared with cDMARDs. Considering that ABN is much cheaper than etanercept (about 1/3 price of etanercept), ABN might be cost-effective in treating RA patients compared with cDMARDs. To this end, we conducted the current study, which found that ABN + MTX produced an incremental cost of ¥22,944.6 while achieved extra 0.22 QALY compared with cDMARDs in 12 months, leading to an ICER of ¥104,293.6 per QALY, which was lower than 2 times of the mean GDP per capita in China, indicating that ABN + MTX was cost-effective in treating RA patients; besides, ABN + MTX was still cost-effective when rising the price of ABN by 20%; The possible reason for the results might be due to that: in consistent with etanercept, ABN also exhibits superior treatment efficacy compared with cDMARDs, which contributes to its higher QALY than that of cDMARDs; besides, the price of ABN is much lower than etanercept, leading to a decreased total cost of ABN compared with etanercept; as a consequence, ABN + MTX is cost-effective while etanercept is not cost-effective compared to cDMARDs. In the current study, we also found that ABN + MTX was more cost-effective in treating severe RA patients compared with moderate RA patients, which might be explained by that: for severe RA patients, cDMARDs is not as effective as ABN in decreasing disease activity, which might increase hospital stays and indirect cost compared with ABN; whereas for moderate RA patients, cDMARDs could not increase indirect cost or the increment is tiny compared to ABN, thus ABN + MTX is more cost-effective in treating severe RA patients compared with moderate RA patients.[2,5] Briefly, our study was the first pharmacoeconomic study to investigate the cost-effectiveness of biological agent in treating Chinese RA patients compared with cDMARDs, which might provide tremendous benefits for millions of RA patients.

There were some limitations in the current study: To begin with, the study only assessed the QALY and ICER in 12 months, thus cost-effectiveness of ABN in the longer period of time was not known. In addition, in this study, the drugs were not covered by the government/insurance. If the drugs were covered by the government/insurance, based on the patient's perspective, it would be more beneficial to patients due to the reduced financial burden of these patients, while based on the government perspective, the use of covered drugs would increase government spending to some extent but it might be worth partly due to relatively increased social benefits from patients who got better. However, the detailed influence was still unclear, thus, further study was great needed when the drugs were covered by the government/insurance. Meanwhile, the acceptable ICER threshold in the current study was based on 3 times of the mean GDP per capita in China, which might cause bias in highly developed areas and lowly developed areas of China considering that the annual GDP per capita among these areas were greatly different. What is more, baseline TJC was higher in ABN + MTX group

compared with cDMARDs group, this discrepancy might induce confounding bias; however, it was reasonable since patients in ABN + MTX group might have higher disease activity. Lastly, the sample size in this study was relatively small, which might decrease statistic power.

In conclusion, ABN + MTX is cost-effective in treating moderate to severe RA patients compared to cDMARDs.

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