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ORIGINAL ARTICLE

Efficacy of adalimumab combined with Tripterygium wilfordii Hook F in the treatment of patient with rheumatoid arthritis: A multicenter, open-label, randomized-controlled trial

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Abstract

Objectives: To evaluate the efficacy and safety of adalimumab (ADA) combined with *Tripterygium wilfordii* Hook F (TwHF) in the treatment of methotrexate (MTX)-inadequate response patients with rheumatoid arthritis (RA).

Methods: In this multicenter, open-label, randomized controlled clinical trial, 64 RA patients with inadequate response to MTX were 1:1 randomly assigned into treatment or control groups. The treatment group was treated with ADA in combination with TwHF, and the control group was treated with ADA in combination with MTX for 24 weeks. The primary endpoint was the percentage of patients having low disease activity ($2.6 \leq$ DAS28-ESR < 3.2) and remission rates (DAS28-ESR < 2.6) at week 24.

Results: In total, 53 of the 64 patients (82.8%) completed this 24-week clinical trial. By intent-to-treat (ITT) analysis, a comparable outcome was observed between the two groups. The percentage of patients achieving low disease activity in the treatment group and control group were 43.8% and 46.9% (95% CI, 21.28 to 27.48, $p = .802$).

Feng Luo, Yu-xia Wu, Hou-li Liao and Fang Tang contributed equally to this manuscript.

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Percentage of patients achieving low disease activity rates were respectively 28.1% and 31.3% in the treatment group and control group (95% CI, 19.18 to 25.58, $p = .784$). In per-protocol (PP) analysis, the results were consistent with the ITT model. The incidence of adverse events was comparable between the two groups.

Conclusions: There were no significant differences in efficacy and safety between ADA combined with TwHF versus ADA combined with MTX in the treatment of RA. TwHF might be an alternative treatment for RA patients who are intolerant to MTX.

KEYWORDS
adalimumab, clinical trial, methotrexate, rheumatoid arthritis, Tripterygium wilfordii Hook F

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovitis and cartilage destruction. It has a high incidence, recurrence rate, and disability rate, significantly impacting patients' sleep quality and mental well-being.[1,2] Epidemiological studies show that the worldwide prevalence of RA is 0.24%. In developed countries, the RA prevalence was reported to be 0.3%–1%,[3] and in China, it was reported to be 0.28%–0.45%.[4] At present, treatment drugs for RA include disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids.[5] DMARDs are divided into conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), and biological antirheumatic drugs (bDMARDs).[6] For RA treatment, some medications were thought to be associated with various adverse effects such as cardiovascular events, infection and tuberculosis.[7]

As anchor treatment of RA, methotrexate (MTX) is widely used in clinical practice to improve clinical symptoms and control disease progression.[8] It has been found that MTX can effectively control the condition of two-thirds of patients with RA, but more than one third of patients still have poor efficacy after using MTX. Moreover, retaking MTX after RA relapsing might be insensitive, or even ineffective.[9–11] According to the 2021 American College of Rheumatology (ACR) guidelines, bDMARDs can be added to patients with RA who respond poorly or are intolerable to MTX and other csDMARDs.[6] Tumor necrosis factor-α (TNF-α) inhibitors are well-documented and widely used bDMARDs for the treatment of RA.[12] Adalimumab (ADA) has a high affinity for TNF-α, can specifically bind to TNF-α in vivo and can alleviate and inhibit the progression of joint injury, improve joint mobility, reduce disease activity, and improve patient quality of life when used in patients with poor response to MTX treatment.[13,14] At present, the treatment of RA is mainly based on drug intervention. If there is a poor response or drug resistance after MTX medication, it is urgent to find a new alternative drug program.

TwHF (Tripterygium wilfordii Hook F, NCBI:txid458696) is a fat-soluble mixture extracted from the Triptolide plant of the Family Eytidae, which is the first Chinese herbal medicine with anti-inflammatory immunomodulatory effect studied in China. In recent studies, the efficacy of TwHF in the treatment of immune-related diseases, such as chronic urticaria and RA, has been reported.[15,16] The main active ingredient of TwHF is diterpene lactone. It was reported that TwHF has potential anti-inflammatory, immunomodulatory, and bone protection effects. TwHF has been widely used in clinical practice, and was currently one of the traditional Chinese medicines commonly used in the treatment of RA.[17,18] Based on the previous clinical reports and clinical experience of TwHF, we aim to evaluate the efficacy and safety of TwHF combined with ADA in the treatment of RA in this multicenter, randomized-controlled trial.

Plain Language Summary

Tripterygium wilfordii Hook F (TwHF) was reported to have anti-inflammatory, immunomodulatory, and bone protection effects, has been widely used in clinical practice and serves as one of the commonly used traditional Chinese medicines for rheumatoid arthritis (RA) treatment. However, the efficacy and safety of using TwHF combined with adalimumab for RA treatment have not been evaluated. There were no significant differences in efficacy or safety in the treatment of adalimumab combined with TwHF and adalimumab combined with methotrexate in the treatment of RA. Given that no significant difference between TwHF combining adalimumab and adalimumab combined with methotrexate, TwHF combining adalimumab could be a potential treatment option for RA patients inclined to use traditional Chinese medicine for RA treatment.

2 | METHODS

2.1 | Design overview

This study is a multicenter, open-label, randomized controlled study. All enrolled patients signed an informed consent, and the Ethics Committee of the Second Affiliated Hospital of Guizhou University

of Chinese Medicine approved the ethical review and protocol. The clinical trial number of this study is ChiCTR2100050865, which can be found at http://www.chictr.org.cn/.

2.2 | Study population and randomization

Figure 1A,B presents the disposition of the patients in this study.

2.2.1 | Enrollment criteria

Patients who meet all of the following criteria will be eligible for enrollment in the current study: (1) patients aged 50–65 (including the boundary value) or patients without fertility requirements; (2) Meet the 2010 ACR/EULAR RA classification standards[19]; (3) DAS28-ESR >3.2 after treatment of two or more traditional DMARDs (one of which is MTX ≥ 15 mg) for 6 months or more; (4) subjects are ready to start using Gretel (ADA injection); (5) informed consent obtained. Once a patient meets the inclusion criteria, he/she will be assigned a study number in the order of each site. From 3 general hospitals with rheumatology and immunology (the *Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine*, *Xingyi People's Hospital* and *QiandongnanZhou People's Hospital*), study participants were continuously enrolled and using computer-generated random codes to be assigned in 2 separate treatment groups in a 1:1 ratio. Participants in the experimental group received 20 mg TwHF orally three times a day in combination with subcutaneous ADA 40 mg once a week. Folic acid was not administered in the experimental group. Participants in the control group took 15 mg MTX orally once a week in combination with subcutaneous ADA 40 mg once a week, taking folic acid 10 mg the day after each administration of MTX.

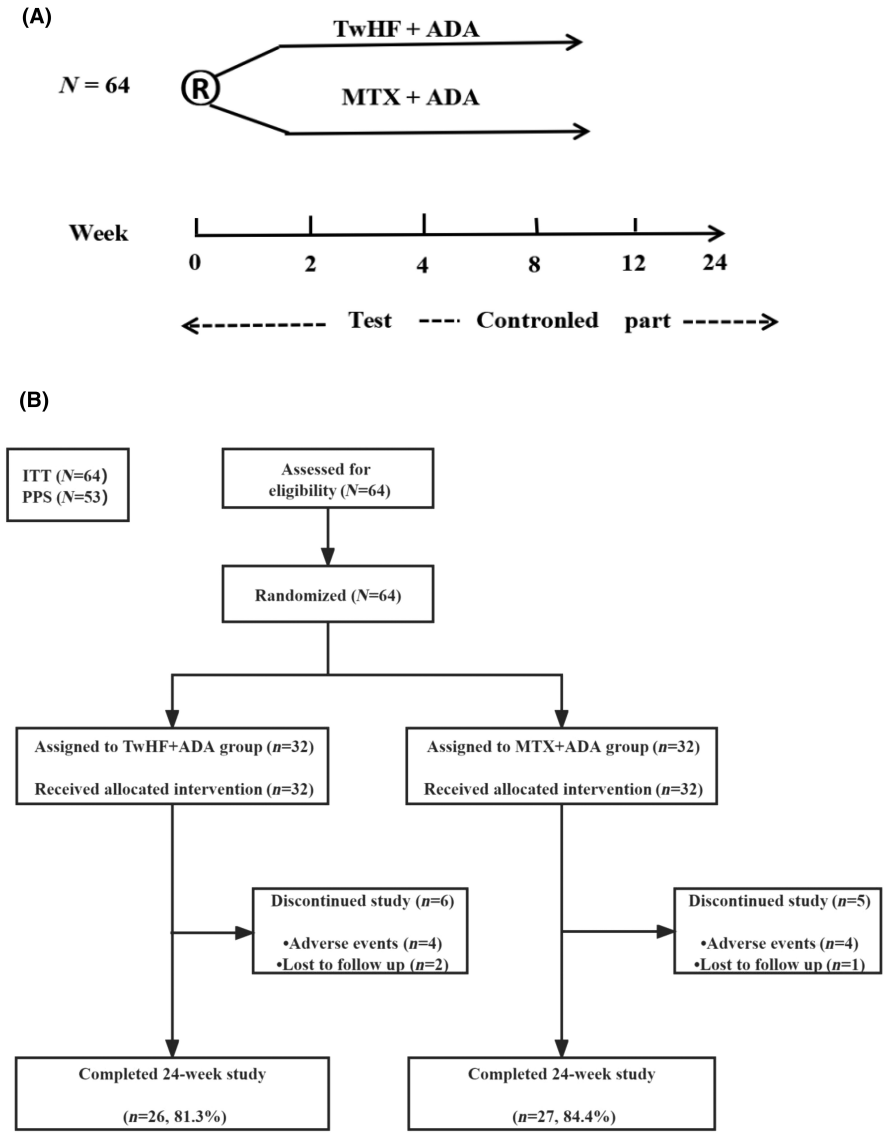


FIGURE 1 Study design and patient selection flowchart. (A) Study design. (B) Patient selection process.

2.2.2 | Exclusion criteria

Patients who meet any of the following criteria will be excluded from the current study: (1) Patients who are allergic to other components of experimental drugs or preparations; (2) Pregnant or lactating women and women planning to become pregnant who are unwilling or have not taken adequate contraceptive measures; Male patients who are unwilling or have not taken adequate contraception; (3) Patients who are in the period of acute or chronic infection of the whole body, old or active tuberculosis, and patients in the active period of viral hepatitis B; (4) Patients with malignant tumors; (5) Patients with moderate to severe heart failure (New York Heart Association grades 3–4); (6) Patients with demyelination diseases of the central nervous system; (7) Diagnosed with other rheumatic immune system diseases, such as systemic lupus erythematous, ankylosing spondylitis, etc; (8) Abnormal liver function, AST or ALT is twice higher than the upper limit of the normal range; (9) use of biological/targeted DMARDS in the last 3 months; (10) Have a long-term history of glucocorticoid application, and the daily dose of application in the past 1 month is equivalent to that of prednisone≥10 mg; (11) White blood cell count (WBC) $< 4.0 \times 10^9$/L, platelet count (PLT) $< 100 \times 10^9$/L, haemoglobin (HGB) < 90 g/L; (12) Those who are able or unwilling to provide informed consent or cannot comply with the requirements of the test; (13) Patients evaluated to be inappropriate to participate in this study.

2.2.3 | Patients' criteria for discontinuation

If any of the following conditions occur, the drug should be discontinued: (1) ALT or AST is 2.0 times greater than the upper limit of normal; (2) the blood Cr value is 1.25 times greater than the upper limit of normal value; (3) the blood white blood cell count (WBC) $< 3.0 \times 10^9$/L; (4) Platelet count (PLT) $< 80 \times 10^9$/L; (5) haemoglobin (HGB) < 90 g/L; (6) Chest radiograph suggests infection.

2.2.4 | Patients' termination criteria due to personal issues

If any of the following conditions occur, the participant will stop participating in the current study and the data will be censored: (1) the subject terminates on his or her own, such as withdrawing the informed consent; (2) The subject is pregnant (must withdraw from the study); (3) The subject uses a combination of drugs within the scope of non-regulations, which affects the effectiveness and safety judgment; (4) The subject has an adverse event or deterioration of the condition, and the researcher believes that the subject must withdraw early; (5) Other researchers believe that the subject is not suitable to continue the study and need to withdraw; (6) The subjects' compliance with the study protocol was poor, and the number of drugs and the course of medication were not between 80% and 120%.

2.2.5 | Termination criteria of the entire experimental study

If any of the following conditions occur, the current study will be terminated: (1) Occurrence of serious adverse reactions related to the study drug; (2) It is found that there are major errors in the clinical research plan set in the study, and it is difficult to evaluate the efficacy of the drug; or for a well-designed protocol, significant deviations have occurred in the implementation, making it difficult to evaluate the effect of the drug.

2.2.6 | Criteria for censoring

If any of the following conditions occur, the participant's data would be censored and would not be analyzed in the current study: (1) lack of important indicators and incomplete information, affecting subsequent statisticians; (2) the disease progresses and there is system damage; (3) For personal reasons, the person who voluntarily requests to withdraw from the test; (4) The patient is unwilling to continue participating in the clinical trial; (5) lost visits; (6) Death.

2.3 | Study endpoints

The primary efficacy endpoints include low disease activity rates (2.6 ≤ DAS28-ESR < 3.2) and remission rates (DAS28-ESR < 2.6) at week 24. Secondary efficacy endpoints include: (1) Rate of participants achieving the low disease activity (2.6 ≤ DAS28-ESR < 3.2) and clinical response rate (DAS28-ESR < 2.6) at week 12. (2) Ratio of ACR 20/50/70 reaction evaluated in weeks 2, 4, 8, 12, 24 (3) Value changes in disease activity-related indicators including DAS28-CRP and DAS28-ESR. (4) Value changes in inflammatory-related lab data including erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) (5) Improvement of health assessment questionnaire- disability index (HAQ-DI). In order to evaluate whether the treatment effect in both groups meets the ACR standard, improvement (more than 20%, 50% or 70%) of the swelling/paining joints, VAS, Patients' global assessment of disease activity (PtGA), Physicians' global assessment of disease activity (PGA) would be recorded. For safety evaluation, any adverse events or changes after taking treatments were recorded.

2.4 | Statistical methods

According to the literature, the response rate of MTX combined with ADA is PC = 51%. The difference D = 25% between the experimental group and the control group is established.[20] Based on clinical data from previous similar trials,[21,22] the non-inferior cut-off value validated in this clinical trial was determined = −10%. The parameters are as follows: $\alpha = .05$ (bilateral), test efficacy power $(1 - \beta) = .8$, using

the non-inferior test sample size calculation formula, the calculation results show that each group needs to include 28 subjects' cases, a total of 56 cases. Approximately 15% of the cases that may fall off during the clinical trial are expected, as well as the centre's sample size allocation and the requirement of randomization of the block, the sample size of each group is expanded to 32 cases, and the total sample size required by the two groups is 64. The sample size of the non-inferior test is calculated as follows:

$$n_T = n_C = \frac{\left(z_{1-\alpha/2}+z_{1-\beta}\right)^2\left[P_C(1-P_C)+P_T(1-P_T)\right]}{(D-\Delta)^2}$$

Among them, the sample size of the experimental group and the control group, respectively; is a non-inferior cutoff.

$$\text{Attach: } n_T = n_C = \frac{\left(z_{1-0.05/2}+z_{1-0.2}\right)^2\left[0.76\times(1-0.76)+0.51\times(1-0.51)\right]}{(0.76-0.51-(-0.1))^2} = 28$$

In the current study, intent-to-treat analysis (ITT) and per-protocol analysis (PP) to analyze experimental data. With the ITT analysis as the main outcome analysis, it includes all patients who received at least one treatment. PP analysis refers to subjects who strictly follow the protocol and complete the entire process of medication according to the protocol. Subjects who withdraw from the trial prematurely or are not followed will be excluded from the analysis. Patients who withdraw from the trial too early are considered missing data, which will be calculated using the last observation carry-over method when performing the ITT analysis. Furthermore, baseline characteristics, such as demographic characteristics and endpoints of exposure to treatment, will be descriptively summarized. Comparative analyses will be performed at a 5% significance level using a bilateral chi-square test or a Fisher precision test. Efficacy before and after treatment will be tested by paired t-tests or non-parametric tests. Continuous data will be expressed as mean (SD) or median (25th–75th percentile), and categorical data as number (*N*) or proportion (%). All analyses were calculated using SPSS statistics V.26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) and GraphPad Prism.

3 | RESULTS

3.1 | Baseline characteristics of participants

The basis for the classification is shown in Table 1. A total of 64 subjects enrolled in the three centres of the trial signed informed consent forms, of which 8 (12.5%) withdrew from the case, 3 cases (4.7%) appeared in the time window, and 53 cases (82.8%) completed the trial within the specified time. A total of 32 patients were enrolled in the experimental group, 26 (81.3%) patients with good compliance, 6 (18.7%) patients with poor compliance, including 4 (12.5%) patients who resigned from the group and 2 (6.3%) patients who were not followed out of the group. A comparative analysis of adherence showed that there was no statistically significant difference in adherence between the two groups ($\chi^2=0.41$, $p=.522$). According to the data set, there were 64 cases of full analysis set (FAS), 53 cases of conforming scheme set (PPS), and 64 cases of security data set (SS). According to the status of SW-28, TEN-28, ESR, and CRP of participants, all enrolled individuals were in the active status of RA and the activity of disease between the two groups was insignificant.

From Table 1, there are no significant differences in the demographic baseline of the two groups, including sex, age, height, weight, and ethnicity. Among the two sets of baseline indicators, there were no significant differences in SW-28, TEN-28, VAS, PtGA, PGA, CRP, ESR, HAQ-DI score, DAS-28ESR, DAS-28CRP, RF, and Anti-CCP.

TABLE 1 Demographics and clinical characteristics at baseline.

	Experimental group (*n* = 32)	Control group (*n* = 32)
Sex, *n* (%)		
Male	4 (12.5)	7 (21.9)
Female	28 (87.5)	25 (78.1)
Age, years, mean (SD)	54.7 (9.3)	54.3 (7.7)
Heigh, cm, mean (SD)	155.0 (6.4)	157.0 (6.4)
Weight, kg, mean (SD)	53.9 (8.5)	54.9 (7.4)
TEN-28, mean (SD)	21.1 (5.1)	21.4 (4.2)
SW-28, mean (SD)	14.5 (3.8)	15.1 (3.0)
VAS score, mean (SD)	80.3 (9.9)	79.9 (10.9)
PtGA score, mean (SD)	78.1 (11.6)	78.0 (12.1)
PGA score, mean (SD)	76.7 (11.7)	74.5 (12.8)
HAQ-DI score, mean (SD)	1.6 (0.4)	1.60 (0.3)
ESR, mm/h, median (IQR)	45.5 (24.5, 73.8)	30.5 (20.0, 49.0)
CRP, mg/L, median (IQR)	15.9 (5.2, 49.5)	7.2 (1.5, 42.3)
DAS28-ESR, mean (SD)	7.4 (0.7)	7.2 (0.7)
DAS28-CRP, mean (SD)	6.7 (0.7)	6.6 (0.7)
RF[a], U/mL, median (IQR)	110.0 (42.8, 323.1)	119.6 (49.4, 226.4)
Anti-CCP[a], U/mL, median (IQR)	392.9 (35.5, 400.0)	400.0 (132.5, 400.0)

Note: Data are presented as mean (SD), median (IQR) or *n* (%).

Abbreviations: Anti-CCP, anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; DAS-28, 28-jointcount Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; RF, rheumatoid factor; SD standard deviation; SW-28, Swollen joint number-28; TEN-28, Tender joint number-28.

[a]RF was measured by immunonephelometry with a cut-off value of 20 U/mL. Anti-CCP was measured using a commercially available second-generation ELISA kit (Euro-Diagnostica, Malmo, Sweden) with a cut-off value of 20 U/mL.

3.2 | Efficacy

3.2.1 | Primary endpoint

In the ITT analysis, at week 24, 14 (43.8%) of the patients in the experimental group achieved a low rate of disease activity and 15 (46.9%) of patients in the control group achieved a low rate of disease activity. 9 (28.1%) of the patients who achieved clinical response in the experimental group and 10 (31.3%) of the patients in the control group achieved a clinical response rate. The main evaluation indicators between the two groups were not statistically significant ($p > .05$) (Figure 2A). In the PPS dataset, 53 subjects were included. At 24 weeks of follow-up, 14 (53.8%) of the patients in the experimental group reached a low disease activity rate and 15 (55.6%) of the patients in the control group reached a low disease activity rate. 9 (34.6%) of the patients in the trial group achieved a clinical response rate, while 10 (37.0%) of patients in the control group achieved a clinical response rate. There were no significant differences in the main evaluation indicators between the two groups ($p > .05$) (Figure 2B).

3.2.2 | Secondary endpoints

Secondary efficacy indicators between the two groups were not statistically significant (Figure 3A). In the ITT analysis, 7 (21.9%) of the patients in the experimental group achieved low disease activity rates at week 12, while 9 (28.1%) of patients in the control group achieved low disease activity rates. Regarding clinical response rates, 3 (9.4%) of the patients in the experimental group achieved clinical response rates and 4 (12.5%) of the patients in the control group achieved clinical response rates. A similar trend was also observed in the PP analysis (Figure 3B).

In ITT analysis, at the follow-up time of 24 weeks, there were 68.8% of patients (22 out of 32 participants) met ACR20 criteria (at least 20% improvement in disease activity) in the experimental group, whereas in a control group, the ratio for participants meeting ACR20 was 71.9% (23/32). However, the difference between the experimental and the control group was not significant. Similar trends were also observed in ACR 50 (at least 50% improvement in disease activity) and ACR70 (at least 70% improvement in disease activity) (Figure 4A–C). Moreover, throughout the treatment period, the decrease of DAS28-ESR, DAS28-CRP, ESR, and CRP of both groups were statistically significant ($p < .001$) compared to baseline in the 2-week-follow-up and 24-week follow-up (Figure S1a–d).

3.2.3 | Safety

Occurred adverse events were presented in Table S1. A total of 37 patients out of 64 patients (57.8%) in this study had adverse reactions of varying degrees during treatment, with 19 (59.4%) in the experimental group and 18 (56.3%) in the control group. The difference in incidence of adverse reactions between the two groups was not statistically significant ($p = .800$). Adverse reactions with high incidence include elevated leukocytes, elevated aspartate aminotransferase (AST), elevated Alanine aminotransferase (ALT), and elevated creatinine. In addition, in both groups, liver dysfunction was the most common adverse reaction, and the rate of presenting

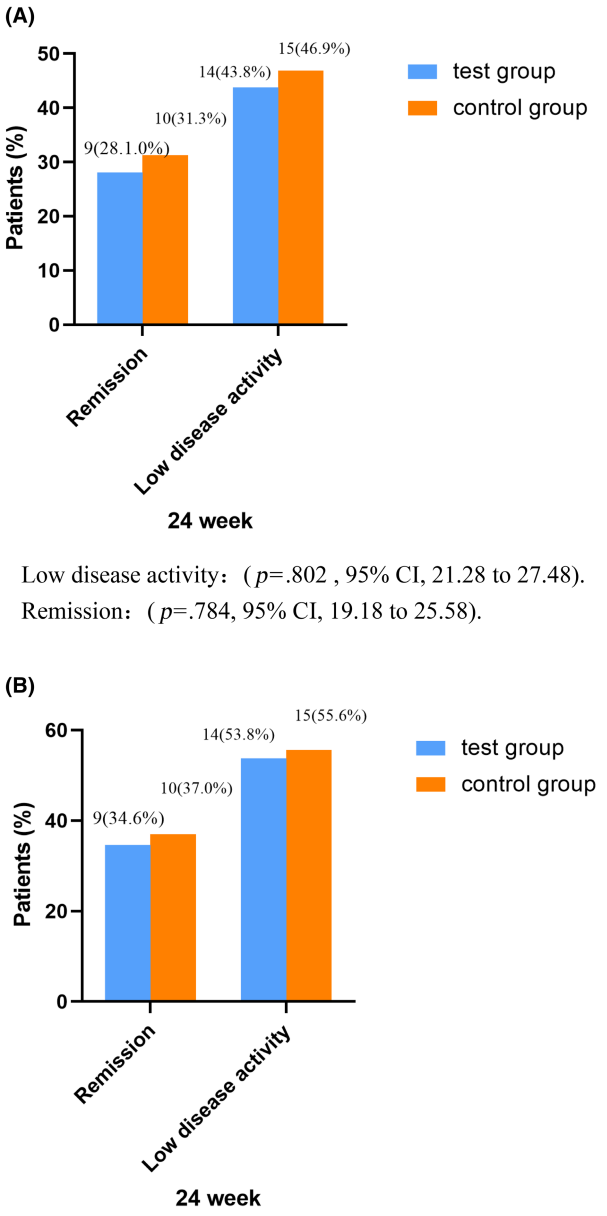
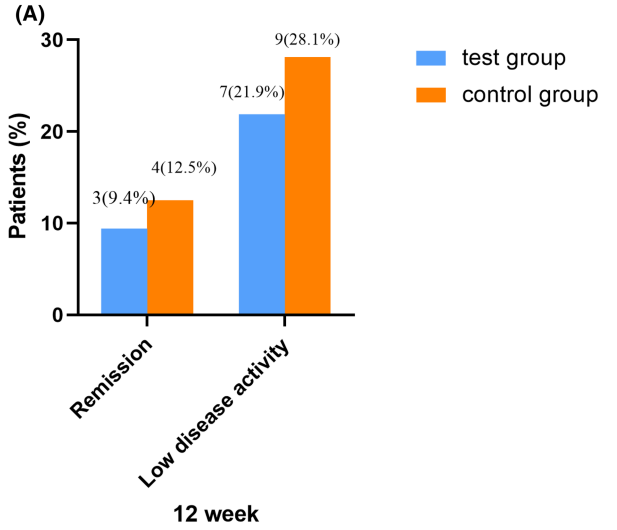
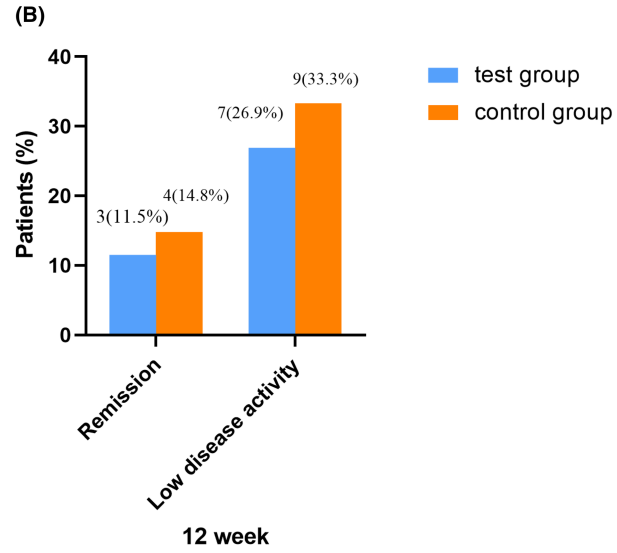


FIGURE 2 Percentage of response calculated by denominator of all selected patients. The *p* values between the test group and the control group were calculated using the diversity test. Comparison of the test and control group was calculated using the χ^2 test. (A) Main observation indicators in intent-to-treat analysis. (B) Main observation indicators in per-protocol analysis.



Low disease activity：(p=.901 , 95% CI, 14.96 to 27.36).
Remission：(p=.564, 95% CI, 12.18 to 18.38).



Low disease activity：(p=.611 , 95% CI, 14.86 to 21.46).
Remission：(p=.725, 95% CI, 23.41 to 28.21).

FIGURE 3 Percentage of response calculated by denominator of all selected patients. Those patients who withdrew from the trial prematurely or switched to the combination group were classed as missing data. The p values between the test group and the control group were calculated using the diversity test. Comparison of the test and control group was calculated using the χ^2 test. (A) Secondary evaluation indicators in intent-to-treat analysis. (B) Secondary evaluation indicators in per-protocol analysis.

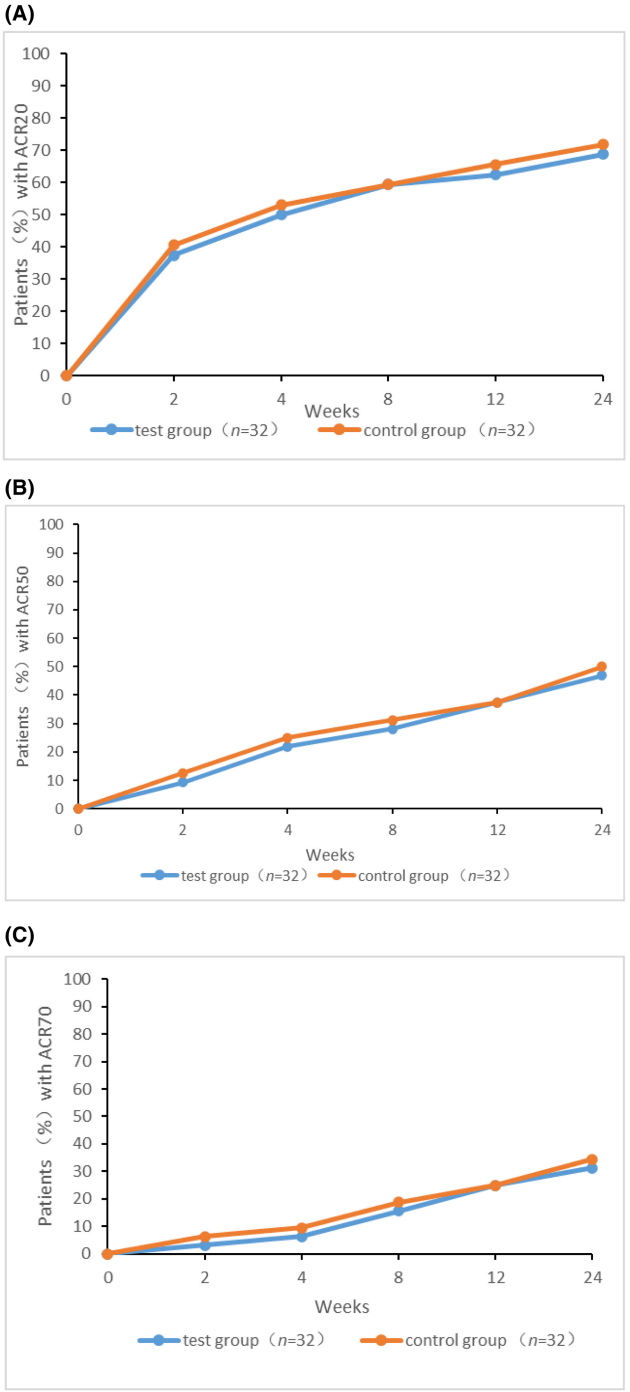


FIGURE 4 (A) Proportion of patients achieving a clinical response according to ACR 20 responses in the intent-to-treat (ITT) analysis over time. (B) Proportion of patients achieving a clinical response according to ACR 50 responses in the ITT analysis over time. (C) Proportion of patients achieving a clinical response according to ACR 70 responses in the ITT analysis over time.

liver dysfunction was numerically higher in the control group. In the experimental group, 9 of the participants (28.1%) presented liver dysfunction during the trial, whereas in the control group, 17 participants presented liver function (53.1%). Among the patients who were withdrawn or absent from the visit, the number of adverse events in the control group was 5 (41.7%) and the number of adverse events in the experimental group was 5 (41.7%). Among participants in the experimental group, the observed adverse events included: 1 case of severe adverse events (lung infection), 2 cases of mild symptoms of anemia, 1 case of abnormal liver function, and 1 case of joint pain (addressed by add-on glucocorticoid treatment). In the control group, 1 case had a severe rash at the

injection site, 2 cases had allergy symptoms at the injection site, 1 case had intermittent dizziness symptoms, and 1 case had mild nausea symptoms. Patients with abnormal liver function during follow-up were treated with hepatoprotective drugs after evaluation by professional physicians. After the liver function returned to normal, the study could be continued. No special treatments for mild adverse reactions were applied.

4 | DISCUSSION

This randomized-controlled trial demonstrated that ADA in combination with Chinese herbal medicine TwHF was comparable to ADA in combination with MTX on response rate, disease activity, and quality of life in patients with RA. TwHF could potentially serve as an alternative treatment option for RA patients who were not able to take MTX.

Rheumatoid arthritis is a chronic, progressive, systemic autoimmune disease that can occur at any age. Synovitis and joint structure destruction are its main pathogenic features, which can cause cartilage, bone damage, and disability.[23] While managing RA patients, the goal is to get the disease under control or make the status of RA less active. DMARDs are one of the first-line options. Within DMARDs, MTX is usually the first choice unless the patient presents severe adverse events. Aside from DMARDs, glucocorticoids could also be added. However, the use of these steroids should be reduced as soon as possible based on the patient's condition.[24] The latest 2022 EULAR guidelines suggest that for patients with RA who have an underreactor or intolerance to MTX, MTX should be reduced first, and other csDMARDs can be considered as part of the preferred treatment regimen.[25] As a part of traditional Chinese medicine in China, TwHF has the characteristics of anti-inflammatory, immune regulation, and alleviating clinical symptoms in the treatment of RA, and was believed to have the effect of increasing the efficacy and reducing the incidence of adverse reactions when combined with DMARDs, non-steroidal anti-inflammatory drugs and glucocorticoids.[26,27]

The effect of Traditional Chinese Medicine on rheumatic diseases has been long discussed.[28] The current study found that ADA combined with TwHF was effective in treating RA patients who did not respond well to MTX and that there were no significant differences in efficacy and safety in the treatment of ADA combined with TwHF and ADA combined with MTX. Previous studies have shown that TwHF monotherapy for RA is not less effective than MTX monotherapy and that the combination of TwHF and MTX is more effective than MTX alone.[29] Moreover, it was reported that TwHF in combination with ADA had greater efficacy and safety than ADA alone in the treatment for patients with RA and having low MTX response,[30] which was similar to the findings of the current study. At weeks 12 and 24, we report significant improvements in disease activity indicators in patients utilizing ADA combining TwHF treatment, including VAS, PtGA, PGA, SW-28, TEN-28, ESR, CRP, and HAQ-DI scores. As for other indicators including ACR20/50/70, DAS28-ESR, and DAS28-CRP, similar efficacy was observed in the ADA combining TwHF group and MTX group.

Triptolide extract can inhibit the proliferation of macrophages, T lymphocytes, and B lymphocytes. Through down-regulation of the expression of cyclooxygenase-2 (COX-2) genes, Triptolide was able to reduce the production of synovial fibroblast-like synoviocytes (FLS), consequently inhibiting the production of matrix metalloproteinase (MMP), which in turn plays a role in cartilage protection.[31] TwHF has been reported to inhibit the expression of pro-inflammatory cytokines such as interleukin-1, interleukin-2, interleukin-17, TNF-α, high-mobility group protein B1, cyclooxygenase and lipoxidase.[32] Several clinical trials and underlying trials have suggested that a significant decrease in ESR may be associated with the anti-inflammatory activity of TwHF.[33,34] At the beginning of treatment in this trial (at 2 weeks), the group in which ESR received TwHF and ADA showed a faster downward trend.

The safety assessment of this study showed that the overall incidence of adverse events in ADA plus TwHF therapy was not significantly higher than in ADA plus MTX therapy. No new adverse reaction events were observed in the current study. With the widespread use of bDMARDs in RA or other immune diseases around the world, cases of severe infections (including tuberculosis) and tumors have been reported, and no similar serious infections have occurred during the follow-up period of this study. The incidence of tuberculosis and hepatitis was high in China; hence before the use of bDMARDs, related works for the prevention and early detection of tuberculosis and hepatitis infection were necessary. In the current study, all enrolled patients were tested for tuberculosis antibodies, hepatitis markers, and other indicators to ensure participants were free from tuberculosis and hepatitis.

This study has several limitations. First of all, because this study is an open-label clinical trial, doctors and patients are aware of the situation of trial grouping, and it is difficult to achieve a double-blind design. To avoid the bias caused by subjective factors of study subjects and researchers to make the study more objective, future researchers can try to conduct double-blind randomized controlled trials. Secondly, since most of the patients enrolled in this study were postmenopausal women, adverse effects regarding the reproductive function were not observed. Third, in the current study, the scale of 64 patients, subdivided into 2 groups, is very few. Hence, the evidence power of the current study should be prudently considered. Considering that population-based databases offer potential real-world evidence through cross-sectional or cohort designs,[35,36] we believe that future studies involving larger populations, particularly in real-world settings, are warranted to validate the findings of our current study. Fourth, given that this study was based on the Chinese population, the generalizability of the results could not be demonstrated. Furthermore, due to the difficulty of trial implementation, the images of painful and swollen joints were not evaluated. Finally, this study only explored the efficacy and safety of ADA combined with TwHF therapy for RA. No further results were available at the cellular and molecular levels.

5 | CONCLUSIONS

Adalimumab combined with TwHF presented similar efficacy and safety as ADA combined with MTX. The use of TwHF could possibly serve as an alternative choice for patients who showed low response to MTX therapy or were not able to take MTX for RA treatment.

AUTHOR CONTRIBUTIONS

W-kM and X-mY conceived and designed the study. W-kM, JC-CW, X-mY, E-tJ, and S-YG provided valuable advice on research design and draft papers. W-kM, X-mY, FL, YW, H-IL, FT, QZ, YH, LH, Z-qL, J-lC, Y-pC, D-mL, YA, and W-yL recruited patients for this study and completed most of the recruitment work. W-kM, X-mY, FL, Y-xW, H-IL, FT, QZ, YH, LH, Z-qL, J-lC, Y-pC, D-mL, YA, W-yL, CL, and C-mC evaluated the participants and recorded their information. FL analyzed the data and drafted a paper. W-kM, JC-CW, and X-mY revised the paper. All authors read and approved the final manuscript.

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The Second Affiliated Hospital and research investigators of Guizhou University of Chinese Medicine are solely responsible for all data collection and management, statistical analysis, manuscript preparation, and decisions to publish these results. Bio-Thera Solutions, Co. Ltd provides the gretel (adalimumab injection) used in this study, which has no role in the collection, analysis, or interpretation of study designs or data, the preparation of manuscripts, or the decision to submit publications.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The analyzed dataset could be provided by the authors upon reasonable request.

ETHICS STATEMENT

The Ethics Committee of the Second Affiliated Hospital of Guizhou University of Chinese Medicine has discussed and passed the ethical review and agreed to the experimental protocol. The clinical trial number of this study is ChiCTR2100050865, which can be found at http://www.chictr.org.cn/ approved by the institutional ethical review board.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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