

A double-blind, double-dummy, randomized controlled, multicenter trial of ⁹⁹Tc-methylene diphosphonate in patients with moderate to severe rheumatoid arthritis

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Abstract

Background: Clinical observational studies revealed that ⁹⁹Tc-methylene diphosphonate (⁹⁹Tc-MDP) could reduce joint pain and swollenness in rheumatoid arthritis (RA) patients. This multicenter, randomized, double-blind, double-dummy study aimed to evaluate the effects of ⁹⁹Tc-MDP plus methotrexate (MTX) *vs.* MTX alone or ⁹⁹Tc-MDP alone on disease activity and structural damage in MTX-naïve Chinese patients with moderate to severe RA.

Methods: Eligible patients with moderate to severely active RA were randomized to receive ⁹⁹Tc-MDP plus MTX (*n* = 59) *vs.* MTX (*n* = 59) alone or ⁹⁹Tc-MDP (*n* = 59) alone for 48 weeks from six study sites across four provinces in China. The primary outcomes were the American College of Rheumatology 20% improvement (ACR20) response rates at week 24 and changes in modified total Sharp score at week 48.

Results: At week 24, the proportion of participants achieving ACR20 was significantly higher in the MTX + ⁹⁹Tc-MDP combination group (69.5%) than that in the MTX group (50.8%) or ⁹⁹Tc-MDP group (47.5%) (*P* = 0.03 for MTX + ⁹⁹Tc-MDP *vs.* MTX, and MTX + ⁹⁹Tc-MDP *vs.* ⁹⁹Tc-MDP, respectively). The participants in the MTX + ⁹⁹Tc-MDP group and the ⁹⁹Tc-MDP group had significantly less important radiographic progression than the participants in the MTX group over the 48 weeks (MTX + ⁹⁹Tc-MDP *vs.* MTX: *P* = 0.03, ⁹⁹Tc-MDP *vs.* MTX: *P* = 0.03, respectively). There was no significant difference in terms of adverse events (AEs) among the groups. No serious AEs were observed.

Conclusions: This study demonstrated that the combination of ⁹⁹Tc-MDP with MTX inhibited structural damage and improved disease activity in RA patients compared with MTX and ⁹⁹Tc-MDP monotherapies, without increasing the rate of AEs. Additional clinical studies of ⁹⁹Tc-MDP therapy in patients with RA are warranted.

Trial Registration: Chicttr.org, ChiCTR-IPR-14005684; <http://www.chicttr.org.cn/showproj.aspx?proj=10088>.

Keywords: Rheumatoid arthritis; Methotrexate; ⁹⁹Tc-MDP; Efficacy; Safety

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterized by synovial hyperplasia and joint damage, eventually leading to damage of articular cartilage and subchondral bone, joint destruction, and

substantial loss of function.^[1] In RA, the arthritis is typically bilateral and symmetrical. Involvement of the small joints of the hands is the most common initial

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presentation. Conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX), leflunomide, and sulfasalazine are generally used as a first-line treatment based on low costs and prominent efficacy in China.^[2] When patients fail to initial treatments, biologic (b) DMARDs and targeted synthesis DMARDs (such as Janus kinase [JAK] inhibitors) are usually considered.^[3-5] Although these drugs effectively control the disease activity of patients with RA, there is still a significant unmet need in the field of RA, especially for those at high risk of bone structural damage.

⁹⁹Tc-methylene diphosphonate (⁹⁹Tc-MDP), a chemical compound of technetium-99 conjugated with methylene diphosphonate (⁹⁹Tc-MDP), or Yunke, Chengdu Yunke Pharmaceutical Co., Ltd., Chengdu, Sichuan, China), is an anti-inflammatory and anti-bone destruction drug patented in China (patent No. ZL94113006.1), which has long been widely used and showed good efficacy for the treatment of RA and osteoporosis in China since 2000. Clinical observational studies revealed that ⁹⁹Tc-MDP could notably and quickly reduce joint pain and swollen-ness in RA patients.^[6] Previous studies found that ⁹⁹Tc-MDP could increase the proportion of $\gamma\delta$ T cells and CD4⁺ CD25⁺ Foxp3⁺ Tregs,^[7] leading to a decrease in rheumatoid factors (RF).^[8] Still, whether ⁹⁹Tc-MDP could act as a DMARD requires a randomized controlled clinical trial (RCT) for evaluation.

In the current study, we reported a multicenter, randomized, double-blind study to evaluate the efficacy of ⁹⁹Tc-MDP in RA treatment. We found that patients treated with the ⁹⁹Tc-MDP and MTX combination had a higher American College of Rheumatology 20% improvement (ACR20) response at 24 weeks and significantly lower radiographic progression at 48 weeks compared with patients treated with MTX monotherapy, suggesting that ⁹⁹Tc-MDP could help to alleviate disease activity and prevent bone damage in RA.

Methods

Ethical approval

The multicenter, randomized, double-blind, double-dummy study was conducted in accordance with the good clinical practice (GCP) guidelines and the *Declaration of Helsinki*. The ethical committees of Renji Hospital (The Medical Ethics Committee of Renji Hospital, Shanghai Jiaotong University School of Medicine, approval #Renji Lun Shen [2009]02) and all other participating centers approved the protocol. This study was registered in the Chinese Clinical Trial Registry (No. ChiCTR-IPR-14005684). Written informed consent was obtained from each participant before entering the study.

Participants

A total of 178 patients with moderate to severely active RA were recruited between September 2010 and March 2012 from six study sites across four provinces in China. The eligible patients were 18 to 80 years of age with RA for ≤ 3 years according to the revised 1987 American College of

Rheumatology criteria.^[8] Active RA was defined as having at least four swollen joints and six tender joints plus one of the following three criteria: morning stiffness ≥ 45 min, erythrocyte sedimentation rate (ESR) ≥ 28 mm/h, or C-reactive protein (CRP) ≥ 10 mg/L, the disease activity score of 28 joints counted by ESR (DAS28-ESR) had to be at least ≥ 3.2 . The participants of reproductive potential had to agree to use reliable contraception methods. All participants were newly diagnosed patients and MTX-naïve. If the participants were taking other DMARDs during screening, they had to stop taking them for at least 4 weeks before entering the trial. The doses of non-steroidal anti-inflammatory drugs and prednisone (≤ 10 mg daily) had to be stable for at least 4 weeks and had to remain the same during the trial.

The exclusion criteria were: (1) any serious illness of the heart, liver, kidney, blood, or other vital organs; (2) liver function tests equal to or greater than two times the upper limit of normal (ULN), serum creatinine greater than the ULN, white blood cell count (WBC) $< 4 \times 10^9/L$, hemoglobin < 85 g/L, or platelet count $< 80 \times 10^9/L$; (3) pregnant or breast-feeding women; (4) previous treatment with tumor necrosis factor (TNF) inhibitors or other biological agents; (5) joint injection of corticosteroids within 4 weeks; (6) any acute or chronic infection or history of active tuberculosis; (7) any tumor or a family tumor history; or (8) hepatitis B surface antigen positive, hepatitis C viral-antibody positive, or any history of viral hepatitis.

Sample size estimation

A sample size of 180 participants was estimated. With the assumption that 45% of participants would achieve ACR20 at week 24,^[9] a sample size of 60 participants per treatment group was calculated to be necessary for 90% power to reject the null hypothesis of no difference between the treatment groups with an α of 0.05.

Randomization and masking

Randomization was carried out by a biostatistician using the Proc Plan Procedure in SAS 9.2 (SAS Institute, Cary, NY, USA). The participants were randomly allocated 1:1:1 to receive ⁹⁹Tc-MDP plus MTX, MTX alone, or ⁹⁹Tc-MDP alone. The drug packages for each participant were identified and labeled with a unique code number, linked with the random allocation scheme. Participants, investigators, and monitors were all masked to treatment allocation.

Drug administration

The participants were randomized into three groups: the ⁹⁹Tc-MDP group (⁹⁹Tc-MDP + MTX dummy), the MTX group (MTX + ⁹⁹Tc-MDP dummy), and the combined treatment group (MTX + ⁹⁹Tc-MDP). MTX was initially given at 10 mg per week and incrementally increased to 15 mg per week in 4 weeks. ⁹⁹Tc-MDP (as well as the dummy drug) was applied as follows: for each course of treatment, ⁹⁹Tc-MDP 16.5 mg (5.5 mg \times three sets) was injected intravenously once a day for 7 successive days, one course every 4 weeks until week 8 (0, 4, and 8 weeks), followed by the extending course for every 8 weeks until

week 40 (16, 24, 32, and 40 weeks). Placebos for ^{99}Tc -MDP and MTX were both identical to their respective active drugs in appearance.

Endpoints and assessments

The primary endpoints were the proportion of participants with an ACR20 response at week 24 and the changes in the van der Heijde-modified total Sharp score (mTSS) at week 48. The secondary endpoints were the proportion of participants with ACR70 and ACR50 responses and the changes in DAS28-ESR at week 24.

Treatment failure was defined as not reaching the ACR20 response, premature withdrawal due to disease progression, or concomitant treatment with DMARDs other than MTX. DAS28-ESR was used to assess disease activity.

An independent radiologist assessed participants' radiographs of both hands and both feet. The mTSS of both hands and both feet were calculated to evaluate the changes in bone erosion and joint space narrowing.

The clinical variables recorded included swollen joint count, tender joint count, joint function, participant's visual analogue score (VAS) of pain, Health Assessment Questionnaire (HAQ), participant's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), and acute-phase proteins. Blood pressure, heart rate, temperature, and respiratory rate were examined at each visit. Laboratory examinations included complete blood count, urinalysis, occult blood, liver function test including alanine aminotransferase, aspartate transaminase, total bilirubin, renal function test (creatinine), ESR, CRP, RF, chest X-ray, radiographs of both hands and both feet (including wrists), electrocardiography, human chorionic gonadotropin (HCG) test for female participants, hepatitis B surface antigen, and hepatitis C viral-antibody tests.

Safety

The adverse events (AEs) were monitored and carefully followed by the investigators and recorded in detail regarding AEs, serious AEs, infections, withdrawals due to AEs, and clinically significant changes in vital signs and laboratory tests.

Quality control

The researchers at each center were trained and followed the GCP requirements. The clinical data were collected by the researchers in each center by filling in case report forms (CRFs). Monitors were appointed by the sponsor, and they verified that source documents and other trial records were accurate, complete, and kept up to date. They checked the accuracy and completeness of the CRF entries. The EpiData software (Centers for Disease Control, Atlanta, GA, USA) was used for data management. Double data entry by two independent individuals was used. If inconsistencies or logical errors were found, a query form was generated. The researcher verified the data and responded to the queries.

Statistical analysis

All analyses were performed using SAS 9.3 (SAS Institute). The primary endpoints were tested at a two-sided type I error rate of 5% with Bonferroni adjustment, which yielded an α of 0.0167. The significance level of all other tests was set at 0.05. The modified intention-to-treat and safety populations included all patients who received at least one dose of study medication. Missing values for efficacy variables were treated by the last observation carried forward method.

Data were expressed as means \pm standard deviations for continuous variables and total number (percentage) for categorical variables. The primary endpoint was analyzed with the Cochran-Mantel-Haenszel test of general association. Continuous variables were analyzed with one-way analysis of variance or Kruskal-Wallis test. The chi-squared test or Fisher exact test was used to compare categorical variables. Repeated measured continuous variables were analyzed with mixed-effect models. Safety was assessed using descriptive statistics.

Results

Characteristics of the participants

Finally, 180 patients were screened between September 2010 and March 2012, and 178 were enrolled in the trial (148 [83.1%] women and 30 [16.9%] men). The participants were randomized to receive either MTX and ^{99}Tc -MDP ($n = 59$), MTX ($n = 60$), or ^{99}Tc -MDP ($n = 59$) [Figure 1]. One patient in the MTX group was excluded due to not fulfilling the diagnostic criteria of active RA. Most participants completed the 48 weeks of treatment: 47 patients in the MTX plus ^{99}Tc -MDP group, 45 patients in the MTX group, and 46 patients in the ^{99}Tc -MDP group.

The general demographic and baseline characteristics are described in Table 1. There were no significant differences among the three groups in terms of disease duration, HAQ scores, tender or swollen joint count, glucocorticoid use, non-steroidal antiinflammatory drugs use, DAS28-ESR, and radiological staging. DAS 28-ESR of all participants was more than 5.1. Most participants had their disease staging from stage I to III.

Clinical efficacy

At week 24, the proportion of participants achieving ACR20 was significantly different: 69.5% in the MTX plus ^{99}Tc -MDP group, 50.8% in the MTX group, and 47.5% in the ^{99}Tc -MDP group (relative risk [RR] 1.36, 95% confidence interval [CI] 1.02–1.81 for MTX plus ^{99}Tc -MDP group *vs.* MTX group, and 1.50, 95% CI 1.10–2.03 for MTX plus ^{99}Tc -MDP group *vs.* ^{99}Tc -MDP group, $P = 0.0308$ and $P = 0.0084$, respectively) [Figure 2A]. The ACR20 response rate was not significantly different between the MTX and ^{99}Tc -MDP groups ($P = 0.69$). The ACR50 responses at week 24 were 35.6% for the MTX plus ^{99}Tc -MDP group compared with 33.9% for the MTX group (RR 1.08, 95% CI 0.68–1.71; $P = 0.7438$) and 11.9% for the ^{99}Tc -MDP group (RR 3.16, 95% CI 1.52–6.56; $P < 0.001$)

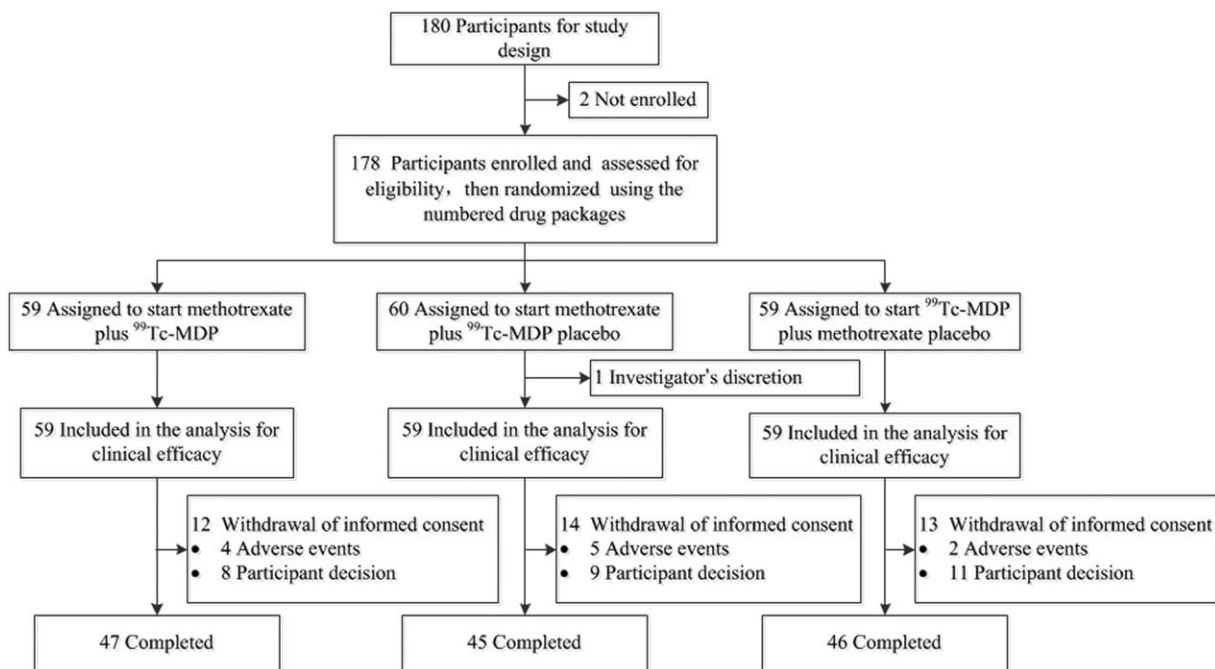


Figure 1: Flow chart showing the randomized distribution of the participants in the three groups: ⁹⁹Tc-MDP combined with MTX, MTX, and ⁹⁹Tc-MDP. ⁹⁹Tc-MDP: ⁹⁹Tc-methylene diphosphonate; MTX: Methotrexate.

Table 1: Demographic and baseline disease characteristics of the RA participants.

Demographic data at baseline	MTX + ⁹⁹ Tc-MDP (n = 59)	MTX (n = 59)	⁹⁹ Tc-MDP (n = 59)	P values
Female	51 (86.4)	48 (81.4)	49 (83.1)	NS
Age (years)	51.1 ± 9.0	50.9 ± 9.5	52.0 ± 8.5	NS
NSAIDs use	40 (67.8)	33 (55.9)	34 (57.6)	NS
Oral glucocorticoids use	18 (30.5)	16 (27.1)	19 (32.2)	NS
ESR (mm/h)	41.8 ± 25.9	42.6 ± 28.3	44.4 ± 25.1	NS
C reactive protein (mg/L)	17.15 ± 25.09	21.89 ± 28.64	26.09 ± 27.22	NS
RF (IU/mL)	211.36 ± 235.01	240.41 ± 323.83	361.93 ± 743.79	NS
Rest pain (VAS, cm)	6.7 ± 1.4	6.6 ± 1.6	7.1 ± 1.7	NS
Morning stiffness (min)	105.6 ± 65.6	102.9 ± 76.2	122.4 ± 84.4	NS
Physical function (HAQ)	1.4 ± 0.7	1.2 ± 0.6	1.4 ± 0.6	NS
Swollen joints count	11.0 ± 5.1	10.7 ± 5.5	11.6 ± 5.3	NS
Tender joints count	14.0 ± 5.6	13.1 ± 6.3	14.8 ± 5.8	NS
Patient's global assessment (VAS, cm)	6.8 ± 1.4	6.4 ± 1.6	7.1 ± 1.5	NS
Physician's global assessment (VAS, cm)	6.6 ± 1.5	6.2 ± 1.6	6.8 ± 1.5	NS
DAS28-ESR	5.5 ± 0.8	5.4 ± 1.0	5.6 ± 1.0	NS
Stages of RA				
Stage I	11 (18.6)	15 (25.4)	13 (22.0)	NS
Stage II	32 (54.2)	30 (50.9)	29 (49.2)	NS
Stage III	16 (27.1)	13 (22.0)	17 (28.8)	NS
Stage IV	0	1 (1.7)	0	NS

Data are presented as mean ± SD or n (%). ⁹⁹Tc-MDP: ⁹⁹Tc-methylene diphosphonate; DAS 28: Disease activity score for 28 joints; ESR: Erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; MTX: Methotrexate; NSAIDs: Non-steroidal antiinflammatory drugs; NS: Not significant; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SD: Standard deviation; VAS: Visual analogue score.

[Figure 2B]. At week 24, 20.3% of the participants in the MTX plus ⁹⁹Tc-MDP group achieved an ACR70 response compared to 11.9% in the MTX group and 6.8% in the ⁹⁹Tc-MDP group (RR 3.24, 95% CI 1.20–8.78 for MTX plus ⁹⁹Tc-MDP group *vs.* ⁹⁹Tc-MDP group; *P* = 0.01; no significant difference in others) [Figure 2C].

As shown in Figure 2A, before week 24, the MTX plus ⁹⁹Tc-MDP group showed a quicker ACR20 response compared with the MTX group (35.5% *vs.* 22.0% at week 4, 54.2% *vs.* 40.7% at week 8, 62.7% *vs.* 49.2% at week 16, and 69.5% *vs.* 50.9% at week 24). Similar results were found in ACR70 showed in Figure 2C (6.8% *vs.* 0% at week 4, 15.3% *vs.*

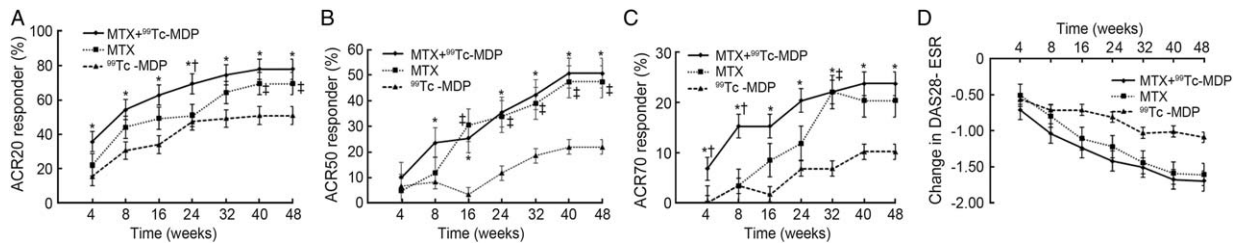


Figure 2: ACR20/50/70 response rates and changes in DAS28[ESR] in the participants. (A) ACR20 at weeks 24 and 48. (B) ACR50 at weeks 24 and 48. (C) ACR70 at weeks 24 and 48. (D) Mean changes in DAS28[ESR] at week 48. **P* < 0.05, MTX + ⁹⁹Tc-MDP group vs. ⁹⁹Tc-MDP group; †*P* < 0.05, MTX + ⁹⁹Tc-MDP group vs. MTX group; ‡*P* < 0.05, MTX group vs. ⁹⁹Tc-MDP group. ⁹⁹Tc-MDP: ⁹⁹Tc-methylene diphosphonate; ACR: American College of Rheumatology; ESR: Erythrocyte sedimentation rate; MTX: Methotrexate.

3.4% at week 8, 15.3% vs. 6.8% at week 16, and 20.3% vs. 11.9% at week 24). ⁹⁹Tc-MDP combined with MTX for RA was superior to MTX in ACR20 response rates [Figure 2A]. During the extended therapy, the ACR20 response rates continued to level off without obviously improving the ⁹⁹Tc-MDP group [Figure 2A]. Still, the ⁹⁹Tc-MDP combined with the MTX group tended to be superior to the MTX and ⁹⁹Tc-MDP groups in ACR20, ACR50, and ACR70 response rates [Figure 2A–C] until week 48, although the differences were not significant.

As shown in Table 1, the participants in all three groups had a high degree of disease activity at baseline, as measured by DAS28-ESR. Figure 2D shows the time course of the mean changes in DAS28-ESR among the three groups. The DAS28-ESR scores continued to improve during treatment, showing a conspicuous decrease in the MTX plus ⁹⁹Tc-MDP and MTX groups.

Imaging outcomes

The cumulative percentage of change in the mTSS score was significantly lower in the MTX plus ⁹⁹Tc-MDP and ⁹⁹Tc-MDP groups than that in the MTX group [Figure 3]. The radiographic scores at baseline and changes from baseline to week 48 are shown in Figure 4. The baseline mTSS scores were not significantly different among the treatment groups in the study, with lower mTSS in the MTX group.

There was a significantly greater proportion of participants in the MTX plus ⁹⁹Tc-MDP group (72.2%) and the ⁹⁹Tc-MDP group (60.0%) that did not have an increase in the total Sharp score (ie, change from baseline to week 48 was less than 0), compared with the participants in the MTX monotherapy group (36.4%) (MTX vs. MTX plus ⁹⁹Tc-MDP or ⁹⁹Tc-MDP, both *P* < 0.01); the difference between these percentages in the combination group and the ⁹⁹Tc-MDP group was not statistically significant [Figure 4A].

The participants in the MTX plus ⁹⁹Tc-MDP group and the ⁹⁹Tc-MDP group had significantly less radiographic progression than the participants in the MTX group over the 48 weeks (MTX + ⁹⁹Tc-MDP vs. MTX: *P* = 0.03, ⁹⁹Tc-MDP vs. MTX: *P* = 0.03, respectively) [Figure 4B]. No differences in the scores for participants in the combination group and the ⁹⁹Tc-MDP group were observed. The changes in total scores in the MTX group were mainly due

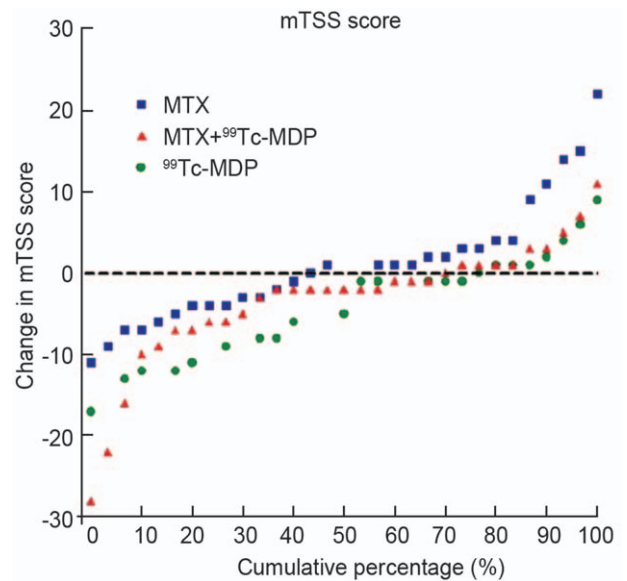


Figure 3: Cumulative percentage of radiographic progression. The changes in mTSS score were obvious in the MTX + ⁹⁹Tc-MDP group and ⁹⁹Tc-MDP alone group compared with the MTX alone group. ⁹⁹Tc-MDP: ⁹⁹Tc-methylene diphosphonate; MTX: Methotrexate; mTSS: Modified total Sharp score.

to increases in the joint space narrowing score, which was less prominent in the combination group and ⁹⁹Tc-MDP group. Meanwhile, there were notable decreases in the erosion scores in the ⁹⁹Tc-MDP group and MTX + ⁹⁹Tc-MDP group compared with that in the MTX group, suggesting a potential bone-repair effect of ⁹⁹Tc-MDP, either alone or in combination with other DMARD [Figures 4C and 4D].

Safety

No serious AEs were observed during the study. There were no significant differences in AEs among the three groups (all *P* > 0.05) [Table 2]. Eleven participants withdrew from the study due to AEs, including four (6.8%) in the MTX plus ⁹⁹Tc-MDP group, five (8.5%) in the MTX group, and two (3.4%) in the ⁹⁹Tc-MDP group. The most common AEs were decreased WBC and elevated liver enzymes in the three groups. WBC decrease occurred in two (3.4%) of the 59 participants in the MTX plus ⁹⁹Tc-MDP group, five (8.5%) of the 59 participants in the MTX group, and one (1.7%) of the 59 participants

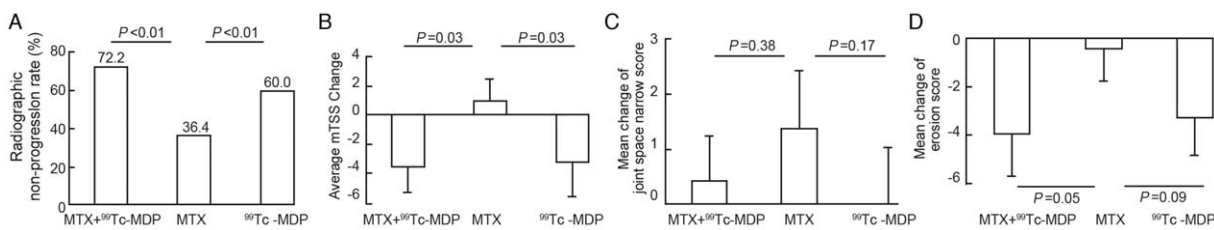


Figure 4: Radiographic changes of RA for the three treatment strategies. (A) Radiographic non-progression. (B) Mean changes in mTSS. (C) The mean changes in the joint space narrowing score at 48 weeks. (D) The mean change in the mTSS score at 48 weeks. mTSS: Modified total Sharp score; RA: Rheumatoid arthritis.

Table 2: Incidence of AEs during the entire treatment period through to week 48.

Items	⁹⁹ Tc-MDP + MTX (n = 59)	Placebo + MTX (n = 59)	Placebo + ⁹⁹ Tc-MDP (n = 59)
Any adverse event	16 (27.1)	24 (40.7)	13 (22.0)
Related AEs	7 (11.9)	15 (25.4)	8 (13.6)
Serious AEs	0	0	0
AEs leading to withdrawal	4 (6.8)	5 (8.5)	2 (3.4)
Infections and infestations (total)			
Upper respiratory tract infection	1 (1.7)	3 (5.1)	2 (3.4)
Urinary tract infection	3 (5.1)	2 (3.4)	0
Interstitial pneumonia with infectious tuberculosis	1 (1.7)	0	0
Pulmonary infection	0	0	1 (1.7)
Pulmonary tuberculosis	1 (1.7)	0	0
Oral ulcer	0	0	1 (1.7)
Labial numbness	0	0	2 (3.4)
Phlebitis	1 (1.7)	0	0
Biliary pancreatitis	0	1 (1.7)	0
Fever	0	5 (8.5)	0
Leukocytopenia (WBC decrease)	2 (3.4)	5 (8.5)	1 (1.7)
Anemia	1 (1.7)	0	3 (5.1)
Gastrointestinal disorders (total)			
Nausea	1 (1.7)	0	1 (1.7)
Elevated liver enzymes	1 (1.7)	5 (8.5)	2 (3.4)
Nervous system disorders (total)			
Chest tightness and palpitation	1 (1.7)	0	0
Dizziness	2 (3.4)	1 (1.7)	0
Leg cramps	0	1 (1.7)	0
Arrhythmia	1 (1.7)	0	0
Hemoptysis	0	1 (1.7)	0

Data are presented as n (%). ⁹⁹Tc-MDP: ⁹⁹Tc-methylene diphosphonate; AEs: Adverse events; MTX: Methotrexate; WBC: White blood cell.

in the ⁹⁹Tc-MDP group. Elevation of liver enzymes occurred in one (1.7%) of the 59 participants in the MTX plus ⁹⁹Tc-MDP group, five (8.5%) of the 59 participants in the MTX group, and two (3.4%) of the 59 participants in the ⁹⁹Tc-MDP group. Dizziness and urinary tract infection were numerically more frequent in the MTX plus ⁹⁹Tc-MDP group (two of 59 participants, 3.4%; three of 59 participants, 5.1%, respectively) and MTX group (one of 59 participants, 1.7%; two of 59 participants, 3.4%, respectively). Besides, only participants in the MTX group showed fever (five of 59 participants, 8.5%), biliary pancreatitis (one of 59 participants, 1.7%), leg cramps (one of 59 participants, 1.7%), and hemoptysis (one of 59 participants, 1.7%) during the study, but resolving later.

Discussion

Bone destruction is a central feature of RA.^[10] Increased osteoclast activity contributes to local bone remodeling and systemic abnormalities, including bone erosions and focal and systemic osteoporosis.^[11] Several clinical studies have shown that the combinations of MTX plus several bDMARDs (adalimumab, certolizumab, etanercept, and infliximab) were associated with a significant radiographic reduction progression compared to MTX monotherapy, mostly due to the anti-inflammatory property of the drugs.^[12,13] In the present RCT, ⁹⁹Tc-MDP could slow down RA patients' radiographic progression. The participants in the MTX plus ⁹⁹Tc-MDP group and ⁹⁹Tc-MDP monotherapy group had significantly smaller

changes in mTSS compared with those in the MTX monotherapy group. Besides, a significantly greater proportion of participants in the MTX plus ^{99}Tc -MDP combination group and ^{99}Tc -MDP monotherapy group did not have an increase in mTSS score over 48 weeks. The bone protective role of ^{99}Tc -MDP is probably, at least in part, due to its chemical structure as technetium-99 conjugated with methylene diphosphonate. Therefore, it has potential anti-resorptive effects as a bisphosphonate derivative to target osteoclasts, slow down bone turnover, and prevent bone resorption. An *in vitro* study revealed that ^{99}Tc -MDP could suppress the expression of bone destruction factors, such as TNF- α , and inhibit the viability and differentiation of osteoclasts.^[14] When ^{99}Tc -MDP enters the joint cavity and reaches an area of synovitis or abnormal bone, it binds to immature collagen or is absorbed by hydroxyapatite crystals, thereby persisting and exerting a long-lasting therapeutic effect.^[15] In animal models of RA, ^{99}Tc -MDP was shown to promote bone repair and increase joint space.^[16] A previous clinical trial also found that short-term treatment of ^{99}Tc -MDP could significantly suppress serum markers of the bone turnover biomarkers Dickkopf-related protein 1 and tartrate-resistant acid phosphatase in RA patients.^[6] The present study results proved that ^{99}Tc -MDP has significant effects on preventing and slowing down the bone destruction process in RA patients.

In the study, we also found that ^{99}Tc -MDP combined with MTX could improve disease activity in RA. The MTX plus ^{99}Tc -MDP combination group showed a quicker ACR response than MTX monotherapy in the first 16 weeks. At week 24, the ACR20 response rate was significantly higher in MTX plus ^{99}Tc -MDP combination group than in the MTX and ^{99}Tc -MDP monotherapy groups. At the end of week 48, although there was a trend toward higher ACR20 and ACR70 in the MTX plus ^{99}Tc -MDP combination group than in the MTX monotherapy group, the difference did not reach statistical significance. The results suggested that ^{99}Tc -MDP should have some clinical benefits in reducing disease activity in RA patients, especially in combination with MTX. The reason why it did not show persistent clinical efficacy was probably due to the treatment regimen during the clinical trial. According to the treatment protocol, ^{99}Tc -MDP was given once a month for three times, then tapered to once every 2 months in the extended course. Therefore, the dosage of ^{99}Tc -MDP was decreased starting on week 16, probably leading to the observation that ACR20 in the ^{99}Tc -MDP group and the combination group seemed to reach a plateau starting on week 24.

Preliminary clinical trials also suggested that ^{99}Tc -MDP had anti-inflammatory and immune modulation properties. A previous report indicated that ^{99}Tc -MDP could increase the frequency of both $\gamma\delta\text{T}$ cells and $\text{CD4}^+\text{CD25}^+\text{Foxp3}^+$ Tregs in the peripheral blood of active RA patients, paralleled with decreased serum levels of TNF- α and interleukin (IL)-6 and increased levels of serum transforming growth factor- β .^[17] ^{99}Tc -MDP also has been reported to inhibit the mitogen-activated protein kinase signaling pathway, thus reducing the production of TNF- α , IL-1 β , and IL-6 by macrophages.^[18] Given that

bisphosphonate agents and receptor activator of nuclear factor- κ B ligand (RANKL) inhibitor denosumab only regulate bone metabolism with no effect on disease activity,^[19,20] ^{99}Tc -MDP has a broader impact in RA treatment. It has anti-inflammatory properties, controlling disease activity, and anti-bone resorption properties, preventing structural damage. ^{99}Tc might contribute to the clinical effects upon that of methylene diphosphonate, but the exact mechanism is yet to be elucidated.

The present study also suggested that ^{99}Tc -MDP had a good safety profile. There were no SAEs in the trial. Most of the AEs were mild and reversible. ^{99}Tc -MDP did not increase the AEs compared to MTX treatment. In a real-world experience, ^{99}Tc -MDP is not associated with any serious side effects and has been safely used in China for two decades.

This trial has limitations. Only Chinese patients with moderately to severely active RA were enrolled, limiting the generalizability of the results. It is unknown whether ^{99}Tc -MDP with MTX could benefit patients with milder or early RA.

In conclusion, this study's results demonstrated that the combination ^{99}Tc -MDP with MTX inhibited structural damage and improved disease activity in RA patients compared with MTX and ^{99}Tc -MDP monotherapies, without increasing the rate of AEs. Future clinical studies are needed to optimize the dosage and course of ^{99}Tc -MDP therapy in patients with an early and advanced stage of RA.

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Conflicts of interest

None.

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