

Original Article

Efficacy, adverse drug reactions, and symptom relief from different doses of tofacitinib combined with methotrexate for rheumatoid arthritis

Li Zhang¹, Haili Shen²

¹Department of Rheumatology, The Second Hospital of Lanzhou University, Lanzhou 730000, Gansu, China; ²The Second Clinical Medical College, Lanzhou University, Lanzhou 730000, Gansu, China

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Abstract: Objective: To evaluate the efficacy of tofacitinib (TOF) at different doses combined with methotrexate (MTX) in patients with rheumatoid arthritis (RA) and their effects on adverse drug reactions (ADRs) and symptom relief. Methods: The study enrolled 123 patients with RA treated at the Second Hospital of Lanzhou University (February 2023 to February 2026), divided by TOF dose into a low-dose group (5 mg/day, n=60) and a high-dose group (10 mg/day, n=63). Outcomes compared between the two groups included treatment efficacy; adverse drug reactions (ADRs) (transient hepatic dysfunction, leukopenia, upper respiratory infection, nausea/vomiting, rash, and diarrhea); symptom relief (tender joint count (TJC), swollen joint count (SJC), and morning stiffness duration); pain (Visual Analogue Scale (VAS)); disease activity (Disease Activity Score 28 (DAS28)); inflammatory markers (interleukin (IL)-6, IL-17, and interferon (IFN)- γ); bone turnover markers (osteocalcin (BGP) and procollagen type 1 N-terminal propeptide (PINP)); other laboratory indices (erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and C-reactive protein (CRP)); and quality of life (36-Item Short Form Health Survey (SF-36)). Finally, this study stratified patients by baseline DAS28 and inflammatory and bone turnover markers for subgroup analysis. Results: The high-dose group showed superior efficacy to the low-dose group ($P=0.045$) and a comparable ADR rate ($P>0.05$), with lower post-treatment TJC, SJC, morning stiffness duration, VAS, DAS28, IL-6, IL-17, IFN- γ , ESR, RF, and CRP (all $P<0.05$) and higher post-treatment BGP, PINP, and SF-36 scores (all $P<0.05$). In addition, no significant interaction was observed between the treatment groups and baseline DAS28, inflammatory markers, or bone turnover markers. Conclusion: High-dose TOF + MTX was highly effective in treating RA, providing effective symptom relief without significantly increasing ADRs; moreover, the effect may not be significantly affected by baseline disease activity, inflammation level, or bone turnover status.

Keywords: Tofacitinib, methotrexate, rheumatoid arthritis, curative effect, adverse drug reactions, symptom relief

Introduction

Rheumatoid arthritis (RA), an autoimmune disease featuring chronic inflammation, poses a serious threat to patient health, especially in women [1]. The disease typically manifests as joint tenderness, swelling, and morning stiffness, and its age-standardized prevalence and incidence are rising worldwide [2]. In addition to impairing joint function, RA causes various extra-articular complications, which damage patients' quality of life (QoL), impair social and occupational function, and may even shorten lifespan [3]. Known risk factors include genetic inheritance, environmental factors, and expo-

sure to second-hand smoke in adolescence; these increase the likelihood of developing RA and add to the economic burden on patients and their families [4]. RA arises from highly inflammatory autoimmune synovitis. Early targeted treatment is therefore critical for preventing disease progression and irreversible functional loss [5]. The main treatment options for RA include conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), and biologic DMARDs (bDMARDs). Although these treatments are effective, they must be tailored to individual patients to further improve efficacy and reduce side effects [6, 7].

Methotrexate (MTX), a csDMARD, has anti-inflammatory and immunomodulatory effects [8]. In a RA mouse model, it exerted anti-RA activity by inhibiting osteoclast formation and reducing bone loss, effects that may be mediated through enhanced interactions between adenosine A2A receptors (A2AR) and interferon (IFN)- γ receptor (IFN- γ R), as well as activation of the IFN- γ R/signal transducer and activator of transcription 1 (STAT1) signaling cascade [9]. A randomized controlled trial pointed out that MTX combined with other therapies demonstrated greater clinical advantage in enhancing efficacy, ameliorating symptoms, and improving QoL than MTX monotherapy [10]. Tofacitinib (TOF), a tsDMARD and a Janus kinase (JAK) inhibitor, is also a first-line DMARD for RA, as is MTX [11]. TOF has been reported to yield significantly higher American College of Rheumatology (ACR) 20/50/70 response rates than adalimumab in RA management, suggesting its high clinical efficacy and the ability to achieve deep remission [12]. Another double-blind, head-to-head, randomised controlled trial showed that TOF + MTX was superior to adalimumab + MTX for RA patients with an inadequate response to MTX, with no new or unexpected safety concerns within one year, supporting the efficacy and safety of the combination [13].

Given the limited data on TOF at different doses combined with MTX in RA management, this study compared the two dose regimens to determine whether high-dose TOF plus MTX is more effective, aiming to provide a more effective treatment option for RA patients.

Materials and methods

Baseline information

This study enrolled 123 patients with RA who received treatment at The Second Hospital of Lanzhou University over a three-year period (February 2023 to February 2026). Allocation was based on the TOF dose administered, yielding a low-dose group (5 mg/day, n=60) and a high-dose group (10 mg/day, n=63). The two groups were clinically comparable, with well-balanced baseline data ($P>0.05$). This study was approved by the Ethics Committee of The Second Hospital of Lanzhou University.

Case selection criteria

Inclusion criteria: met the diagnostic criteria for RA [14]; received first-line treatment; had taken no antirheumatic drugs within the past year; had normal communication and cognitive abilities; showed good adherence to treatment and medication; and had complete clinical data.

Exclusion criteria: hematological diseases or autoimmune deficiency; pregnancy or lactation; plans for conception (in either sex); tuberculosis, hepatitis B, or duodenal ulcer; allergy to the study drugs; active gastrointestinal disease; malignancy; severe cardiac, pulmonary, or renal dysfunction; or coagulation dysfunction.

Treatment methods

Patients in the low-dose group received low-dose TOF (5 mg once daily) and MTX (10 mg once weekly).

Patients in the high-dose group received high-dose TOF plus MTX. TOF was administered at 5 mg twice daily, and MTX was given at the same dose and frequency as in the low-dose group (10 mg once weekly).

Both groups were treated for three months.

Outcome measures

Efficacy. Treatment was considered markedly effective if it produced significant improvement in clinical symptoms (joint swelling, tenderness, morning stiffness, etc.) compared to baseline and a clear improvement in activities of daily living. It was considered effective if there was some alleviation of clinical symptoms and partial recovery of daily living function. Cases that met neither criterion were judged ineffective. The total effective rate (%) was calculated as the number of markedly effective and effective patients divided by the total number of patients.

Adverse drug reactions (ADRs). Post-treatment occurrences of transient hepatic dysfunction, leukopenia, upper respiratory infection, nausea/vomiting, rash, and diarrhea were recorded in both groups, and the incidence rate was calculated.

Symptom relief. Symptom relief was assessed by recording and comparing the tender joint count (TJC), swollen joint count (SJC), and morning stiffness duration before and after treatment.

Pain perception. Pain was evaluated using the Visual Analogue Scale (VAS) [15], a 0-10 scale (0 = none, 10 = intense and unbearable pain), with higher scores indicating greater pain.

Disease activity. Disease activity was assessed before and after treatment using the Disease Activity Score 28 (DAS28) [16] according to the following criteria: <2.6, remission; 2.6-3.2, low disease activity; >3.2-5.1, moderate disease activity; and >5.1, high disease activity.

Inflammatory markers. Venous blood (5 mL) was collected by venipuncture from all patients in the early morning after fasting, both before and after treatment. After serum isolation by centrifugation, enzyme-linked immunosorbent assays (ELISAs) were used to measure serum levels of interleukin (IL)-6, IL-17, and IFN- γ . All tests strictly followed the instructions of the corresponding human ELISA kits (Abbkine (Wuhan) Biotechnology Co., Ltd., KTE6017-1, KTE6022-1, KTE6011-1).

Bone turnover markers (BTMs). Serum osteocalcin (BGP) and procollagen type 1 N-terminal propeptide (PINP) were measured before and after treatment using an automatic biochemical analyzer and human chemiluminescence immunoassay test kits (Shanghai Caiyou Industrial Co., Ltd., CL06709, CL02283). The kit instructions were followed throughout.

Other laboratory indices. The erythrocyte sedimentation rate (ESR) was measured before and after treatment using an automatic ESR analyzer without reagent kits. Rheumatoid factor (RF) and C-reactive protein (CRP) were also quantified before and after treatment using an automatic biochemical analyzer and human latex-enhanced immunoturbidimetric assay kits. All tests were performed in strict accordance with the corresponding kit instructions (Shanghai Huzhen Industrial Co., Ltd., hz-E035, hz-E023).

QoL. Patients' quality of life was assessed using the 36-Item Short Form Health Survey

(SF-36) [17] before and 3 months after treatment. The survey covered four domains (physical, psychological, and social functioning, and mental health), each scored on a 100-point scale, with higher scores indicating better QoL.

Statistical analysis

Measured data were expressed as mean $\pm$ standard deviation (SD); between-group differences were assessed by independent-samples t-tests, and pre- and post-treatment differences by paired t-tests. Counted data were presented as counts/percentages (n/%), and between-group comparisons were performed using the χ^2 test. In the subgroup analysis, binary logistic regression with interaction terms was used. In this model, baseline DAS28, inflammatory markers, and BTMs were set as continuous variables and multiplied by the treatment groups to obtain interaction terms for inclusion in the analysis. Data were analyzed with SPSS 22.0. A *P* value <0.05 was considered significant.

Results

Baseline data analysis

The low- and high-dose groups exhibited no significant differences in sex, age, disease course, body mass index (BMI), joint function classification, hypertension, diabetes, or educational level (all *P*>0.05; **Table 1**).

Efficacy comparison

In the low-dose group, 18, 27, and 15 patients showed markedly effective, effective, and ineffective outcomes, respectively. The corresponding numbers in the high-dose group were 31, 25, and 7. Overall efficacy was significantly higher in the high-dose group than in the low-dose group (*P*=0.045; **Table 2**).

ADRs in two groups

The low-dose group had 2, 1, 1, 2, 1, and 3 cases of transient hepatic dysfunction, leukopenia, upper respiratory infection, nausea/vomiting, rash, and diarrhea, respectively, and the high-dose group had 3, 1, 3, 2, 2, and 3 cases. The total ADR rate was comparable between the two groups (*P*>0.05; **Table 3**).

Table 1. General patient information

Indicator	Low-dose group (n=60)	High-dose group (n=63)	$\chi^2/Z/t$	P
Sex			0.356	0.551
Male	27 (45.00)	25 (39.68)		
Female	33 (55.00)	38 (60.32)		
Age (years)	47.22±6.51	47.71±7.76	0.378	0.706
Disease course (years)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	-0.278	0.781
Body mass index (kg/m ²)	23.07±2.14	22.90±2.53	0.401	0.689
Joint function classification			0.330	0.848
II	15 (25.00)	17 (26.98)		
III	28 (46.67)	31 (49.21)		
IV	17 (28.33)	15 (23.81)		
Comorbid hypertension			1.351	0.245
No	28 (46.67)	36 (57.14)		
Yes	32 (53.33)	27 (42.86)		
Comorbid diabetes			0.238	0.626
No	35 (58.33)	34 (53.97)		
Yes	25 (41.67)	29 (46.03)		
Educational level			3.936	0.140
Primary school or below	12 (20.00)	5 (7.94)		
Secondary school	26 (43.33)	29 (46.03)		
University degree or above	22 (36.67)	29 (46.03)		

Table 2. Curative effect comparison

Indicator	Low-dose group (n=60)	High-dose group (n=63)	χ^2	P
Markedly effective	18 (30.00)	31 (49.21)		
Effective	27 (45.00)	25 (39.68)		
Ineffective	15 (25.00)	7 (11.11)		
Overall efficacy	45 (75.00)	56 (88.89)	4.036	0.045

Table 3. Adverse drug reactions in the two groups

Indicator	Low-dose group (n=60)	High-dose group (n=63)	χ^2	P
Transient hepatic dysfunction	2 (3.33)	3 (4.76)		
Leukopenia	1 (1.67)	1 (1.59)		
Upper respiratory infection	1 (1.67)	3 (4.76)		
Nausea/vomiting	2 (3.33)	2 (3.17)		
Rash	1 (1.67)	2 (3.17)		
Diarrhea	3 (5.00)	3 (4.76)		
Total	10 (16.67)	14 (22.22)	0.604	0.437

Comparative symptom relief evaluation

As shown in **Figure 1**, the two groups were comparable in pre-treatment TJC, SJC, and morning stiffness duration (all $P>0.05$). Both groups showed significant reductions in these indices after treatment (all $P<0.01$), and the high-dose group had better post-treatment outcomes than the low-dose group (all $P<0.05$).

VAS and DAS28 scores in two groups

As shown in **Figure 2**, baseline VAS and DAS28 scores were comparable between the two groups (both $P>0.05$) and decreased significantly after treatment in both groups (both $P<0.01$). Post-treatment scores were markedly lower in the high-dose group than in the low-dose group (both $P<0.05$).

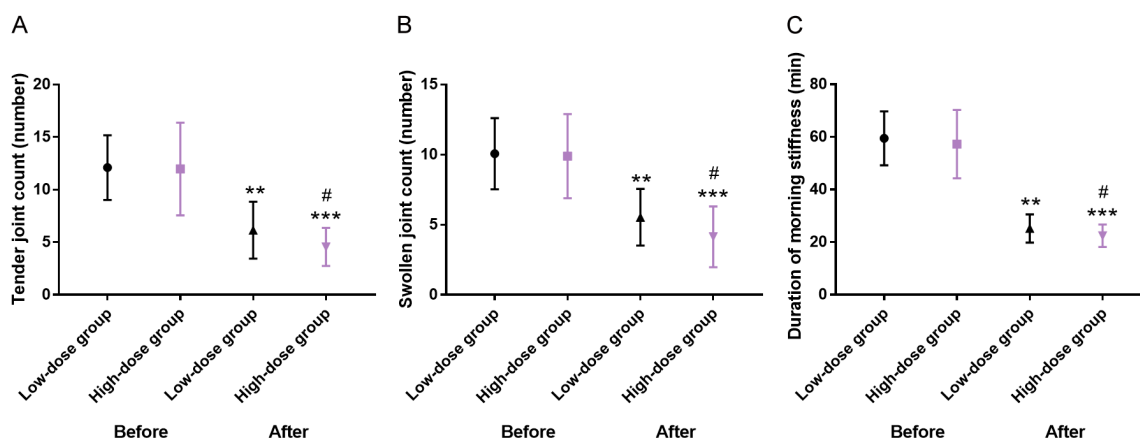


Figure 1. Symptom relief in two groups. A. Tender joint count in low- (n=60) and high-dose (n=63) groups before and after treatment. B. Swollen joint count in low-dose group (n=60) and high-dose group (n=63) before and after treatment. C. Morning stiffness duration before and after treatment in low-dose group (n=60) and high-dose group (n=63). Note: **P<0.01, ***P<0.001, vs. the pre-treatment level within the group; #P<0.05 vs. low-dose group at the same time point.

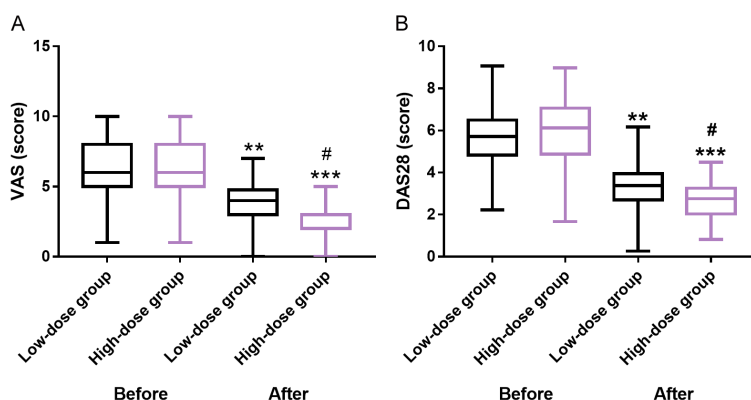


Figure 2. VAS and DAS28 scores of two groups. A. Pre- and post-treatment VAS scores in low-dose (n=60) and high-dose (n=63) groups. B. DAS28 score variations in low-dose group (n=60) and high-dose group (n=63). Note: VAS, Visual Analogue Scale; DAS28, Disease Activity Score 28. **P<0.01, ***P<0.001, vs. the pre-treatment level within the group; #P<0.05 vs. low-dose group at the same time point.

P>0.05). Both BTMs increased after treatment in both groups, and post-treatment levels were higher in the high-dose group than in the low-dose group (all P<0.05; Table 4).

Other laboratory indices in two groups

The two groups exhibited similar baseline levels of ESR, RF, and CRP (all P>0.05). Both groups showed reductions in these indices after treatment, with lower post-treatment levels in the high-dose group than in the low-dose group (all P<0.05; Table 5).

Comparative evaluation of inflammatory markers

As shown in Figure 3, there were no significant differences in baseline IL-6, IL-17, or IFN- γ levels between the two groups (all P>0.05). All three markers decreased significantly after treatment in both groups (all P<0.01), with lower post-treatment levels in the high-dose group than in the low-dose group (all P<0.05).

BTMs in two groups

At baseline, the low- and high-dose groups did not differ significantly in BGP or PINP (both

QoL

There were no significant inter-group differences in pre-treatment QoL domain scores (physical, psychological, and social functioning, and mental health; all P>0.05). After treatment, all domain scores increased in both groups, and the high-dose group had higher scores in all domains than the low-dose group (all P<0.05; Table 6).

Subgroup analysis based on baseline DAS28, inflammatory markers, and BTMs

To further clarify RA populations most likely to benefit from high-dose TOF therapy, we sepa-

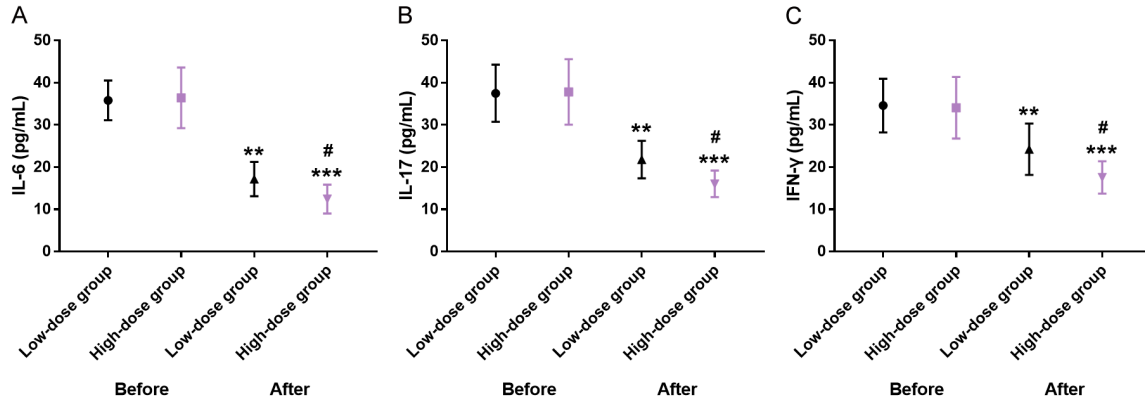


Figure 3. Comparative evaluation of inflammatory markers. A. Pre- and post-treatment IL-6 levels in low-dose (n=60) and high-dose (n=63) groups. B. Pre- and post-treatment IL-17 levels in low-dose (n=60) and high-dose (n=63) groups. C. IFN- γ in low-dose (n=60) and high-dose (n=63) groups before and after treatment. Note: IL-6/17, interleukin-6/17; IFN- γ , interferon γ . **P<0.01, ***P<0.001, vs. the pre-treatment level within the group; #P<0.05 vs. low-dose group at the same time point.

Table 4. Bone turnover markers in the two groups

Indicator	Low-dose group (n=60)	High-dose group (n=63)	t	P
BGP ($\mu\text{g/L}$)				
Pre-treatment	19.33 $\pm$ 4.73	19.30 $\pm$ 5.12	0.034	0.973
Post-treatment	23.32 $\pm$ 5.82	28.27 $\pm$ 5.44	4.875	<0.001
PINP ($\mu\text{g/L}$)				
Pre-treatment	76.10 $\pm$ 13.14	78.25 $\pm$ 16.73	0.790	0.431
Post-treatment	83.68 $\pm$ 15.98	90.59 $\pm$ 17.56	2.279	0.024

Note: BGP, osteocalcin; PINP, procollagen type 1 N-terminal propeptide.

Table 5. Other laboratory indices in the two groups

Indicator	Low-dose group (n=60)	High-dose group (n=63)	t	P
ESR (mm/h)				
Pre-treatment	79.75 $\pm$ 11.85	79.81 $\pm$ 12.35	0.027	0.978
Post-treatment	39.37 $\pm$ 13.47	34.68 $\pm$ 10.41	2.167	0.032
RF (U/mL)				
Pre-treatment	202.38 $\pm$ 29.29	200.46 $\pm$ 26.36	0.394	0.694
Post-treatment	166.78 $\pm$ 17.16	140.11 $\pm$ 13.29	9.663	<0.001
CRP (mg/L)				
Pre-treatment	14.45 $\pm$ 3.52	14.10 $\pm$ 3.13	0.583	0.561
Post-treatment	11.15 $\pm$ 2.50	7.87 $\pm$ 2.59	7.140	<0.001

Note: ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; CRP, C-reactive protein.

rately constructed interaction items between the treatment groups and baseline DAS28, inflammatory markers (IL-6, IL-17, IFN- γ), and BTMs (BGP, PINP) for binary logistic regression analysis. The results indicated no significant

interaction between the treatment groups and baseline DAS-28 DAS28 (P=0.109), IL-6 (P=0.952), IL-17 (P=0.502), IFN- γ (P=0.936), BGP (P=0.912), or PINP (P=0.294; **Table 7**).

Discussion

RA is a chronic inflammatory joint disease that can cause cartilage and bone damage and even disability [18]. Optimizing treatment strategies is therefore important to improve clinical outcomes and enhance efficacy.

In this study, high-dose TOF plus MTX achieved higher overall efficacy, greater relief of clinical symptoms (joint swelling, tenderness, and morning stiffness), and more marked improvement in activities of daily living than the low-dose regimen. MTX, a first-line drug for RA, inhibits the expression of proinflammatory cytokines, purine synthesis, and demethylation reactions, as well as the nuclear translocation of

nuclear factor κB (NF- κB), thereby reducing bone destruction and suppressing disease progression [19]. TOF, by contrast, prevents immune cell activation and cytokine release by modulating intracellular JAK signaling, thereby

Table 6. Quality-of-life level in two groups

Indicator	Low-dose group (n=60)	High-dose group (n=63)	t	P
Physical functioning (points)				
Pre-treatment	45.40±4.21	46.37±5.01	1.160	0.249
Post-treatment	54.33±5.22	64.65±6.54	9.642	<0.001
Psychological functioning (points)				
Pre-treatment	38.93±5.97	40.30±6.52	1.214	0.227
Post-treatment	53.45±5.68	63.00±6.62	8.567	<0.001
Mental health (points)				
Pre-treatment	41.88±4.41	43.00±6.18	1.152	0.252
Post-treatment	50.45±6.66	58.65±5.45	7.489	<0.001
Social functioning (points)				
Pre-treatment	43.03±5.48	44.13±6.01	1.059	0.292
Post-treatment	57.28±5.93	62.17±7.49	4.002	<0.001

Table 7. Subgroup analysis based on base-line DAS28, inflammatory markers, and bone turnover markers

Interaction term	Interaction OR (95% CI)	Interaction P value
Group × DAS28	1.934 (0.863-4.334)	0.109
Group × IL-6	0.995 (0.842-1.176)	0.952
Group × IL-17	0.955 (0.835-1.092)	0.502
Group × IFN-γ	0.994 (0.862-1.147)	0.936
Group × BGP	0.989 (0.811-1.205)	0.912
Group × PINP	0.965 (0.902-1.032)	0.294

Note: DAS28, Disease Activity Score 28; IL-6/17, interleukin-6/17; IFN-γ, interferon γ; BGP, osteocalcin; PINP, procollagen type 1 N-terminal propeptide; OR, odds ratio.

inhibiting the inflammatory cascade and exerting an anti-RA effect [20]. The superior efficacy of high-dose TOF may be attributable to stronger inhibition of the JAK signaling pathway, which more effectively suppresses downstream cytokine expression [21]. Kremer et al. [22] reported that additional TOF treatment (≥3 mg twice daily) produced a sustained effect over 24 weeks in patients with active RA and an inadequate response to MTX alone, which is consistent with our findings.

From a safety perspective, high-dose TOF + MTX did not significantly increase the total ADR rate in RA patients. Consistent with our findings, Takeuchi et al. [23] reported comparable rates of adverse events in Japanese patients with RA treated with low- or high-dose TOF combined with MTX. Szekanecz et al. [24] also support the clinical safety of TOF, reporting lower incidences of major adverse

cardiovascular events and malignant tumors in patients on TOF than in those on tumor necrosis factor inhibitors. In addition, TOF monotherapy has been shown to be non-inferior to TOF combined with non-biologic antirheumatic drugs in terms of clinical safety [25], similar to our findings.

High-dose TOF + MTX was also more effective in relieving symptoms, as reflected by greater reductions in TJC, SJC, and morning stiffness duration, which may be attributed to its stronger efficacy without an increase in ADRs. The high-dose regimen likewise produced more marked relief of pain and reduction in disease activity. Regarding inflammatory markers, patients treated with high-dose TOF + MTX showed more pronounced decreases in IL-6, IL-17, and IFN-γ than those on the low-dose regimen, consistent with stronger suppression of systemic inflammation and, in turn, greater symptom relief and lower disease activity.

Regarding bone metabolism, patients receiving high-dose TOF + MTX showed greater increases in BGP and PINP, indicating improved bone metabolism. The JAK-signal transducer and activator of transcription axis is closely linked to bone metabolism and can influence skeletal development and metabolism; by modulating this pathway, TOF improves the balance of bone metabolism [26, 27]. High-dose TOF + MTX also significantly decreased ESR, RF, and CRP, supporting its ability to inhibit the immuno-inflammatory cascade and thereby indirectly maintain bone metabolic balance. Furthermore, the high-dose regimen

improved patients' QoL across physical, psychological, and social functioning and mental health domains, which may be explained by its greater efficacy, comparable safety, more marked symptom relief, and stronger reduction of pain and disease activity. Prawjaeng et al. [28] similarly reported that MTX combined with a tsDMARD reduced disease activity and improved QoL, which is consistent with our results. Finally, the subgroup analyses revealed no significant interaction between treatment regimens and the baseline disease activity level, inflammatory markers, and turnover status. This indicates that in the current research cohort, the therapeutic benefits brought by high-dose TOF were largely consistent among patients with different baseline characteristics. However, given the insufficient sample size of this study, the current negative conclusion based on the data obtained is not sufficient to exclude the possibility that high-dose TOF can benefit certain specific subgroups of patients. Further exploration and verification through larger-scale prospective studies are still needed.

There are several limitations to this study. (1) This study used a single-center, retrospective, non-randomized design without randomization or blinding, and propensity score matching was not used to adjust for potential confounders (e.g., baseline inflammation levels or prior use of anti-inflammatory drugs alone). Multi-center, prospective, randomized controlled trials would strengthen causal inference about dose-related efficacy differences and help establish standardized dose-stratification schemes and clinical medication guidelines. (2) Follow-up was limited to a short-term observation at 3 months; extended monitoring (e.g., to 6 and 12 months after treatment) is needed to evaluate the long-term cumulative toxicity of high-dose TOF to the liver, kidneys, and blood system. (3) Only a limited set of inflammatory markers (IL-6, IL-17, and IFN- γ) was measured, without quantification of key downstream regulatory molecules of the JAK pathway or biomarkers related to synovial hyperplasia and cartilage injury; future quantitative evaluations should clarify the dose-dependent differences in the inhibition of immune pathways between the two dose levels, thereby providing a molecular-level explanation for the intrinsic connection underlying the differences in therapeutic

effects between the two groups. (4) This study focused on retrospective efficacy comparison rather than outcome prediction modeling, and the sample size was limited. Decision curve analysis was not used to quantify the clinical net benefit of the different dose regimens. (5) Regarding safety, only minor adverse reactions were recorded, without data on the core long-term high-risk adverse events of JAK inhibitors (e.g., thrombosis, malignancy, and serious infection); longer follow-up is needed to assess the comprehensive long-term risk-benefit balance of the high-dose regimen, so as to provide sufficient safety-supporting data for the optimal clinical dosage of the drugs. (6) For inflammatory and bone metabolism markers, only endpoint measurements were obtained; including longitudinal data in future studies could help clarify the dose-dependent mode of action of pathway inhibition. (7) Long-term imaging follow-up and basic cell or animal experiments are lacking; these should be added to clarify the effects of high-dose TOF combined with MTX on imaging outcomes and the underlying anti-RA mechanism.

In summary, compared to the low-dose strategy, high-dose TOF combined with MTX achieved superior efficacy, with greater relief of clinical symptoms and pain, greater reduction of disease activity and inflammation, better balance of bone metabolism, stronger suppression of the immuno-inflammatory cascade, and improved QoL. Moreover, this therapeutic advantage may be universally applicable across different groups with varying baseline disease activity, inflammation levels, and bone turnover status.

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Disclosure of conflict of interest

None.

Address correspondence to: Haili Shen, The Second Clinical Medical College, Lanzhou University, Lanzhou 730000, Gansu, China. Tel: +86-139-193329146; E-mail: shenhl@lzu.edu.cn

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