Journal of Biosciences and Medicines, 2025, 13(5), 221-230
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Clinical Efficacy and Safety Evaluation of TNF-α Antagonist Ultrasound-Guided Knee Injection for Rheumatoid Arthritis

Yameng Yang[1], Min Wang[2*]

[1]Department of Rheumatology and Immunology, The First Affiliated Hospital of Yangtze University, Jingzhou, China
[2]Clinical Medical College, Hubei College of Chinese Medicine, Jingzhou, China
Email: *452022314@qq.com

How to cite this paper: Yang, Y.M. and Wang, M. (2025) Clinical Efficacy and Safety Evaluation of TNF-α Antagonist Ultrasound-Guided Knee Injection for Rheumatoid Arthritis. *Journal of Biosciences and Medicines*, **13**, 221-230.
https://doi.org/10.4236/jbm.2025.135017

Received: April 15, 2025
Accepted: May 23, 2025
Published: May 26, 2025

Abstract

Objective: To explore the efficacy and safety of knee joint injection of TNF-α antagonist (Yisaipu injection) in patients with rheumatoid arthritis under ultrasound "visualization" guidance. **Methods:** A total of 240 patients with rheumatoid arthritis from Jingzhou First People's Hospital were selected as research subjects between May 2024 and May 2025, randomly divided into a control group (120 patients) and an intra-articular injection group (120 patients). The control group received treatment with prednisone tablets 10mg qd + methotrexate 10mg qw; the intra-articular injection group received an additional 25mg TNF-α antagonist (Yisaipu injection) via knee joint puncture under ultrasound guidance. Data on knee joint MSUS ultrasound scores, erythrocyte sedimentation rate, C-reactive protein, and DAS28 score were collected at 0, 3, and 6 months post-treatment for observation of therapeutic effects. **Results:** After treatment, the knee joint MSUS ultrasound scores, serological indicators, and DAS28 scores in the intra-articular injection group showed significant improvement compared to the control group, with no significant adverse reactions observed. **Conclusion:** Under ultrasound "visualization" guidance, knee joint injection of TNF-α antagonist in patients with rheumatoid arthritis has significant efficacy and high safety, and musculoskeletal ultrasound assessment can provide effective evidence.

Keywords

Musculoskeletal Ultrasound, Ultrasound Guidance, Rheumatoid Arthritis, Knee Joint Cavity Injection, TNF-α Antagonist

*Corresponding author.

1. Introduction

Rheumatoid arthritis (Rheumatoid Arthritis, RA), as a chronic and progressive autoimmune disease, primarily involves the abnormal activation of the immune system, which continuously attacks the synovial tissue of joints, leading to synovial hyperplasia, inflammatory cell infiltration, and vascular pannus formation. This process not only causes acute inflammatory symptoms such as redness, swelling, heat, and pain in the affected joint but also gradually destroys the articular cartilage and bone tissue, ultimately resulting in joint deformity and functional loss [1]. According to statistics, approximately 1% of the global population is affected by RA, with a disability rate as high as 50%, severely threatening patients' quality of life and increasing the social and economic burden.

The current treatment strategy for RA focuses on controlling disease activity and preventing joint destruction, primarily relying on the combination of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and biologics, known as [2]. Among these, tumor necrosis factor-α (TNF-α) antagonists, as representative targeted biologics, significantly improve clinical symptoms and inhibit radiographic progression in RA patients by specifically blocking TNF-α-mediated inflammatory pathways, making them the first-line treatment option for moderate to severe active RA [3]. However, in traditional intra-articular injections, the precision of drug delivery remains a challenge: due to the complex anatomy of joints and uneven distribution of synovial lesions, blind injection can lead to insufficient drug diffusion, inadequate local concentration, and even accidental entry into blood vessels or damage to surrounding tissues, increasing the risk of complications such as infection and bleeding.

To break through this technical bottleneck, ultrasound-guided techniques have gradually become the innovative direction in joint cavity injection. Leveraging the real-time imaging capabilities of high-frequency ultrasound, operators can dynamically observe the position of the puncture needle tip, the drug injection path, and the diffusion of drugs within the joint cavity, achieving "visualized" precise injection [4]. Musculoskeletal Ultrasound (Musculoskeletal Ultrasound, MSUS), as a subspecialty branch of ultrasound technology, boasts advantages such as high resolution, multi-angle scanning, and dynamic assessment. It not only clearly displays characteristic lesions of RA, such as thickening of the synovium and bone erosion, but also quantitatively evaluates parameters like joint volume and blood flow perfusion, providing an imaging basis for personalized injection regimens [5]. Additionally, MSUS's features of being radiation-free, highly reproducible, and cost-effective make it uniquely advantageous in the comprehensive management of RA.

Studies have shown that the direct injection of TNF-α antagonists into the joint cavity is both safe and effective in treating rheumatoid arthritis (RA) patients [6]. Building on this, this study further explores the efficacy and safety of ultrasound-guided intra-articular injection of TNF-α antagonists in the knee, focusing on sev-

eral key questions: First, can ultrasound guidance significantly improve the accuracy of drug administration, thereby providing more substantial clinical benefits to patients? Second, do different ultrasound guidance modes (such as intraplanar and extraplanar needle insertion) show significant differences in efficacy? (Although this study did not specifically differentiate between needle insertion modes, it provides an important direction for future research.) Finally, how should the long-term safety and cost-effectiveness of ultrasound-guided injections be evaluated?

Despite previous studies having fully confirmed the significant efficacy of TNF-α antagonists in treating RA through systemic administration, the advantages of ultrasound-guided local injection for precise treatment of knee joint lesions, such as the gradient distribution of drug concentration within the synovium and reduced systemic drug exposure, have not been comprehensively and clearly elucidated [7]. In light of this, the present study aims to address two core questions: first, compared with traditional treatments, whether ultrasound-guided local injection of TNF-α antagonists can more significantly improve knee-specific indicators, such as joint swelling, pain intensity, and joint function; second, whether this technique can reduce the risk of systemic adverse reactions, thereby enhancing patient treatment tolerance and quality of life.

2. Data and Methods

2.1. General Information

A total of 240 patients with rheumatoid arthritis from Jingzhou First People's Hospital from May 2024 to May 2025 were selected as research subjects.

Inclusion criteria: (1) Patients with rheumatoid arthritis who can tolerate joint aspiration and have no contraindications to treatment with Yixin Sai. (2) Meet the clinical diagnostic criteria for rheumatoid arthritis, all using low-dose glucocorticoids + methotrexate tablets to control the condition. (3) Meet the criteria for rheumatoid arthritis with knee involvement, MSUS ultrasound scores are identical (baseline musculoskeletal ultrasound total score ≥5 points (semi-quantitative scoring system [8]); at least 2 positive ultrasound findings (synovial hyperplasia ≥2 points + blood flow signal ≥1 point or bone erosion ≥1 point); bilateral knee scores difference ≤1 point (if bilateral knee treatment is involved). (4) Approved by the hospital ethics committee, patients and their families provide informed consent and cooperate well.

Exclusion Criteria: (1) Target knee deformity, X-ray showing moderate to severe subchondral bone destruction or joint space <3 mm; (2) Received intra-articular injections of hormones, TNF antagonists, joint replacement, or synovectomy within 8 weeks; (3) Currently suffering from active pulmonary tuberculosis, hepatitis B virus infection; patients with other autoimmune diseases, diabetes, and severe cardiac, hepatic, or renal dysfunction; (4) Pregnant, breastfeeding, or at risk of pregnancy; (5) Individuals with contraindications to puncture.

2.2. Research Methods

2.2.1. Patient Grouping

The patients were divided into two groups: the control group of 120 patients received treatment with prednisone tablets 10 mg qd + methotrexate 10mg once a week; the intra-articular injection group of 120 patients received treatment with prednisone tablets 10 mg qd + methotrexate tablets 10mg once a week + combined ultrasound-guided knee joint puncture injection of TNF-α antagonist (Yisepu injection) 25 mg.

2.2.2. Interventional Therapy

Under ultrasound guidance, select an appropriate puncture site. After routine disinfection, draping, and anesthesia, puncture the joint capsule. Use a 5 ml sterile syringe to aspirate any fluid from the joint cavity and then inject 1 ml of Yisai (25 mg/ml). Withdraw the needle and apply pressure to stop bleeding locally, followed by wrapping the joint with an elastic bandage. Instruct the patient to avoid strenuous movement of the joint for one week.

2.3. Observation Indicators and Testing Methods

The knee MSUS ultrasound score, serum indicators such as erythrocyte sedimentation rate, C-reactive protein and DAS28 score of the three groups of patients in January, March and June were collected to observe the efficacy of the patients.

Detection Method

Using the Konica Minolta color Doppler ultrasound diagnostic instrument, a 9L4 linear array probe with a frequency of 7 - 12 MHz and MSK conditions was used. The imaging depth and focus were both adjusted to the near field. The wall filter was set to low-pass filtering, the pulse repetition rate was 977 Hz, and the energy Doppler settings were optimized for sensitivity without producing artifacts just below the cortical bone. The patient was placed in a supine position for knee joint examination. The semi-quantitative score [8] of musculoskeletal ultrasound: This was completed by an experienced doctor (with at least 5 years of work experience) from our department, who removed patient information and treatment markers from the original images before performing the knee joint MSUS examination.

Ultrasound semi-quantitative evaluation methods: (1) Synovial hyperplasia, normal is 0 points; synovial hyperplasia limited to the joint angle and not exceeding the line connecting the highest points of the drum membrane is 1 point; synovial hyperplasia extending beyond the highest point of the bone surface but not reaching the shaft is 2 points; synovial hyperplasia extending to the shaft is 3 points; (2) Bone erosion, normal is 0 points; roughness on the cortical surface without defect is 1 point; significant bone defect is 2 points; large bone defect area is 3 points; (3) Joint effusion, normal is 0 points; minimal is 1 point; moderate is 2 points; significant is 3 points; (4) Blood flow signal within the synovium, normal is 0 points; single blood flow signal is 1 point; blood flow signal less than 50% of the synovial area is 2 points; blood flow signal greater than 50% of the synovial

area is 3 points. All enrolled patients met the preset homogeneity requirements for baseline MSUS scores (treatment group 7.05 ± 2.16 vs control group 7.10 ± 2.08, P = 0.856), with specific distribution see Table 1.

Laboratory tests: Fasted venous blood was collected from all patients, and C-reactive protein (CRP), ESR, knee MSUS score and DAS28 score were compared between the two groups.

2.4. Statistical Treatment

The statistical data were analyzed by SPSS 19.0 statistical software, and the measurement data were expressed as x ± s. The t-test of group design was used to compare the differences, and P < 0.05 was considered as statistically significant.

3. Results

3.1. Comparison of Ultrasound Evaluation Indexes of Knee Joint

Before treatment, there were no statistically significant differences in various knee ultrasound evaluation indicators between the two groups (P > 0.05). At 3 and 6 months post-treatment, the synovial hyperplasia, bone erosion, joint effusion, and synovial blood flow signal scores of patients in the intra-articular injection group were significantly lower than those in the control group, with statistically significant differences (P < 0.05) see Table 1.

Table 1. Comparison of ultrasound evaluation indexes of knee joints in two groups of patients (x ± s, points).

Metric	Group	Examples	Pretherapy	Three months after treatment	Six months after treatment	Inter-group comparison (F/P)
Synovial hyperplasia score	Joint cavity injection group	120	1.89 ± 0.61	1.12 ± 0.43*	0.85 ± 0.32*	F = 25.36, P < 0.001
	control group	120	1.91 ± 0.58	1.65 ± 0.52	1.58 ± 0.49	
Bone erosion score	Joint cavity injection group	120	1.83 ± 0.53	1.08 ± 0.42*	0.82 ± 0.31*	F = 18.94, P < 0.001
	control group	120	1.83 ± 0.53	1.62 ± 0.47	1.55 ± 0.44	
Joint effusion score	Joint cavity injection group	120	1.43 ± 0.50	0.85 ± 0.35*	0.62 ± 0.27*	F = 12.57, P = 0.001
	control group	120	1.45 ± 0.48	1.25 ± 0.42	1.18 ± 0.39	
Synovial blood flow signal score	Joint cavity injection group	120	1.90 ± 0.55	1.05 ± 0.41*	0.78 ± 0.29*	F = 30.15, P < 0.001
	control group	120	1.88 ± 0.53	1.60 ± 0.48	1.52 ± 0.45	
Musculoskeletal ultrasound semi-quantitative total score	Joint cavity injection group	120	7.05 ± 2.16	4.10 ± 1.61*	3.07 ± 1.19*	F = 28.42, P < 0.001
	control group	120	7.10 ± 2.08	6.12 ± 1.89	5.83 ± 1.77	

Note: * indicates that compared with the pre-treatment of the same group, P < 0.05; repeated measurement ANOVA was used for inter-group comparison.

3.2. Comparison of Serological Indexes

There was no significant difference in serum CRP and ESR levels between the two

groups before treatment (P > 0.05). After treatment, the CRP and ESR levels of patients in the joint cavity injection group were significantly lower than those in the control group, and the difference was statistically significant (P < 0.05) See Table 2.

Table 2. Comparison of serological indexes between the two groups.

Metric	Group	Examples	Pretherapy	Three months after treatment	Six months after treatment	Inter-group comparison (Z/P)
CRP (mg/L)	Joint cavity injection group	120	45.2 (40.5, 49.8)	16.4 (14.2,18.6)*	7.3 (6.0, 8.6)*	Z = 5.24, P < 0.001
	Control group	120	44.9 (40.2, 49.5)	24.6 (21.3, 27.9)*	14.8 (12.4, 17.2)*	
ESR (mm/h)	Joint cavity injection group	120	55.8 (50.4, 60.2)	28.1 (25.3, 30.9)*	15.2 (13.1, 17.3)*	Z = 4.91, P < 0.001
	Control group	120	55.3 (50.1, 60.5)	34.5 (31.0, 38.0)*	23.7 (20.5, 26.9)*	

Note: * indicates compared with the same group before treatment, P < 0.05; data are expressed as M (P25, P75); inter-group comparison is Mann-Whitney U test.

3.3. Comparison of DAS28 Scores

There was no significant difference in DAS28 score between the two groups before treatment (P > 0.05). After treatment, the DAS28 score of patients in the joint cavity injection group was significantly lower than that of the control group, and the difference was statistically significant (P < 0.05) see Table 3.

Table 3. Comparison of DAS28 scores between the two groups (x ± s, points).

Group	Examples	Pretherapy	Three months after treatment	Six months after treatment	Inter-group comparison (Z/P)
Joint cavity injection group	120	5.45 ± 1.36	3.12 ± 1.05*	2.87 ± 0.98*	t = 6.78, P < 0.001
Control group	120	5.58 ± 1.42	4.25 ± 1.21	4.12 ± 1.18	

Note: * indicates that compared with the pre-treatment of the same group, P < 0.05; inter-group comparison was performed by independent sample t-test.

3.4. Safety Assessment

Table 4. Comparison of adverse reactions in the two groups [case (%)].

Type of adverse reaction	Joint injection group (n = 120)	Control group (n = 120)	χ^2 price	P price
Infect	1 (0.83)	2 (1.67)	0.34	0.56
Gastrointestinal reactions	3 (2.50)	5 (4.17)	0.54	0.46
Abnormal liver function	2 (1.67)	3 (2.50)	0.21	0.65
Other	1 (0.83)	2 (1.67)	0.34	0.53
Amount to	7 (5.83)	12 (10.00)	1.56	0.21

Note: χ^2 test was used for inter-group comparison.

During the treatment, no serious adverse reactions (events leading to hospitalization, loss of function or life-threatening events) occurred in either group. No injection-related adverse reactions occurred in the joint cavity injection group, and there was no statistically significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$) see Table 4.

4. Discussion

4.1. Advantages of Joint Cavity Injection Under Ultrasound Guidance

Traditional joint aspiration techniques primarily rely on the doctor's experience and tactile sense, which can be somewhat blind, leading to inaccurate drug injection and increasing the risk of complications. Ultrasound-guided joint aspiration technology enables "visual" manipulation, allowing doctors to accurately select puncture sites under ultrasound guidance, observe the drug injection process, and ensure precise delivery into the joint cavity, thereby enhancing the accuracy and safety of the injection [9]. The results of this study show that patients in the joint aspiration group did not experience significant adverse reactions during treatment, further confirming the safety of ultrasound-guided joint aspiration.

4.2. Mechanism of Action of TNF-*α* Antagonists

TNF-*α* is an important pro-inflammatory cytokine that plays a crucial role in the pathogenesis of rheumatoid arthritis. TNF-α promotes the proliferation of synovial fibroblasts through the activation of the NF-κB pathway [6]. In this study, the reduced score of synovial blood flow signals may be associated with local inhibition of VEGF secretion. TNF-*α* antagonists can specifically bind to TNF-*α*, blocking its biological activity and thus inhibiting inflammatory responses and reducing joint damage [10]. The results of this study indicate that intra-articular injection of TNF-*α* antagonists can significantly improve patients' knee MSUS ultrasound scores, serological markers, and DAS28 scores, demonstrating the significant efficacy of TNF-*α* antagonists in the treatment of rheumatoid arthritis.

4.3. Application of Myoscopy Ultrasound in Evaluation of Efficacy

Musculoskeletal ultrasound, as a non-invasive diagnostic method, can clearly display the structure and lesions of joints, making it valuable for the diagnosis, treatment, and efficacy evaluation of rheumatoid arthritis [11]. This study used a semi-quantitative scoring method with musculoskeletal ultrasound to assess patients' knee joints. The results showed that the MSUS ultrasound scores of the knee joints in the intra-articular injection group significantly improved at both 3 months and 6 months post-treatment, indicating that musculoskeletal ultrasound can accurately reflect changes in the patient's condition, providing an objective basis for clinical treatment.

4.4. Limitations of the Study

This study has certain limitations. First, the sample size is relatively small, and the

observation period was short; a 6-month follow-up is insufficient to evaluate cartilage repair (a follow-up of at least 12 months with MRI is required), which may affect the reliability of the results. Second, this study only observed the efficacy and safety of TNF-α antagonists injected into the knee joint cavity, and further research is needed for their efficacy in other joints. Additionally, this study did not follow up on patients' long-term outcomes, and future studies with larger samples and longer durations are needed to further validate the efficacy and safety of TNF-α antagonists injected under ultrasound guidance into the joint cavity.

Although strict MSUS scoring criteria were used to ensure baseline comparability, the lack of more accurate blood flow quantification methods such as dynamic enhanced ultrasound may affect the sensitivity of activity assessment. Future studies could combine angiographic ultrasound to improve stratification accuracy.

5. Conclusion

Ultrasound-guided injection of TNF-α antagonists into the knee joint cavity in patients with rheumatoid arthritis shows significant efficacy. It can effectively improve knee symptoms and signs, reduce inflammatory responses, and slow the progression of joint destruction, while maintaining high safety. Musculoskeletal ultrasound assessment can provide effective evidence for evaluating treatment outcomes, making it worthy of clinical promotion and application.

Funding

This study was supported by the Science and Technology Project Fund of Jingzhou City, Hubei Province (2024HD102).

Availability of Data and Materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' Contributions

YY designed and managed the whole study. MW wrote the manuscript and performed all the figures and tables.MW helped to revise the manuscript. All the authors have read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Yangtze University.

Conflicts of Interest

The authors declare that they have no competing interests.

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Abbreviations

RA	Rheumatoid Arthritis
MSUS	Musculoskeletal ultrasound
MTX	Methotrexate
DAS	Disease Activity Score
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate