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Original Article

Iguratimod in combination with conventional therapy suppresses inflammation and improves joint structure and function in rheumatoid arthritis

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Abstract: Objective: To evaluate the therapeutic efficacy of iguratimod in combination with conventional therapy in patients with rheumatoid arthritis (RA) and to explore changes in hematological and ultrasonographic parameters, as well as their correlations with disease activity. Methods: This single-center, retrospective clinical study involved 79 RA patients, including 49 in the combination therapy group (iguratimod plus conventional therapy) and 30 in the standard therapy group (conventional therapy alone). The following parameters were assessed at baseline and after 12 weeks of treatment: the Disease Activity Score in 28 joints (DAS28), Visual Analogue Scale (VAS) scores, inflammatory markers (high-sensitivity C-reactive protein, hs-CRP; erythrocyte sedimentation rate, ESR; rheumatoid factor, RF), joint function grades, and ultrasonographic features-including synovial thickness, cartilage thickness, blood flow signals, joint effusion, and synovial arterial resistance index (RI). Adverse events were recorded to assess drug safety. Results: After 12 weeks of treatment, the overall clinical efficacy rate was significantly higher in the combination therapy group than in the standard therapy group (95.92% vs. 76.67%, $P<0.05$). Patients in the combination therapy group showed significant decreases in DAS28, VAS scores, morning stiffness duration (all $P<0.05$). After 12 weeks of treatment, the levels of serum hs-CRP, ESR and RF levels in the combined therapy group decreased significantly and were lower than those in the standard therapy group (all $P < 0.05$). Ultrasonography revealed marked reductions in synovial thickness, joint effusion, and synovial blood flow signals in the combination therapy group after treatment, along with a reduction in RI ($P<0.05$). Moreover, the proportion of Grade I joint function increased, while Grade IV proportion decreased significantly in the combination therapy group ($P<0.05$). The incidence of adverse events was comparable between groups, and no serious events occurred ($P>0.05$). Conclusion: Iguratimod combined with conventional therapy effectively alleviates inflammation, improves joint function, and mitigates structural damage in RA patients, with a favorable safety profile. Dynamic monitoring of hematological and imaging parameters provides a more comprehensive assessment of disease activity, supporting the clinical utility of iguratimod-based combination therapy in RA management.

Keywords: Rheumatoid arthritis, iguratimod, DAS28, ultrasound, inflammatory markers, blood flow signals, treatment response

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovial inflammation and progressive joint destruction [1, 2]. It follows a prolonged and irreversible course, and if inadequately controlled, may lead to joint deformity, functional disability, and substantial impairment in patients' quality of life [3, 4]. The pathogenesis of RA is multifactorial, involving genetic susceptibility, environmental triggers, and immune dysregulation, with persistent immune-mediated inflammation serving as the principal driver of disease progression [5, 6]. Therefore, accurate assessment of inflammatory activity is crucial for guid-

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ing individualized treatment strategies and improving long-term outcomes.

Iguratimod, a novel oral conventional synthetic disease-modifying antirheumatic drug (csDMARD), has demonstrated potent anti-inflammatory and immunomodulatory properties [7, 8]. Studies have demonstrated that iguratimod inhibits cyclooxygenase-2 (COX-2) and the NF-κB signaling pathway, suppresses the expression of proinflammatory cytokines, and restrains the proliferation and invasion behavior of fibroblast-like synoviocytes. In addition, it helps mitigate bone destruction by modulating the OPG/RANKL/RANK signaling axis. Multiple clinical studies [9, 10] have reported that iguratimod, either as monotherapy or in combination with methotrexate (MTX), can effectively alleviate joint inflammation, improve functional status, increase ACR response rates, and may slow radiographic progression in RA.

Despite these advances, RA remains a heterogeneous and dynamically evolving disease influenced by multiple factors. Conventional disease activity scores, such as the Disease Activity Score in 28 joints (DAS28), remain important clinical tools but may not fully capture subtle variations in systemic inflammation or local joint pathology. In recent years, hematological inflammatory markers (e.g., C-reactive protein, CRP; erythrocyte sedimentation rate, ESR; rheumatoid factor, RF) and imaging modalities such as ultrasonography and MRI have gained prominence in the comprehensive assessment of RA activity. Hematological markers reflect the systemic inflammatory burden, while imaging modalities directly visualize synovial thickening, joint effusion, and bone destruction. The combined and dynamic monitoring of hematological and imaging parameters offers a more comprehensive and accurate evaluation of disease activity, thereby facilitating therapeutic optimization and prognosis prediction.

At present, systematic investigations into the combined dynamic changes in hematological and imaging parameters during iguratimod-based treatment and their relationship with disease activity in RA remain limited. Therefore, this study retrospectively analyzed dynamic trends in hematological and ultrasonographic parameters among RA patients receiving iguratimod in combination with conventional therapy and explored their correlations with disease activity scores, aiming to provide a more evidence-based framework for evaluating treatment efficacy and guiding individualized disease management.

Methods

Study design and ethical approval

This single-center, retrospective clinical study included 79 inpatients and outpatients diagnosed with RA at the Department of Rheumatology and Immunology of our hospital between January 2022 and December 2024. All patients met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA [11]. Based on the treatment regimens, patients were categorized into two groups: the combination therapy group (n=49), receiving iguratimod in addition to conventional therapy, and the standard therapy group (n=30), receiving conventional therapy alone, which included methotrexate (MTX), nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids.

This was a retrospective study utilizing data extracted from the hospital's electronic medical record system and imaging database. Only routine clinical and diagnostic data were included; no additional interventions or tests were performed. The study protocol was reviewed and approved by the Ethics Committee of Wangjing Hospital, China Academy of Chinese Medical Sciences, and was conducted in accordance with the principles of the Declaration of Helsinki. As this was a retrospective study, all patient identifiers were removed prior to analysis to ensure confidentiality, and the requirement for written informed consent was waived by the Ethics Committee.

Inclusion criteria

Patients were included if they met all of the following conditions: 1) Fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA [11]; 2) Aged between 30 and 80 years; 3) Disease duration ≥6 months and in an active disease stage; 4)

Joint function classified as Grade II-III; 5) Complete clinical data and good treatment compliance.

Exclusion criteria

Patients meeting any of the following criteria were excluded: 1) Presence of malignant tumors, hematologic disorders, or severe hepatic, renal, or cardiac dysfunction; 2) Known allergy to study medications, including iguratimod, MTX, or NSAIDs; 3) Pregnancy or lactation; 4) Coexisting autoimmune diseases (e.g., systemic lupus erythematosus, Sjögren's syndrome); 5) Use of glucocorticoids, immunosuppressants, or biological agents within 4 weeks prior to enrollment; 6) Presence of severe infection or psychiatric disorders precluding treatment adherence or follow-up.

Treatment regimen

Patients in the combination therapy group (n=49) received oral iguratimod (25 mg twice daily; Simcere Pharmaceutical (Hainan) Co., Ltd.; batch number: 42-220417) for 12 weeks, in addition to conventional therapy. Conventional treatment included MTX at 10-15 mg per week (Sinomune Pharmaceutical Co., Ltd.; batch number: 211202), NSAIDs, and low-dose glucocorticoids (prednisone ≤10 mg/day; Shandong Xinhua Pharmaceutical Co., Ltd.; batch number: 2105180). During the treatment period, all patients maintained a stable disease-modifying antirheumatic drug (DMARD) regimen, and no adjustments were made to the doses of MTX or glucocorticoids.

Patients in the standard therapy group (n=30) received conventional DMARD therapy alone, consisting of MTX (10-15 mg/week), NSAIDs, and low-dose glucocorticoids (≤10 mg/day), without the addition of iguratimod.

Data collection and outcome measurements

All assessments were conducted before treatment and after 12 weeks of treatment, including the following: (1) Clinical efficacy: Therapeutic efficacy was evaluated according to the American College of Rheumatology (ACR) improvement criteria (ACR20/50/70). (2) Disease activity: Disease activity was assessed using the Disease Activity Score in 28 joints (DAS28) and the Visual Analogue Scale (VAS) for pain. (3) Joint function: Joint function was graded from I to IV according to the national joint function classification standard. (4) Inflammatory and immunological markers: Serum levels of high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF) were determined using assays from Roche Diagnostics GmbH. All reagents were supplied by Roche Diagnostics (Shanghai) Limited (hs-CRP kit: Cat. No. 04628918190; ESR kit: Cat. No. 05882558190; RF kit: Cat. No. 04690425190). Tests were performed strictly according to the manufacturer's instructions. (5) Ultrasonographic parameters: Synovial thickness, cartilage thickness, joint effusion, synovial blood flow grading, and synovial arterial resistance index (RI) were evaluated by the same experienced rheumatologic ultrasonographer using a Philips EPIQ 7 high-frequency color Doppler ultrasound system (Philips Healthcare, Netherlands). (6) Safety assessment: Adverse events such as rash, gastrointestinal reactions, elevated transaminase levels, and leukopenia were documented.

Primary outcome measures: Change in DAS28 score and overall clinical efficacy rate. Secondary outcome measures: Inflammatory biomarkers, ultrasonographic structural changes, joint function grade, and incidence of adverse reactions.

Statistical analysis

Data were analyzed using SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation ($\bar{x} \pm s$), and intergroup comparisons were performed using independent samples t-tests. Categorical variables were expressed as counts and percentages and compared using the chi-square test or Fisher's exact test. Treatment efficacy was assessed based on ACR response rates and changes in DAS28 scores. All statistical tests were two-tailed, and a P value <0.05 was considered statistically significant.

Results

Baseline characteristics

There were no significant differences between the two groups in gender, age, disease duration, joint function grade, body mass index (BMI), DAS28 score, or VAS score (P>0.05), indicating good baseline comparability between the groups (**Table 1**).

Table 1. Comparison of baseline data

Indicator	Combination therapy group (n=49)	Standard therapy group (n=30)	t/χ^2	P
Gender (male/female, n)	20/29	13/17	0.061	0.804
Age (years)	53.12 ± 6.15	52.87 ± 6.32	0.183	0.856
Course of disease (years)	6.48 ± 2.35	6.21 ± 2.27	0.512	0.610
Joint function grade (II/III, n)	25/24	16/14	0.004	0.949
Body mass index B (BMI, kg/m^2)	23.84 ± 2.61	23.57 ± 2.54	0.473	0.638

Table 2. Comparison of clinical efficacy

Group	n	Marked improvement	Improvement	No responses	Overall response rate
Combination therapy group	49	32	15	2	95.92%
Standard therapy group	30	16	7	7	76.67%
x^2					5.058
P					0.025

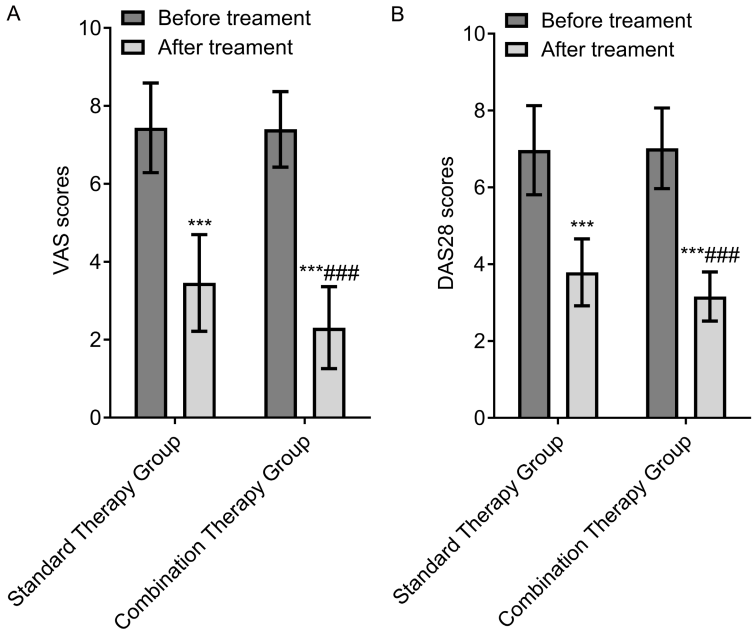

Figure 1. Changes in pain scores in RA patients during iguratimod treatment. A: VAS score; B: DAS28 score. Compared with before treatment, ***P<0.001; Compared with the standard therapy group, ###P<0.001. Note: RA, rheumatoid arthritis; VAS, Visual Analogue Scale; DAS28, Disease Activity Score in 28 joints.

Clinical efficacy

After 12 weeks of treatment, the overall response rate was significantly higher in the combination therapy group (95.92%) than in the standard therapy group (76.67%) (P=0.025). These results indicate that iguratimod combined with conventional therapy markedly enhances clinical remission rates and alleviates joint symptoms and disease activity in RA patients (**Table 2**).

Pain score comparison

After treatment, both groups showed significant reductions in VAS and DAS28 scores compared to baseline values (P<0.05). Moreover, the combination therapy group demonstrated significantly lower post-treatment VAS and DAS28 scores than the standard therapy group. See **Figure 1**.

Improvement in joint function

After 12 weeks of treatment, both groups exhibited significant reductions in morning stiffness duration compared to baseline (P<0.05). The improvement was more pronounced in the combination therapy group, indicating that iguratimod combined with conventional treatment more effectively enhances joint function in RA patients. See **Figure 2**.

Changes in joint function grade distribution

Before treatment, no significant difference was observed in the distribution of joint function

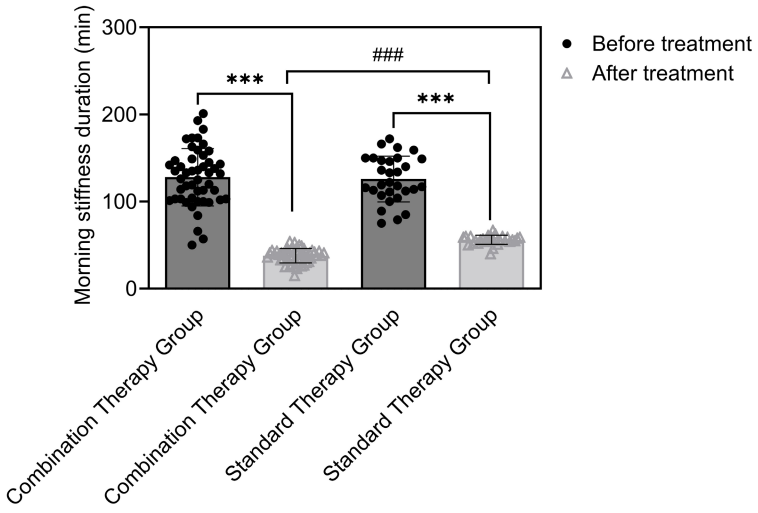

Figure 2. Effect of iguratimod combined with routine treatment on morning stiffness duration in RA patients. Note: Compared with before treatment, ***P<0.001; Compared with the combination therapy group, ###P<0.001.

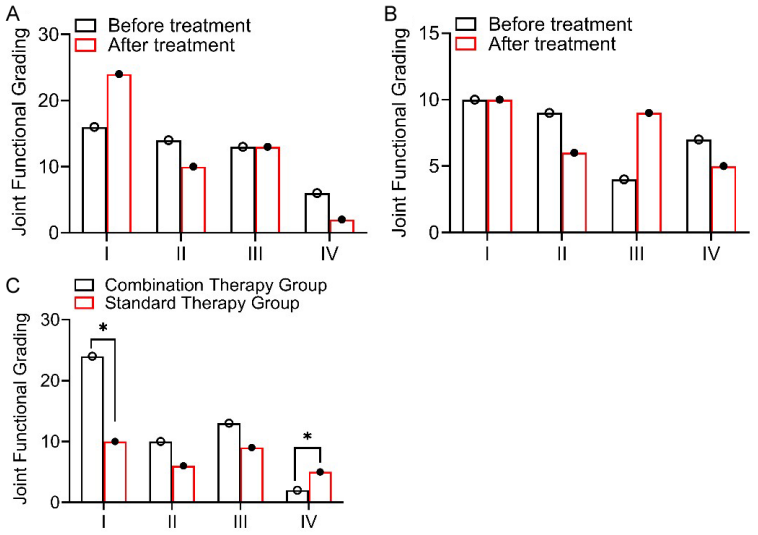

Figure 3. Comparison of joint function grade changes between two RA patient groups before and after treatment (Grades I-IV). A: Changes in joint function grades before and after treatment in the combination therapy group; B: Changes in joint function grades before and after treatment in the standard therapy group; C: Changes in joint function grades after treatment in the combination therapy group and the standard therapy group. Comparison between the combination therapy group and the standard therapy group, *P<0.05.

grades between the two groups (P>0.05). After 12 weeks, the proportion of patients with Grade I joint function was significantly higher in the combination therapy group than in the standard therapy group, while the proportion of Grade IV patients was significantly lower (P<0.05). These results indicate that iguratimod combined therapy substantially improves joint functional status in RA patients. See **Figure 3**.

Safety assessment

During the treatment period, the incidence of adverse reactions did not differ significantly between the two groups (P>0.05). The most common adverse events in both groups were rash, gastrointestinal discomfort, elevated transaminases, leukopenia and Renal function impairment. All events were mild to moderate in severity with low occurrence rates. No serious adverse events were observed. See **Table 3**.

Comparison of ultrasonographic features

After 12 weeks of treatment, ultrasonographic assessments showed that the combination therapy group had significantly reduced synovial thickness compared to the standard therapy group (P<0.05). The cartilage thickness of the medial and lateral femoral condyles was significantly greater in the combination therapy group (P<0.05), indicating better preservation of cartilage integrity. Furthermore, the incidences of synovial proliferation, bone erosion, suprapatellar joint effusion, and positive synovial color Doppler blood flow signals were all significantly lower in the combination therapy group than in the standard therapy group (P<0.05). The synovial arterial RI was also significantly decreased in the combination therapy group (P<0.05). These findings suggest that iguratimod combination therapy effectively alleviates synovial inflammation and mitigates structural joint damage in RA patients. See **Table 4** and **Figure 4**.

Table 3. Incidence of adverse reactions

Group	n	Rash	Gastrointestinal reaction	Elevated transaminase	Leukopenia	Renal function impairment	Total incidence rate
Combination therapy group	49	2	3	1	3	1	20.41% (10/49)
Standard therapy group	30	1	2	1	1	0	16.67% (5/30)
x^2							0.169
P							0.681

Table 4. Comparison of ultrasonographic features between groups

Ultrasonographic features	Combination therapy group (n=49)	Standard therapy group (n=30)	t/x^2	P
Synovial membrane thickness (mm)	0.57 ± 0.12	1.03 ± 0.25	9.570	<0.001
Medial femoral condyle cartilage thickness (mm)	1.85 ± 0.52	1.51 ± 0.12	3.516	0.001
Lateral femoral condyle cartilage thickness (mm)	1.88 ± 0.57	1.21 ± 0.31	6.770	<0.001
Synovial hyperplasia (n/%)	7	27	7.660	0.006
Bone erosion (n/%)	3	8	0.621	0.431
Popliteal joint effusion (n/%)	2	24	15.088	<0.001
Synovial color Doppler blood flow (n/%)	1	21	14.467	<0.001
Intra-synovial artery resistance index	1.22 ± 0.19	0.59 ± 0.12	18.088	<0.001

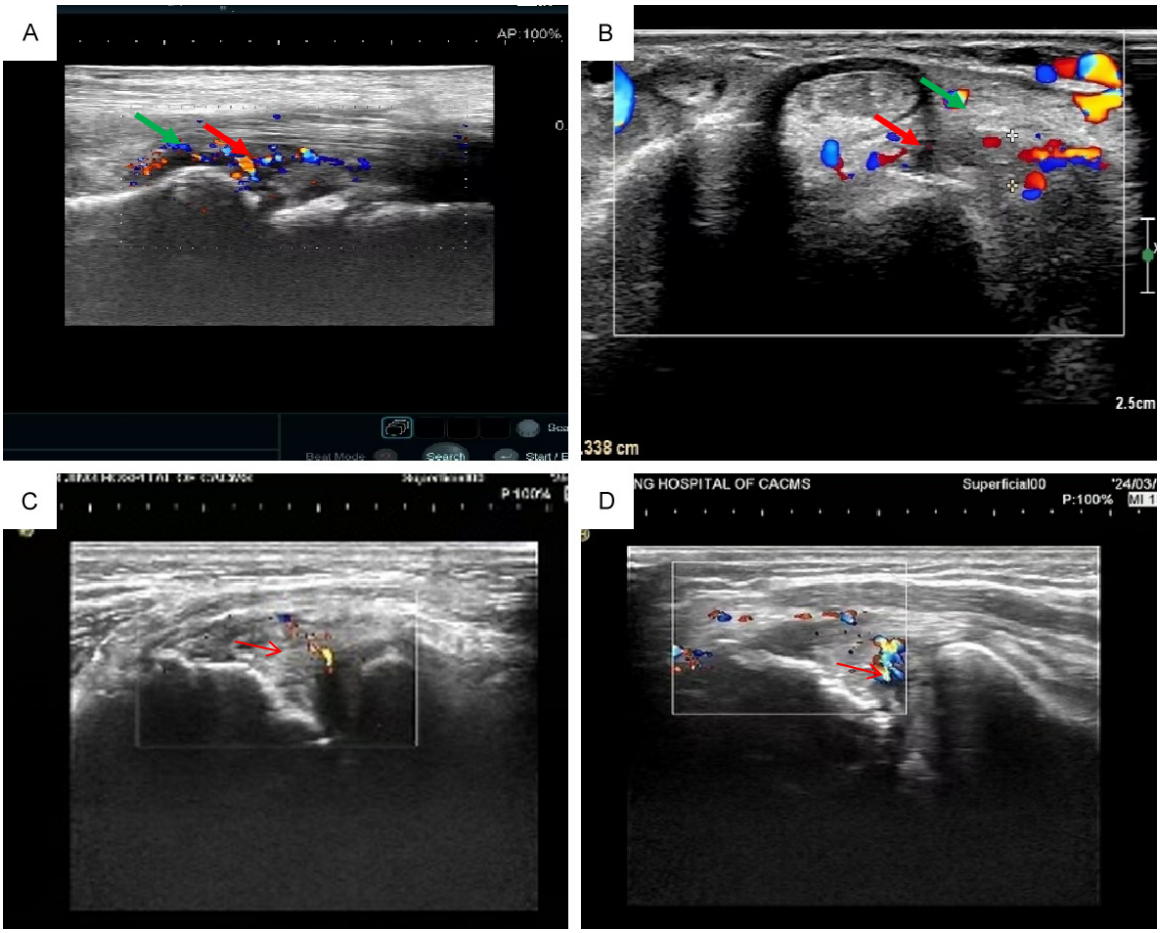

Figure 4. Ultrasound changes of the knee joint before and after treatment in two groups. Patient A: A. Synovial membrane thickening and grade 2 synovial blood flow signal before conventional treatment. B. Reduced synovial thickness and grade 1 blood flow signal after conventional treatment. Patient B: C. Synovial membrane thickening

and grade 1 blood flow signal before the combination treatment. D. Significant thinning of the synovial membrane and disappearance of synovial blood flow signal (grade 0) after combination therapy. Red arrows indicate thickened synovial membrane; green arrows indicate blood flow signals.

Table 5. Comparison of laboratory index levels between groups ($\bar{x} \pm s$)

Laboratory indicators	Combination therapy group (n=49)	Standard therapy group (n=30)	*t*	*P*
Hs-CRP (mg/L)	3.37 ± 1.56	8.95 ± 3.17	10.454	<0.001
ESR (mm/H)	10.83 ± 4.92	22.47 ± 5.37	9.857	<0.001
RF (IU/ml)	12.93 ± 2.55	17.78 ± 3.14	9.055	<0.001

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

Comparison of biochemical marker levels

After 12 weeks of treatment, levels of hs-CRP, ESR, and RF were significantly lower in the combination therapy group than in the standard therapy group (P<0.05). These results indicate that iguratimod combined with conventional therapy exerts a stronger anti-inflammatory effect and more effectively reduces systemic inflammation and autoantibody levels in RA patients. See **Table 5**.

Discussion

This retrospective study investigated the effects of iguratimod in combination with conventional therapy on clinical symptoms, inflammatory levels, joint function, and imaging outcomes in patients with RA. Furthermore, it evaluated the correlations between dynamic changes in hematological and imaging parameters and disease activity. The results demonstrated that combination therapy with iguratimod was superior to conventional treatment alone in improving disease activity, relieving pain, controlling systemic inflammation, and mitigating structural joint damage, highlighting its significant clinical benefits.

In this study, the overall clinical efficacy rate in the combination therapy group was 95.92%, significantly higher than 76.67% in the standard therapy group, highlighting the advantage of iguratimod in improving clinical symptoms in RA patients. Additionally, post-treatment DAS28 and VAS scores decreased significantly compared to baseline, reflecting substantial improvements in disease activity and pain relief. A phase III clinical trial involving 489 RA patients compared different initial doses of iguratimod with methotrexate and reported that a daily dose of 50 mg iguratimod achieved ACR20 response rates comparable to methotrexate (63.8% vs. 62.0%), providing robust evidence for the efficacy of iguratimod in early RA management [12].

Additionally, Hu Chaojun et al. conducted a systematic review and meta-analysis in 2021, including 23 randomized controlled trials (RCTs) evaluating the efficacy and safety of iguratimod (IGU), either as monotherapy or in combination with other DMARDs for the treatment of RA [13]. The results demonstrated that, compared to standard therapy groups (primarily methotrexate monotherapy), patients receiving iguratimod showed significant advantages across multiple efficacy outcomes. These included a higher ACR20 response rate (OR=1.97), significant reductions in DAS28-CRP and DAS28-ESR scores, shorter duration of morning stiffness, and lower Health Assessment Questionnaire (HAQ) scores (all P<0.05). These findings indicate substantial improvements in disease activity, functional status, and quality of life. Together with the phase III clinical trial, this systematic review provides consistent evidence supporting the robust and stable efficacy of iguratimod in improving RA disease control and functional outcomes, closely aligning with the findings of the present study and reinforcing its value as a therapeutic option in clinical practice.

As a novel antirheumatic agent increasingly applied in the treatment of RA, iguratimod exhibits multi-target pharmacological effects. It alleviates both local and systemic inflammation by inhibiting NF-κB signaling and downregulating proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α [14, 15]. In addition, iguratimod exerts protective effects on bone metabolism by suppressing osteoclast activity and bone resorption, while

promoting osteoblast differentiation and functional recovery, thereby slowing the progression of joint destruction [16, 17]. Moreover, it modulates immune dysregulation by inhibiting abnormal immunoglobulin secretion. Extensive evidence indicates that iguratimod, whether administered as monotherapy or in combination with conventional antirheumatic drugs, demonstrates robust clinical efficacy and a favorable safety profile. In terms of joint function, patients receiving combination therapy showed significant reductions in morning stiffness duration and notable improvements in joint function grading, with an increased proportion of Grade I joints and a decreased proportion of Grade IV. These findings suggest that iguratimod effectively improves joint functional status in RA patients, potentially through inhibition of synovial cell proliferation and promotion of cartilage-protective mechanisms. Regarding inflammatory markers, after 12 weeks of treatment, patients in the combination therapy group exhibited significantly lower levels of hs-CRP, ESR, and RF compared to the standard therapy group, indicating effective suppression of systemic inflammation and autoantibody production. Importantly, improvements in these hematological markers correlated closely with reductions in DAS28 scores, supporting their clinical relevance in assessing RA disease activity. These findings are highly consistent with previous studies [18, 19].

In terms of imaging assessment, ultrasound evaluations revealed that patients in the combination therapy group exhibited significant reductions in synovial thickness and better preservation of cartilage integrity, including the medial and lateral femoral condyles. Additionally, the incidences of synovial proliferation, synovial blood flow signals, and joint effusion were significantly lower than those in the standard therapy group. The synovial arterial resistance index was also markedly decreased, indicating effective improvement in synovial inflammation and blood perfusion [20, 21]. These findings suggest that iguratimod not only alleviates systemic inflammation but also inhibits synovial angiogenesis, thereby slowing bone destruction and pathological synovial proliferation. This contributes to the preservation of local joint structure, aligning closely with the expected effects of delayed radiographic progression. Furthermore, the results underscore the critical role of dynamic ultrasound monitoring for precise assessment and management of RA.

Regarding safety, the incidence of adverse reactions was comparable between the two groups, primarily consisting of mild to moderate gastrointestinal discomfort, rash, elevated transaminases, and leukopenia, with no serious adverse events reported. These findings indicate that iguratimod is generally well tolerated and safe over a 12-week treatment period [22]. Previous studies have reported that the incidence of ALT and AST elevation following iguratimod treatment is approximately 10%, with most cases being mild to moderate and reversible, resolving upon drug discontinuation or symptomatic management, consistent with the findings of this study [22]. Evidence also suggests that combining iguratimod with other DMARDs does not significantly increase the risk of liver dysfunction, supporting the safety of combination therapy; however, caution is advised in patients with preexisting liver disease, and individualized treatment adjustments may be necessary. Regarding bone marrow suppression, previous research has indicated that the incidence of leukopenia with iguratimod combined with leflunomide (LEF) is comparable to MTX. In this study, a slight increase in leukopenia was observed in the iguratimod group [23], although the difference compared with the conventional treatment group was not statistically significant. These observations highlight the importance of routine monitoring of liver function and white blood cell counts during iguratimod therapy to ensure patient safety.

Furthermore, no adverse events related to renal function were reported in this study, which is markedly lower than the 5.1% incidence reported in previous studies [1]. This discrepancy may be attributable to the younger age, shorter disease duration, and smaller sample size of participants in the present study. These findings are also consistent with data from phase II and III clinical trials conducted in China, which reported an incidence of iguratimod-associated renal adverse events below 1%, indicating minimal impact on renal function and a favorable safety profile [13, 14, 19].

In summary, iguratimod combined with conventional therapy significantly ameliorates inflam-

matory responses, clinical symptoms, and joint structural damage in RA patients across multiple dimensions, demonstrating substantial clinical value. Additionally, this study confirms that combined dynamic monitoring of hematological and imaging parameters provides a more comprehensive assessment of RA disease activity, supporting more precise disease progression monitoring and individualized treatment planning. However, as a single-center retrospective study with a relatively small sample size and notable individual variability in certain markers, such as RF reduction, further multicenter, large-scale, prospective studies are warranted to validate these findings.

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Disclosure of conflict of interest

None.

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