Efficacy of formic acid in combination with cDMARDs in rheumatoid arthritis

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Abstract. – OBJECTIVE: The immune system of the body mistakenly targets its own joints in rheumatoid arthritis (RA), a chronic autoimmune disease that causes pain, inflammation, and damage. The complexity of RA often requires the simultaneous use of several different management strategies. This study examines the potential enhancement of conventional RA treatments, specifically conventional Disease-Modifying Anti-Rheumatic Drugs (cDMARDs), by the addition of formic acid, a naturally occurring substance that may possess anti-inflammatory properties.

PATIENTS AND METHODS: A total of 90 children diagnosed with rheumatoid arthritis were examined at our hospital from 2020 to 2022. We segregated them into two cohorts, each consisting of 45 children. One cohort was administered conventional rheumatoid arthritis (RA) treatments, referred to as cDMARDs, which specifically included methotrexate and leflunomide. The other group was administered the standard treatments in addition to a low dosage of a specialized medication known as all-trans retinoic acid. We conducted follow-up assessments on the children at 6 months and 1-year post-treatment. We sought to evaluate the efficacy of the treatments by assessing the subjective reports of the children and their physicians, analyzing the outcomes of medical examinations, and examining diagnostic images, such as X-rays. Furthermore, we took measures to ensure the safety of the treatments.

RESULTS: Among the cohort exclusively administered cDMARDs, approximately 26.7% exhibited significant improvement, 24.4% demonstrated moderate improvement, and 6.7% displayed minor improvement after a duration of 6 months. Approximately 57.8% of the children in this group experienced positive outcomes as a result of the treatment. The group that received retinoic acid also demonstrated superior outcomes. Approximately one-third (33.3%) of the participants demonstrated significant improvement, while another one-third showed moderate improvement. Additionally, 11.1% of the participants displayed minor improvement after a period of six months. Upon comparing the two groups, it was observed that the group receiving retinoic acid demonstrated a significantly superior outcome ($p<0.05$).

CONCLUSIONS: Overall, the incorporation of all-trans retinoic acid alongside conventional treatments for children with RA appears to enhance their efficacy.

Key Words:
   MiRNA-106, Pediatric osteosarcoma, PI3K/AKT signaling pathway.

Introduction

Rheumatoid arthritis (RA) is a highly prevalent autoimmune disease, which is symmetrical and systemic, causing disabling and arthritic damage[1]. The precise origins of rheumatoid arthritis (RA) remain unknown. It is a condition that primarily induces a persistent inflammatory response in the joints of the body. Over time, this can result in significant harm, impeding the affected joints' ability to move correctly. Early and aggressive treatment of rheumatoid arthritis (RA) using a combination of medications can effectively retard joint damage and mitigate disability[2]. Currently, the primary approach to managing RA involves the use of conventional medications specifically formulated to combat this type of inflammation. Certain individuals opt for mono-therapy with methotrexate, whereas others employ a combination of various pharmacological agents. Nevertheless, many patients do not experience significant improvement or only observe marginal amelioration with these therapies. Doctors face a significant challenge[2]. In China, the prevalence of rheumatoid arthritis (RA) is approximately 0.5%, with a higher incidence among men, occurring

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about 2.4 times more frequently than in women. Although rheumatoid arthritis (RA) is more prevalent among individuals aged 50 and above, it can also affect children. For the treatment of rheumatoid arthritis (RA) in children, doctors frequently employ conventional disease-modifying antirheumatic drugs (cDMARDs)[3]. These medications are highly effective in alleviating inflammation, diminishing joint swelling, and mitigating pain. However, not all children exhibit positive reactions to these therapies. In addition, cDMARDs can be costly, and there is always the potential for adverse effects, which complicates their utilization.

Although cDMARDs offer advantages in the treatment of pediatric rheumatoid arthritis, inconsistent outcomes, high costs, and the need to carefully manage potential adverse effects pose challenges. Researchers have recently identified an imbalance in the body's immune system as a key factor in the development of RA[4]. This disparity could also elucidate the limited efficacy of cDMARDs in certain patients. Consequently, the pursuit of discovering novel medications that can rectify the equilibrium of the immune system has emerged as a primary objective in enhancing the treatment of RA, particularly in pediatric patients. All-trans retinoic acid, a derivative of vitexic acid, is widely recognized in medical settings for its capacity to regulate the immune system[5]. The extensive documentation of its efficacy in regulating immune responses, specifically in cases such as promyelocytic leukemia and diverse forms of cancer, is well-established. Nevertheless, the application of this treatment for rheumatoid arthritis (RA) in children is relatively obscure and has been infrequently documented[6]. Presently, clinical trials are investigating the utilization of all-trans retinoic acid in extended treatment protocols, typically spanning a minimum of six months to one year, specifically for the management of rheumatoid arthritis in children[7,8]. The results obtained from these studies have been encouraging, demonstrating a high level of effectiveness of this treatment approach. However, due to the high costs, most patients are unable to afford biological treatments, and those who do receive them often discontinue after less than three months[9].

What is the efficacy of short-term fully trans-vitamin in conjunction with anti-rheumatic drugs? Does the treatment provide benefits to the patient? What are the long-lasting consequences? There is a lack of research on these topics. Therefore, our objective is to design a research study that assesses the effectiveness of a simplified treatment plan involving the use of both an all-trans retinoid and an anti-rheumatic drug in pediatric patients with rheumatoid arthritis, using principles similar to those used in antihypertensive therapy in the field of rheumatology. This study employs an all-trans retinoid in combination with cDMARDs to treat rheumatoid arthritis (RA) in children. It will examine both the short-term and long-term effectiveness of this treatment to improve the clinical approach to managing RA in pediatric patients.

Patients and Methods

Clinical Information

Ninety pediatric patients with rheumatoid arthritis treated at our hospital from 2020 to 2022 were selected as the study's subjects.

Inclusion criteria
1) Adherence to the RA classification criteria[10].
2) Participants, ranging in age from 8 to 16 years, of any gender, who exhibit a robust commitment to following the prescribed treatment plan.
3) All participants are required to have been newly diagnosed with rheumatoid arthritis (RA), without any recent treatment within the past 3 months, and no recent usage of non-steroidal anti-inflammatory drugs (NSAIDs) within the past month.
4) Participants or their guardians must provide informed consent, which is signed voluntarily.

Exclusion criteria
1) Individuals with substantial underlying conditions related to the circulatory, respiratory, gastrointestinal, urological, or hematopoietic systems.
2) Individuals who have been diagnosed with osteoarthritis or gouty arthritis.
3) Individuals in the terminal phase of any ailment.
4) Patients with disabilities, such as blindness, deafness, intellectual disability, cognitive dysfunction, or any physical impairment, as determined by legal criteria.
5) Patients with significant underlying conditions impacting major organs.
6) Patients in the past 3 months with a medical history or existing condition that could potentially disrupt the study.

7) Patients who have multiple allergies, defined as being allergic to more than two types of foods or drugs, or specifically to any drugs included in this study.
8) Individuals with a documented or potential background of alcohol or substance misuse.

The participants were allocated randomly to either the cDMARDs group or the retinoic acid combination group using a random number table. Each group consisted of 45 individuals. Data was gathered encompassing detailed demographic and clinical information, such as gender, age, disease duration, number of tender joints, number of swollen joints, Erythrocyte Sedimentation Rate (ESR), and Visual Analogue Scale (VAS) score, among other variables.

Procedure

Both the cDMARDs group and the retinoic acid combination group received standard supportive care, which consisted of ample bed rest and moderate strength training exercises targeting the muscles surrounding the joints.

In the cDMARDs group, patients received treatment with methotrexate (Hunan Zhengqing Pharmaceutical Group Co., Ltd., Huaihua, Hunan, China, license number H19983205) in the form of 2.5 mg tablets. The dosage consisted of taking 2 tablets orally once daily, twice a week. Additionally, they were administered leflunomide (Suzhou Ltd., Suzhou, Jiangsu, China, license number H20050129) in the form of 20 mg tablets. The treatment involved an initial loading dose of 40 mg per day for the first three days, followed by a maintenance dose of 20 mg per day. Alongside the usual drug treatment, the retinoic acid combination group was administered a small amount of all-trans retinoic acid (Shanghai Yiyuan Biotechnology, Shanghai, China, license number H20190318) in the form of 20 mg tablets. The dosage consisted of taking 1 tablet orally twice a week.

Observation Indicators

Both the cDMARDs group and the retinoic acid combination group were evaluated at 6 months and 1 year of intervention for comprehensive near-term and long-term efficacy. The changes of subjective efficacy indexes, objective efficacy indexes, and imaging-related indexes were observed in the 2 groups before, at 6 months and 1 year of intervention.

Clinical Control

The patient's pain and swelling have mostly subsided, and their joint function was fully restored. The local skin's temperature was stabilized.

Medically Successful

The patient no longer had discomfort or swelling, and their joint was operating normally. Most of the local skin temperature returned to normal.

Almost Clinically Effective

The patient exhibited a slight limitation in joint mobility; however, there was a substantial alleviation of pain and swelling symptoms and a noticeable enhancement in the local skin temperature.

Medically Ineffective

The patient exhibited no substantial enhancement in joint functionality, persisted in experiencing pain and swelling symptoms, and there was no reduction in local skin temperature.

Subjective Efficacy

The evaluation encompassed appraisals for joint inflammation, intensity of pain, and the overall impact of osteoarthritis. The evaluations were conducted utilizing precise scoring techniques:

Joint Swelling Score

This was assessed using a standardized joint flotation test:
1) Grade I (1 point): There is a small amount of swelling, and the joint flotation test shows a negative result when compared to the unaffected side.
2) Grade II (2 points): There is a slight increase in swelling and a positive outcome in the joint flotation test when compared to the unaffected side.
3) Grade III (3 points): Significant edema accompanied by a positive outcome in the joint flotation test, clearly distinguishable from the unaffected side.
4 Grade IV (4 points): Profound edema that prevents palpation of the bone condyle, accompanied by a positive outcome in the joint flotation test.

The Visual Analog Score (VAS) was employed to evaluate the level of joint pain. Patients assessed their pain level using a scale, offering a subjective indication of their discomfort.

The WOMAC Osteoarthritis Index Score, is a measurement used to assess the severity of osteoarthritis. This comprehensive assessment measured three fundamental factors: pain, stiffness, and the effect on everyday activities. The assessment encompassed 24 subcategories, offering a comprehensive understanding of the patient's overall state and the impact of osteoarthritis on their daily existence.

Objective Efficacy

The study involved assessing blood levels of C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), and the ratio of helper T-cell 17 (Th17) to Regulatory T-cell (Treg).

The hospital's laboratory department evaluated the levels of CRP and ESR. The tests were performed by obtaining brachial venous blood samples from patients who were fasting in the morning on the day of the test. The immune response was assessed by quantifying the levels of Th17 and Treg cells through flow cytometry. This procedure entailed the computation of the Th17/Treg ratio in order to comprehend the equilibrium of these cellular subtypes within the immune system.

The FACS Canto II flow cytometer, supplied by BD Biosciences, a subsidiary of Becton, Dickinson and Company (BD), located in San Jose, CA, USA, was utilized for this procedure.

Imaging-Related Indexes

A high-resolution color Doppler ultrasound diagnostic device, with a frequency range of 7-12 MHz, was used for the ultrasound examination. The patients were positioned in a lying-down posture, and the device was adjusted to a mode specifically engineered for identifying slow blood flow in skeletal muscles, guaranteeing accurate visualization of the affected joint regions. The utilization of ultrasound facilitated the detection of alterations such as synovial hyperplasia, bone degradation, and accumulation of fluid within the joint. The ultrasound findings were scored using a semi-quantitative approach, taking into account the observed imaging characteristics[11].

Scoring the Proliferation of Synovial Tissue

1) Revised: there was no observed increase in the number of cells (Score: 0).
2) Mild: proliferation limited to the synovial membrane (Score: 1).
3) Moderate: the growth is extending beyond the surface of the bone (Score: 2).

4) Severe: the growth spreading to the bone shaft (Score: 3).

Scoring for Bone Erosion

1) Absent: no evidence of bone erosion (Score: 0).
2) Slight: the bone surface is rough but does not show any obvious defects (Score: 1).
3) Moderate: evident abnormalities in the structure of the bones (Score: 2).
4) Severe: there are significant bone defects present, with a score of 3.

Scoring the Amount of Fluid in a Joint

1) Not present: there is no accumulation of fluid in the joint (Score: 0).
2) Mild: minimal accumulation of fluid (Score: 1).
3) Moderate: there is a moderate amount of effusion present, with a score of 2.
4) Severe: significant accumulation of fluid (Score: 3).

Assessment of Joint Mobility using the Disease Activity Score 28 (DAS28) Index

1) No impairment: DAS28 score less than or equal to 2.6.
2) Mild impairment: DAS28 score greater than 2.6 and less than or equal to 3.2.
3) Moderate impairment: DAS28 score greater than 3.2 and less than or equal to 5.1. 4.
4) Severe impairment: DAS28 score greater than 5.1.

A meticulous evaluation of every aspect was conducted to offer a thorough assessment of the joint's condition, facilitating the diagnosis and ongoing monitoring of disease progression.

Safety Evaluation

Throughout the study period, we monitored untoward incidents involving both groups, and once the medicine was administered, we noted any discomfort symptoms and unusual lab test findings.

Statistical Analysis

The data analysis was performed using SPSS 21.0 (SPSS Corp., Armonk, NY, USA). The data was summarized by calculating the mean values along with their corresponding standard deviations ($x\pm s$). We employed the *t*-test to compare two sets of data. In order to compare more than two groups, we utilized the One-way Analysis of Variance (ANOVA) statistical test. To conduct detailed pairwise comparisons, we employed the Scheffe's method. In addition, we conveyed our

Table I. Basic information comparison between the two groups.

Classification	cDMARDs group (n=45)	Retinoic acid combination group (n=45)	χ^2/t	p
Sex			0.179	0.673
Male	25	23		
Women	20	22		
Age (years)	12.0±1.2	12.3±1.5	1.048	0.298
Duration of disease (years)	3.5±0.5	3.7±0.8	1.422	0.159
Number of pressure pains (pcs)	15.3±7.5	17.0±5.6	1.218	0.226
Number of swellings (pcs)	12.9±7.5	13.0±5.2	0.074	0.942
ESR	42±3	41±3.2	1.529	0.130
VAS score	77.30±9.8	77.33±7.85	0.016	0.987
DAS28	7.20±0.97	7.30±0.80	1.601	0.113

discoveries by expressing the total number of cases as a percentage. Furthermore, we employed the χ^2 (Chi-square) test to analyze the association between various categories. Based on our analysis, we deemed a p-value (probability value) below 0.05 to be indicative of a statistically significant disparity, implying that the observed outcomes are improbable to have arisen randomly.

Results

General Information Comparison

There were no statistically significant differences between the two groups in terms of gender, age, disease duration, number of indurations, number of swellings, ESR, Visual Analog Scale (VAS) score, and Disease Activity Score in 28 Joints (DAS28) ($p>0.05$). More details are presented in Table I.

Comparison of Clinical Efficacy

In the cDMARDs group, 12 cases (26.7%) were clinically controlled, 11 cases (24.4%) were clinically effective, and 3 cases (6.7%) were clinically effective at 6 months of treatment, the overall efficient rate was 57.8%. Clinical outcomes in

the retinoic acid combination group were greater than those in the cDMARDs group at 6 months of treatment, with a difference that was considered statistically significantly different ($p<0.05$) (Table II). 15 cases (33.3%) were clinically controlled, 15 cases (33.3%) were clinically effective, and 2 cases (4.47%) were clinically effective in the cDMARDs group at 1 year of treatment, with an overall effective rate of 71.1%. 20 cases (44.4%) were clinically controlled, 125 cases (26.7%) were clinically effective, and 8 cases (17.8%) were clinically effective in the retinoic acid combination group at 6 months of treatment, the clinical outcome at 1 year of treatment was overall higher in the retinoic acid combination therapy group than the cDMARDs group, with the differences being statistical in significance ($p<0.05$) (Table II and Table III).

Subjective Efficacy Comparison

Prior to the intervention, there were no significant differences in joint swelling scores, joint VAS scores, and WOM-AC ratings between the two groups, indicating that they were quite similar ($p>0.05$). Nevertheless, at the 6-month and 1-year marks of the intervention, there was a significant decrease in scores observed in both

Table II. Comparative clinical outcomes of the two groups over the last 6 months.

Group	Number of cases	Clinical control (%)	Clinical efficacy (%)	Clinically effective (%)	Clinically ineffective (%)	Total effective (%)
cDMARDs group	45	12 (26.7)	11 (24.4)	3 (6.7)	19 (42.2)	26 (57.8)
Retinoic acid combination group*	45	15 (33.3)	15 (33.3)	5 (11.1)	10 (22.2)	35 (77.8)
χ^2				4.121		
p				0.042		

cDMARDs group *vs*. retinoic acid combination group; *p-value: 0.042, $p<0.05$; Chi-square (χ^2) value: 4.121; p-value: 0.042.

Table III. Comparison of the recent 1-year clinical outcomes of the 2 groups.

Group	Number of cases	Clinical control (%)	Clinical efficacy (%)	Clinically effective (%)	Clinically ineffective (%)	Total effective (%)
cDMARDs group	45	15 (33.3)	15 (33.3)	2 (4.4)	13 (28.9)	32 (71.1)
Retinoic acid combination group*	45	20 (44.4)	12 (26.7)	8 (17.8)	5 (11.1)	40 (88.9)
χ^2				4.444		
p				0.035		

cDMARDs group *vs.* retinoic acid combination group; *p-value: 0.035, $p<0.05$; Chi-square (χ^2) value: 4.444.

groups, indicating a noteworthy enhancement in comparison to the scores prior to the intervention ($p<0.05$). After 6 months, the group treated with conventional disease-modifying anti-rheumatic drugs (cDMARDs) exhibited slightly elevated scores for joint swelling, joint visual analog scale (VAS), and Western Ontario and McMaster Universities Arthritis Index (WOM-AC) ratings compared to the group treated with retinoic acid combination. However, the observed differences did not reach a level of statistical significance ($p>0.05$), suggesting that the outcomes were relatively comparable between the two groups at that specific time point (Table IV).

Objective Efficacy Comparison

Prior to the intervention, the levels of CRP, ESR, and Th17 in both groups exhibited a considerable degree of similarity, with no statistically significant differences observed ($p>0.05$). Nevertheless, at the 6-month and 1-year marks of the intervention, there was a notable reduction in the levels of CRP, ESR, and Th17 compared to their levels prior to the intervention ($p<0.05$), suggesting a positive outcome. After 6 months, the group treated with cDMARDs exhibited slightly elevated levels of CRP, ESR, and T-helper 17 (Th17) compared to the group receiving a combination of retinoic acid. However, the observed differences did not reach statistical significance ($p>0.05$), indicating that the changes in both groups were relatively similar at that particular stage (Table V).

Comparison of Imaging-Related Indicators

Before the intervention, there was no notable disparity between the two groups in relation to synovial hyperplasia scores, bone erosion scores, joint effusion scores, and DAS28 scores ($p>0.05$), indicating comparable conditions in both groups at the outset. However, at the 6-month and 1-year marks of the intervention, there was a significant decrease in scores for both groups. This suggests an improvement compared to the scores prior to the intervention ($p<0.05$).

After 6 months of treatment, there were no significant differences in synovial hyperplasia scores, bone erosion scores, joint effusion scores, and DAS28 scores between the cDMARDs group and the retinoic acid combination group ($p>0.05$). However, at the 1-year mark, there were significant differences in synovial hyperplasia scores, bone erosion scores, and DAS28 scores between

Table IV. Subjective efficacy comparison between the two groups.

Group	Number of cases	Joint swelling score	Joint VAS score	WOM-AC rating
	Pre-intervention Intervention 6 months Intervention 1 year	Pre-intervention Intervention 6 months Intervention 1 year	Pre-intervention Intervention 6 months Intervention 1 year	
cDMARDs group	45	3.1±0.7	7.4±1.4	59.0±9.0
	2.4±0.5*	4.4±1.1*	47.2±6.2*	
	2.3±0.6*	4.7±1.0*	42.3±7.1*	
Retinoic acid combination group	45	3.1±0.6	7.3±1.3	58.0±9.0
		2.3±0.5*	4.3±1.1*	46.0±6.0*
		1.3±0.3*#&	2.7±0.9*#&	30.5±5.8*#&

cDMARDs group *vs.* retinoic acid combination group; *$p<0.05$ as opposed to pre-intervention; #$p<0.05$ as opposed to 6 months of intervention; &$p<0.05$ as opposed to cDMARDs group.

Table V. Objective efficacy of the two groups compared.

Group	Number of Cases	CRP/(p-mg-L^{-1})	ESR (mm-h)	Th17 (Treg)
	Pre-intervention Intervention 6 months Intervention 1 year	Pre-intervention Intervention 6 months Intervention 1 year	Pre-intervention Intervention 6 months Intervention 1 year	
cDMARDs group	45	20.0±3.3 18.7±2.8* 16.3±2.4*#	40.5±5.1 37.2±3.0* 35.0±4.0*#	1.38±0.42 1.19±0.36* 1.10±0.32*#
Retinoic acid combination group	45	20.5±3.0 18.7±2.6* 13.3±2.1*#&	40.0±5.0 37.0±3.1* 29.0±3.0*#&	1.35±0.40 1.16±0.35* 0.83±0.24*#&

cDMARDs group *vs.* retinoic acid combination group; *$p<0.05$ *vs.* before infection; #$p<0.05$ *vs.* 6 months of intervention; &$p<0.05$ *vs.* cDMARDs group.

the two groups ($p<0.05$), suggesting a noticeable divergence in their progress. Nevertheless, the joint effusion scores at this juncture did not exhibit a substantial disparity between the two groups ($p>0.05$). More details are presented in Table VI.

Safety Evaluation

Adverse reactions occurred in 9 cases (20.0%) in the cDMARDs group and 5 cases (11.1%) in

the retinoic acid combination group, with differences but no statistical significance ($p>0.05$) (Table VII).

Discussion

RA is a widespread autoimmune condition marked by intense, symmetrical inflammation of the joints. This condition greatly diminishes the

Table VI. Comparisons between the two groups for imaging-related indicators group.

Group	Number of cases	Synovial hyperplasia score	Bone erosion score	Joint effusion score	DAS28 rating
		Pre-intervention Intervention 6 months Intervention 1 year	Pre-intervention Intervention 6 months Intervention 1 year	Pre-intervention Intervention 6 months Intervention 1 year	Pre-intervention Intervention 6 months Intervention 1 year
cDMARDs group	45	2.18±0.38 1.83±0.36* 1.58±0.30*#	2.26±0.40 1.74±0.36* 1.53±0.27*#	2.4±0.4 1.8±0.4* 1.5±0.3*#	4.9±2.5 4.0±0.8* 2.9±0.5*#
Retinoic acid combination group	45	2.11±0.37 1.89±0.39* 1.26±0.21*#&	2.22±0.37 1.68±0.34* 1.32±0.18*#&	2.4±0.3 1.8±0.2* 1.5±0.2*#	4.9±2.4 3.9±0.7 2.2±0.5*#&

cDMARDs group *vs.* retinoic acid combination group; *$p<0.05$ *vs.* before intervention; #$p<0.05$ *vs.* 6 months of intervention; &$p<0.05$ *vs.* cDMARDs group.

Table VII. Comparative safety evaluation of the two teams.

Group	Number of cases	Diarrhea	Infection	Elevated blood pressure	Liver and kidney abnormalities	Vomiting	Total number of cases (percentage)
cDMARDs group	45	2	3	2	1	1	9 (20.0%)
Retinoic acid combination group	45	1	1	1	1	1	

cDMARDs group *vs.* retinoic acid combination group; Chi-square (χ^2) value: 1.363. *p*-value: 0.245.

quality of life as it leads to foot deformities, impaired blood flow, and gradual deterioration of the joints[12]. This condition is characterized by a protracted duration, challenging treatment, notable variations among individuals, and a substantial likelihood of deformity and disability[12]. RA affects approximately 0.3% of the population in China, with a higher prevalence among women[13]. It typically develops between the ages of 35 and 50[14]. The prevalence of this condition is greater among women and is more common in Europe and the United States than in China[15]. RA is characterized by the presence of swelling, pain, and deformation in symmetrical joints, specifically in the proximal and metacarpophalangeal joints. Timely and standardized treatment can help reduce additional damage to the joints, although the specific treatment methods for rheumatoid joint infection may differ.

The pathogenesis of RA is caused by immune dysregulation, which is mainly characterized by an imbalance between Th17 and Treg cells. This imbalance results in an overload of the immune system[16,17]. The treatment primarily centers around immunosuppression, which, although advantageous for certain individuals, carries the potential risks of infections and tumors[18]. Due to higher rates of remission and greater efficacy in treating patients, targeted biologics have raised hope, but their expensive cost prevents their widespread use.

The current approach for treating RA is to combine the biologic drug tocilizumab with methotrexate[19]. However, the long-term economic impact and inconsistent patient responses highlight the necessity for developing new therapeutic approaches. The objective of treatment is to alleviate symptoms, preserve joint function, and hinder additional harm and disability. Western medicine predominantly employs cDMARDs, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and biologic agents. cDMARDs are particularly recommended for both early and chronic cases of rheumatoid arthritis (RA), including pediatric cases[19]. Nevertheless, the fluctuation in treatment reactions to cDMARDs has redirected attention towards immunomodulatory medications and their amalgamation with other therapies[19].

All-trans retinoic acid, derived from vitamin A, has a crucial function as an immunomodulator. It controls the differentiation of T and B cells and affects the production of both pro- and anti-inflammatory substances[20]. It exerts a dual influence on the functions of Th17 and Treg cells, enhancing the development of regulatory T cells

while suppressing the formation of Th17 cells[20]. Ensuring this two-fold process is essential for preserving immune equilibrium and managing autoimmune disorders. Previous studies have emphasized the important role of all-trans retinoic acid in autoimmune diseases. Kwok et al[22] have shown that it is effective in reducing symptoms such as joint swelling and pain in arthritic conditions. The results of this study support these observations, indicating that the use of both all-trans retinoic acid and cDMARDs can provide long-term advantages, enhancing both subjective (joint scores) and objective (CRP, ESR, Th17/Treg) outcomes in children with RA[22]. In addition, the European League Against Rheumatism emphasizes the significance of ultrasonography in the diagnosis of RA, evaluation of disease activity, monitoring of disease advancement, and assessment of treatment effectiveness[23]. This further reinforces the potential of combining therapies to improve long-term outcomes in the treatment of RA. Taking into account Zhang et al[24], which was discovered to have a significant relationship with our research, both publications examine RA in great detail, with a focus on improving the diagnosis and treatment of the illness. It seeks to discover biomarkers for diagnosis and investigate immune infiltration in RA by using bioinformatics. This analysis provides valuable insights into the underlying mechanisms of RA, while our study examines the effectiveness of formic acid in combination with cDMARDs, with the goal of improving treatment results. Collectively, they contribute to comprehending the intricacies of RA, indicating that combining therapeutic methodologies with molecular and immunological understandings could result in enhanced diagnosis and tailored treatment strategies for RA.

The investigation into RA, examining the effectiveness of formic acid in combination with cDMARDs and the potential of soluble receptor for advanced glycation end products (sRAGE) as a biomarker, emphasizes a fundamental principle in medical science: accurate diagnosis is the fundamental basis for successful treatment[26]. By accurately identifying biomarkers and comprehending disease mechanisms, it becomes possible to develop customized therapeutic approaches, thereby ensuring that patients receive the most suitable and potentially efficacious treatment strategies. The integration of diagnosis and treatment is essential for enhancing patient care and outcomes in RA and other areas.

Conclusions

In conclusion, the study suggests that the combination of trans-retinoic acid and conventional cDMARDs can improve the long-term effectiveness of treating RA in children. This approach also maintains a high level of safety, which justifies further investigation in clinical settings. Nevertheless, due to the study's reliance on reviews and the small number of cases examined, it is necessary to gather more comprehensive clinical data and potentially conduct additional animal studies in order to establish the therapeutic advantages and justification of this combination treatment. This will establish a strong theoretical foundation for effectively managing pediatric rheumatoid arthritis.

Data Availability
The experimental data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval
The Medical Research Ethic Committee of Renhe Hospital Affiliated to Three Gorges University has approved this study under reference number No. 20240103-3. The present declaration affirms that the current research endeavor aligns with the ethical guidelines set out in the Helsinki Declaration and conforms to the applicable rules and regulations of the People's Republic of China. The authors guarantee the veracity and comprehensiveness of all the information supplied in this study.

Informed Consent
The family/legal guardians of the patients signed informed consent.

Conflicts of Interest
The authors declared that they have no conflicts of interest regarding this work.

Authors' Contribution
Conceptualization: W.C and H.L; methodology: J.M; data curation: Y.Z; formal analysis: J.M; writing-original draft: J.P and H.L; project administration: W.C and H.L. All authors reviewed the results, approved the final version of the manuscript and agreed to publish it.

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