Research Program

(Version number: 02 Version date: 2025-04-9)

Project name: Clinical efficacy and safety of real-world patients with refractory rheumatoid arthritis (D2TRA) treated with Telitacicept in combination with Tofacitinib

Bidder: Zhejiang Provincial People's Hospital
Department: Rheumatology and Immunology
Principal Investigator: Zhenhua Ying

Investigator's statement and protocol signature page

As the principal person in charge of this research project, I will follow the Ethical Review of Biomedical Research Involving Human Beings (2016) of the Ministry of Health, the Declaration of Helsinki (2013) of the WMA and the International Ethical Guidelines for Human Biomedical Research (2002) of the CIOMS and the ethical principles of the GCP, using the protocol approved by the ethics committee under the guidance of the quality management specifications for drug clinical trials, and conducting the study in accordance with the requirements of this protocol to ensure the scientific validity of the study and to protect the health and rights of the subjects.

Name：_____
Signature：_____
Date：_____

Program Summary

Program Title	Clinical efficacy and safety of real-world patients with refractory rheumatoid arthritis (D2TRA) treated with telitacicept in combination with tofacitinib
Version number/version date	02/2025-04-9
Sponsors and Participating Units	Zhejiang Provincial People's Hospital
Principal Investigator	
Nature of Research	Clinical Studies
Purpose of the study	To observe the clinical efficacy and safety of Telitacicept combined with Tofacitinib in the treatment of D2TRA patients
Sample size	20
Research Subjects	Patients with refractory rheumatoid arthritis
Research Methodology	This real-world observational study prospectively enrolled 20 patients with difficult-to-treat rheumatoid arthritis (D2T RA) from the outpatient and inpatient departments of Zhejiang Provincial People's Hospital between April 2025 and April 2027. Eligible patients met the following criteria: failure of traditional disease-modifying antirheumatic drugs (DMARDs) and inadequate response to ≥2 biological/targeted synthetic DMARDs, requiring combination therapy with Telitacicept and Tofacitinib. Medications were prescribed according to the maximum insurance-covered duration (4-week intervals). Changes in laboratory parameters, tender joint count of 28 joints (TJC28), swollen joint count of 28 joints (SJC28), and Disease Activity Score 28 (DAS28) were evaluated through self-controlled comparisons at baseline (0 weeks) and 4, 8, 12, 16, 20, and 24 weeks. Additionally, joint ultrasound findings and adverse reactions were monitored throughout the study period.
Inclusion Criteria	1.Age 18-85 years; 2.Diagnosed with refractory rheumatoid arthritis according to the 2021 EULAR (European Alliance of Associations for Rheumatology) diagnostic criteria; 3.The traditional disease-improving rheumatic drug treatment is ineffective, and the use of two or more biological/targeted disease-improving anti-rheumatic drugs is ineffective, and telitacicept combined with

	tofacitinib is required treated patients; 4.Voluntarily provided written informed consent.
Exclusion Criteria	1.Exclusion of patients with severe diseases of major organs (e.g., heart, liver, or lungs); 2.Patients with malignancies, hematological disorders, or other autoimmune diseases (excluding rheumatoid arthritis); 3.History of allergy/hypersensitivity to the study medications (Telitacicept or Tofacitinib); 4.Active tuberculosis or active infectious diseases requiring systemic treatment; 5.Pregnancy, lactation, or refusal to use contraception during the study; 6.Failure to complete the prescribed Telitacicept + Tofacitinib regimen due to: Non-adherence or Severe adverse reactions ; 7.Other conditions contraindicating participation per investigator judgment.
Research Progress Plan	2025.4-2027.4
Statistical analysis methods	SPSS software was used for statistical analysis. Normality tests were performed using SPSS software was used for statistical analysis. Normality tests were performed using the Kolmogorov-Smirnov test, and measures conforming to a normal distribution were expressed as mean ± standard deviation (x ± s), and comparisons between groups were made using the two independent samples t-test; measures not conforming to a normal distribution were described by median and interquartile spacing, i.e., median (25th percentile, 75th percentile) [M(P25,P75)], and comparisons between groups were made using the Mann-Whitney U anecdotal test The difference between groups was considered statistically significant at $P < 0.05$. The data were analyzed by the chi-square test or Fisher's exact probability method.
Form of publication of research results	Published 1-2 papers

1. Purpose of the study

(1)To observe the effect of Telitacicept combined with Tofacitinib on the clinical efficacy of D2T RA patients

(2)To observe the safety of Telitacicept combined with Tofacitinib in the treatment of D2T RA patients

2. Background of the study

Rheumatoid arthritis (RA) is a common systemic inflammatory autoimmune disease characterized by synovitis and bone destruction. Epidemiological data indicate a global RA prevalence of 0.5%-1%, with approximately 0.42% in China, totaling over 5 million affected individuals. RA is also one of the most disabling diseases in China, with a disability rate as high as 61.3%. The pathogenesis of RA remains unclear, but its fundamental pathology involves synovitis, pannus formation, and progressive destruction of articular cartilage and bone, ultimately leading to joint deformity and functional loss. RA is associated with comorbidities such as pulmonary diseases, cardiovascular disorders, malignancies, and depression. Beyond impairing physical function, quality of life, and social participation, RA imposes substantial economic burdens on patients, families, and society. Early detection, diagnosis, and treatment are critical for optimizing therapeutic outcomes.

Current RA management relies primarily on pharmacotherapy. The 2018 Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis classify therapeutic agents into four categories: nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), glucocorticoids (GCs), and herbal medications. While these drugs control symptoms and slow disease progression, they cannot fully halt structural damage. Over the past three decades, breakthroughs have been achieved with biological DMARDs (bDMARDs, e.g., TNF-α inhibitors, IL-6 inhibitors, B-cell-depleting antibodies, and co-stimulation molecule inhibitors) and targeted synthetic DMARDs (tsDMARDs, e.g., pan-JAK and JAK1/2 inhibitors).

Despite advancements in drug development and the clinical implementation of treat-to-target strategies, approximately 5%–20% of RA patients exhibit persistent disease activity and are classified as having difficult-to-treat RA (D2T RA). In 2021, the European Alliance of Associations for Rheumatology (EULAR) established three diagnostic criteria for D2T RA:(1) failure of csDMARDs after treatment according to the EULAR recommendations (unless there is a contraindication) after failure of ≥ 2b/tsDMARDs (with a different mechanism of action); (2) presence of at least one of the following: at least moderate disease activity; signs and/or symptoms suggestive of active disease; inability to taper glucocorticoid therapy; rapid imaging progression; RA symptoms leading to decreased quality of life; (3) rheumatologists and/or patients who believe that signs and/or symptoms of treatment is problematic.

D2T RA patients often exhibit poor adherence, lower socioeconomic status, and comorbidities such as fibromyalgia, osteoarthritis, and pain syndromes. These individuals experience suboptimal clinical responses, higher rates of joint deformity, and greater disease-related economic burdens compared to typical RA patients, making D2T RA a critical unmet need in rheumatology.

Exploring novel therapeutic strategies for D2T RA has become a priority. While RA pathogenesis remains incompletely understood, it is recognized as an immune-pathological process triggered by environmental factors in genetically predisposed individuals, with immune dysregulation playing a central role. Emerging evidence highlights abnormal activation of autoreactive B cells — which breach immune tolerance and produce autoantibodies (key RA biomarkers) — as pivotal in RA progression. B-cell-targeted therapies (e.g., rituximab) are widely used, yet single-target approaches face limitations due to the complexity of immune regulatory networks. Consequently, multi-target strategies modulating multiple pathways have gained traction, offering enhanced efficacy and reduced adverse effects.

China's first domestically developed dual-target biologic drug, Telitacicept, is a TACI-Fc fusion protein composed of the extracellular domain of the human transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI)

receptor and the Fc domain of human immunoglobulin G (IgG). This novel structure enables dual-target inhibition of two cytokines critical for B-lymphocyte development: B-lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL). By suppressing B-cell-mediated autoimmune responses, Telitacicept effectively treats autoimmune diseases. Clinical studies have demonstrated the safety and tolerability of dual BLyS/APRIL inhibition in healthy populations. Approved in 2021 for systemic lupus erythematosus (SLE), Telitacicept has shown robust efficacy and safety in SLE management, with infections being the most common adverse event. Phase III trials for IgA nephropathy (IgAN), myasthenia gravis (MG), and neuromyelitis optica spectrum disorder (NMOSD) are ongoing. Notably, Telitacicept reduces glucocorticoid dependence and improves clinical stability in steroid-intolerant autoimmune disease (AID) patients, demonstrating promising potential for rheumatoid arthritis (RA) treatment.

In the quest for optimized difficult-to-treat RA (D2T RA) therapies, targeting alternative pathways is pivotal. The 2021 ACR guidelines recommend switching to JAK inhibitors after initial treatment failure. JAK kinases, non-receptor tyrosine kinases associated with cytokine receptors, activate the JAK-STAT signaling pathway-a key driver of RA pathogenesis. JAK inhibitors, as targeted synthetic DMARDs (tsDMARDs), competitively bind to ATP sites on JAK1/JAK2/JAK3, blocking phosphorylation and downstream inflammatory cascades.

Tofacitinib, a selective JAK1/JAK3 inhibitor and the first tsDMARD approved for RA, suppresses RA inflammation by disrupting JAK-STAT signaling. It also modulates T-cell responses by inhibiting Th1/Th17 differentiation while enhancing regulatory T-cell (Treg) activity, thereby rebalancing immune homeostasis. Lei et al. demonstrated that tofacitinib as first-/second-line therapy significantly reduces costs in moderate-to-severe RA patients refractory to conventional DMARDs, while maintaining cost-effectiveness as third-line treatment. Safety data indicate common adverse events (e.g., infections, transient lab abnormalities) with rare severe complications (e.g., cardiovascular events, thromboembolism).

The Phase III trial of Telitacicept for RA, completed in 2023 and presented at the ACR Annual Meeting, met all primary endpoints with favorable safety. Telitacicept's dual BLyS/APRIL inhibition reduces autoantibody production by targeting B cells, complementing tofacitinib's suppression of T-cell-driven cytokines (e.g., IL-6, IL-17) via JAK-STAT blockade. This dual-pathway strategy addresses both B- and T-cell dysregulation in RA, mirroring successful multi-target approaches in other autoimmune diseases (e.g., rituximab-abatacept combinations in refractory RA, albeit with infection risks).

The 2022 EULAR guidelines emphasize stratified combination therapy for RA. For patients with poor prognostic factors (autoantibody positivity, high disease activity, early erosions, or dual csDMARD failure), adding bDMARDs/tsDMARDs to csDMARDs is recommended after 3-6 months of inadequate response to methotrexate/glucocorticoids. Subsequent treatment failure warrants switching to alternative b/tsDMARDs. Abbasi et al. propose that combining biologics (or biosimilars) with DMARDs enhances outcomes, highlighting the therapeutic rationale for Telitacicept-tofacitinib synergy. Given their distinct mechanisms-Telitacicept’s B-cell modulation and tofacitinib’s cytokine inhibition-this combination may offer new hope for D2T RA patients, leveraging targeted efficacy, safety, and cost-effectiveness.

3. **Test basis**

(1)Pre-study animal experiments and literature base

Clinical Trial：Lv J, Liu L, Hao C,et al. Randomized Phase 2 Trial of Telitacicept in Patients With IgA Nephropathy With Persistent Proteinuria. Kidney Int Rep. 2022 Dec 29;8(3):499-506. doi: 10.1016/j.ekir.2022.12.014.

Cai S, Hu Z, Chen Y,et al. BLyS/APRIL dual inhibition for IgG4-RD: a prospective single-arm clinical trial of telitacicept. Ann Rheum Dis. 2023 Jun;82(6):881-883. doi: 10.1136/ard-2022-223529.

Wu D, Li J, Xu D, et al. Telitacicept in patients with active systemic lupus erythematosus: results of a phase 2b, randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2024 Mar 12;83(4):475-487. doi: 10.1136/ard-2023-224854.

(2)Subject selection basis Patients diagnosed with refractory rheumatoid arthritis who meet the 2021 European League Against Rheumatism (EULAR) diagnostic criteria for refractory rheumatoid arthritis

4. Resear ch Content

(1) Test population: patients with refractory rheumatoid arthritis

(2) Sample size: 20 D2TRA patients

(3) Specific study:This real-world observational study prospectively enrolled 20 patients with difficult-to-treat rheumatoid arthritis (D2T RA) from the outpatient and inpatient departments of Zhejiang Provincial People's Hospital between April 2025 and April 2027. Eligible patients met the following criteria: failure of traditional disease-modifying antirheumatic drugs (DMARDs) and inadequate response to ≥2 biological/targeted synthetic DMARDs, requiring combination therapy with Telitacicept and Tofacitinib. Medications were prescribed according to the maximum insurance-covered duration (4-week intervals). Changes in laboratory parameters, tender joint count of 28 joints (TJC28), swollen joint count of 28 joints (SJC28), and Disease Activity Score 28 (DAS28) were evaluated through self-controlled comparisons at baseline (0 weeks) and 4, 8, 12, 16, 20, and 24 weeks. Additionally, joint ultrasound findings and adverse reactions were monitored throughout the study period.

5. Resear ch Methodology:

Enrollment criteria (diagnostic criteria, inclusion criteria, exclusion criteria)

(1) Diagnostic criteria

The diagnostic criteria for D2TRA refer to the definition criteria proposed by EULAR 2021：

1. Failure of ≥2b/tsDMARDs (with different mechanisms of action) after failure of csDMARDs therapy (unless contraindicated) according to the European Rheumatology Consortium recommended treatment.
2. Presence of ≥ 1 of the following signs indicative of active/progressive

disease.

a. At least moderate disease activity (based on validated composite metrics including joint counts such as DAS28-ESR > 3.2 or CDAI > 10).

b. Signs (including acute phase reactants and imaging) and/or symptoms (joint related or otherwise) suggestive of active disease.

b. Inability to taper glucocorticoid therapy (prednisone below 7.5 mg/day or equivalent dose).

c. Rapid progression of imaging (with or without signs of active disease).

d. Good control of the disease according to the above criteria, but still have RA symptoms that lead to a reduced quality of life.

3. Rheumatologists and/or patients who perceive signs and/or symptoms as problematic in the treatment.

All three criteria need to be present in D2T RA.

b, Biological; CDAI, clinical disease activity index; cs, conventional synthesis; DAS28-ESR, the disease activity score of 28 joints was evaluated by ESR; DMARD, disease-modifying antirheumatic drug; mg, milligram; RA, rheumatoid arthritis; ts, targeted synthetic.

* Unless restricted by access to treatment due to socioeconomic factors.

† If csDMARD treatment is contraindicated, failure of ≥ 2 b/tsDMARDs with different mechanisms of action is sufficient.

‡ Rapid radiographic progression: change in van der Heijde-modified Sharp score ≥ 5 points at 1 year.

(2) Inclusion Criteria:

1.Age 18-85 years;

2.Diagnosed with refractory rheumatoid arthritis according to the 2021 EULAR (European Alliance of Associations for Rheumatology) diagnostic criteria;

3.The traditional disease-improving rheumatic drug treatment is ineffective, and the use of two or more biological/targeted disease-improving anti-rheumatic drugs is ineffective, and telitacicept combined with tofacitinib is required treated patients;

4.Voluntarily provided written informed consent.

(3) Exclusion Criteria:

1.Exclusion of patients with severe diseases of major organs (e.g., heart, liver, or lungs);

2.Patients with malignancies, hematological disorders, or other autoimmune diseases (excluding rheumatoid arthritis);

3.History of allergy/hypersensitivity to the study medications (Telitacicept or Tofacitinib);

4.Active tuberculosis or active infectious diseases requiring systemic treatment;

5.Pregnancy, lactation, or refusal to use contraception during the study;

6.Failure to complete the prescribed Telitacicept + Tofacitinib regimen due to:Non-adherence or Severe adverse reactions ;

7.Other conditions contraindicating participation per investigator judgment.

6. Test procedure

1. Subject management

Subject recruitment method: Direct recruitment during the clinical care process

2. Informed consent process: Subjects voluntarily joined the study and voluntarily signed the informed consent form.

7. Research Program

This observational study prospectively enrolled 20 patients with difficult-to-treat rheumatoid arthritis (D2T RA) from the outpatient and inpatient departments of Zhejiang Provincial People's Hospital between April 2025 and April 2027. Eligible patients had inadequate responses to both conventional disease-modifying antirheumatic drugs (DMARDs) and at least two biological or targeted synthetic DMARDs, requiring combination therapy with Telitacicept and Tofacitinib. No additional interventions were applied during the study. Telitacicept (National Medical Products Administration approval number S202110008; manufactured by Yantai Rongchang Biopharmaceutical Co., Ltd.) was administered at a dose of 160 mg via

subcutaneous injection once weekly for six months. Tofacitinib (National Medical Products Administration approval number H20203420; manufactured by Simcere Pharmaceutical Co., Ltd.) was prescribed at 5 mg orally twice daily. Medications were dispensed in 4-week intervals according to the maximum duration covered by medical insurance. Clinical and laboratory parameters, including rheumatoid factor, anti-cyclic citrullinated peptide antibodies, immunoglobulins (IgG, IgA, IgM), C-reactive protein, erythrocyte sedimentation rate, complete blood count, liver and kidney function, 28-joint tender and swollen joint counts, joint ultrasound findings, and DAS28-ESR scores, were assessed at baseline (Week 0) and at 4, 8, 12, 16, 20, and 24 weeks after treatment initiation. Adverse events were monitored throughout the study period. Self-controlled comparisons were performed to evaluate changes in laboratory markers, joint counts, and DAS28 scores over time. Disease activity was categorized as follows: clinical remission (DAS28 ≤2.6), low disease activity (2.6 < DAS28 ≤3.2), moderate disease activity (3.2 < DAS28 ≤5.1), and high disease activity (DAS28 >5.1). The study aimed to analyze the clinical efficacy and safety profile of the Telitacicept-Tofacitinib combination regimen in this refractory patient population.

8. Start and end of the experiment

2025.4-2027.4

9. Data Security and Monitoring Program

(This paragraph cannot be deleted, if not, fill in none. According to the requirements of the Ministry of Health's Measures for Ethical Review of Biomedical Research Involving Human Beings (2016), all research projects are required to have a data security and monitoring plan, and this item is one of the criteria for the ethics committee to review the project, please describe it specifically according to the requirements.)

(1) Overview of data management methods

1.Data are traceable. All clinical trial data correspond to specific subjects and investigators, and all modifications to the data are recorded in detail to create a series of traceable verification traces.

2.Correctness of data. The correctness of data mainly includes the authenticity and accuracy of data, all clinical trial data reflect the actual situation of the study truthfully without any falsification, fiction and tampering; the accuracy is reflected in the verifiable data sources, i.e. CRF, study records and entered data should be consistent with the data obtained from the actual study.

3.Data completeness. Study data were collected completely for each subject, and missing data due to special reasons were stated as to why they were missing.

4.Logical reasonableness of the data. To determine whether the data are logically unreasonable from a clinical perspective.

5.Timeliness of data. The data are observed and completed in a timely manner at the specified time points in the clinical trial.

(2) Adverse events and serious adverse events are reported and collected.

Reporting principles: 1. Report only adverse events related to the study drug. 2. Complete the Spontaneous Adverse Event Report Form for all related adverse events (serious and non-serious)

The following information should also be included to determine if the event is related, possibly related, or potentially related to the drug. Determination of event-drug relevance includes: 1. reasonable temporal sequence 2. dose-response relationship 3. pharmacology 4. discontinuation of dosing and/or positive re-dosing.

Classification of the severity of drug-related adverse events：

Mild	The symptoms do not alter the patient's normal function.
Moderate	The symptoms result in some degree of functional impairment, but are not damaging, uncomfortable, or embarrassing.
Severe	The symptoms are definitely detrimental to health, with significant functional impairment or incapacity.

3) Medical safety measures

1. Collect information, focus on prevention. Supervise the department to report the risk information of clinical medical research in a timely manner, so that the information monitoring is in place and the risk prevention is effective.

2. Early warning, timely disposal. The department strengthens the monitoring of risks,

regularly monitors and inspects, and once problems are found, reports them to the department head in a timely manner and takes decisive measures to control and resolve the risks in a timely manner, prevent the expansion and spread of risks, and minimize them.

3. We regularly assess risks and propose corrective measures to prevent them.

4. Before clinical research begins, the investigator must provide the subject with information about the treatment and the subject's rights and obligations, so that the subject fully understands and agrees to it, and signs an "informed consent" before the clinical research experiment can begin. If one of the following situations occurs, the emergency handling procedures should be started immediately to stop the scientific clinical medical research and report to the Science and Education Section.

1. The research clinical medical research in the technical staff or key equipment, facilities and other auxiliary conditions change, can not properly carry out clinical research or may bring uncertain consequences.

2.The occurrence of serious adverse consequences directly related to the research clinical medical study.

3.The ethical flaws in this research-based clinical medical study.

4.The medical quality and medical safety risks associated with this research-based clinical medical

study.

5. The clinical application of this research-based clinical medical study is inexact.

4) Communication with ethics committee and higher pharmacovigilance department

1.The research protocol needs to be developed and submitted to the Medical Ethics Committee for approval prior to the start of the project.

2.The project research should be filed with the higher drug regulatory authorities in a timely manner, and actively accept the guidance and supervision of the higher drug regulatory authorities.

5）Internal analysis plan for data

1.Data Collection

Information about patients who met the enrollment criteria and data from laboratory-related tests functional impairment or incapacity.were collected.

①Case collection form: includes basic information of enrolled patients, related diseases, disease duration, treatment, and test data of related indicators for individual data analysis.

②Summary table: includes the patient's disease and related index examination data for overall data analysis.

2.Assessing the overall data situation

①Evaluate the integrity of each data source: timely recording of patient-related data to ensure data integrity.

②Evaluate the accuracy and consistency of aggregated data: randomly check whether the extracted data are consistent with those in the database to ensure data accuracy.

3.Data cleaning and collation

①Check for errors and outliers in the data that clearly defy common sense, and when found, first check that the same patient metadata are the same, then check how this data was collected, and finally how to assess whether it is an outlier from a technical point of view, by using relevant statistical indicators and methods such as setting upper and lower limits to deal with outliers.

②For special numbers, first mark "missing value", there is a perfect data dictionary to query the actual situation of this field, if not need to promptly communicate to confirm such issues

4.Data Collation

①Uniform formatting and naming rules for data

②Recoding of certain information to meet subsequent analysis needs

5.Data Visualization

Histograms, line graphs, scatter plots or heat maps are used to visualize the data of patient-related indicators to show the data results and trends more clearly, so that the study results can be presented more clearly.

6.Data Analysis

Complete the data and perform statistical analysis on those that meet the criteria

1 ） Frequency of data security and monitoring reports submitted to the ethics committe

The research in this project is a low-risk study, so an annual review frequency is used. Also, the principal investigator holds regular study meetings and notifies the ethics committee if there are changes in the risk/benefit ratio of the study.

10. Respect for ethical principles and related regulations

The study was conducted in strict compliance with international and domestic standards and norms,including the Declaration of Helsinki ethical guidelines for human medical research and the relevant Chinese clinical research study norms and regulations. In the course of the study, if there is a need to revise this protocol, the revised protocol must be submitted to the Ethics Committee again for approval before implementation.

The Informed Consent Form for this study has been approved by the Medical Ethics Committee. If the Informed Consent Form is amended in writing, it will be sent to the Ethics Committee for approval to obtain the subject's consent again. Before the start of the study, the investigator provides patients with detailed information about the study, including the nature of the study, the purpose of the study, the possible benefits and risks, and the rights and obligations of the patients. The patient is fully informed and agrees, and signs the Informed Consent Form before the study can begin.

11. Statistical analysis plan

SPSS software was used for statistical analysis. Normality tests were performed using the Kolmogorov-Smirnov test, and measures conforming to a normal distribution were expressed as mean ± standard deviation (x ± s), and comparisons between groups were made using the two independent samples t-test; measures not conforming to a normal distribution were described by median and interquartile spacing, i.e., median (25th percentile, 75th percentile) [M(P25,P75)], and comparisons between groups were made using the Mann-Whitney U anecdotal test

Comparisons between groups were made using the Mann-Whitney U anecdotal sum test; count data were expressed as percentages, and comparisons between groups were analyzed using the chi-square test or Fisher's exact probability method, with differences considered statistically significant at $P < 0.05$.

12. Form of publication of research results

Published 1-2 papers

13. Data Logging Form

Observed indicators		Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Rheumatoid factor	IU/ml							
Anti-cyclic citrullinated peptide antibody	U/ml							
Immunoglobulin G	g/L							
Immunoglobulin A	g/L							
Immunoglobulin M	g/L							
C-reactive protein	mg/L							
Blood sedimentation	mm/h							
Leukocytes	$x10^9$ /L							
Blood platelets	$x10^9$ /L							
Glutathione aminotransferase	U/L							
Glutathione transaminase	U/L							

Globulin	g/L							
Creatinine	umol/L							
Glomerular filtration rate	ml/min							
Glomerular filtration rate	pcs							
Swollen number of 28 joints	pcs							
DAS28-ESR score	score							
Ultrasound of joints								

14. Adverse reaction record form

No adverse events have occurred	□yes □no
Name of undesirable events	
Start date of occurrence	____Year_____month_____day
Dosing time and dosage	_____ year _____ month _____ day_____mg
Severity*	□ Mild□ Moderate□ Severe
Whether to take measures	□yes □no
Relationship to study drugs	□Definitely related □Likely related □Possibly related □Possibly Unrelated □Definitely not related
Outcome of adverse events that occurred	□Still exists □Eased □No idea Relief Date_____ year _____ month _____ day
Whether the patient withdrew from the trial because of the adverse event	□yes □no

Severity*: mild (no treatment, no discontinuation), moderate (discontinuation, no treatment), severe(discontinuation, control treatment)