

Informed consent for clinical treatment

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

Scheme version number and version date: 02, 2025/4/9

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Dear subjects:

We invite you to participate in the efficacy and safety of Abatacept Combined With JAK Inhibitor in the treatment of refractory rheumatoid arthritis approved by Zhejiang Provincial People's hospital. This study will be carried out in Zhejiang Provincial People's Hospital, and 120 subjects are expected to participate voluntarily. This study has been reviewed and approved by the ethics committee of Zhejiang Provincial People's hospital.

These instructions will provide you with some information to help you decide whether to participate in this clinical study. Whether you participate in this study is entirely voluntary, and your decision will not affect your normal diagnosis and treatment rights and treatment in our hospital. If you choose to participate in this study, our research team will try its best to ensure your safety and rights in the research process!

These instructions provide you with some information to help you decide whether to participate in this clinical study. Please read it carefully. If you have any questions, please ask the researcher in charge of the study.

Objective:

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 ≥ 2 b/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.

Method:

If you agree to participate in this study, we will number you and establish medical records. In the study, no intervention factors were applied to you. This study is aimed at the observation of refractory RA patients who need to be treated with Telitacicept Combined With Tofacitinib. Therefore, you need to be able to go to the hospital for outpatient follow-up before drug treatment and at 4, 8, 12, 16, 20 and 24 weeks after treatment, and test the DAS28 score and relevant laboratory indexes (DAS28 score, C-reactive protein, ESR, bone metabolism index, blood routine, liver and kidney function). It is used to record the changes of your condition and observe the clinical efficacy and safety of Telitacicept Combined With Tofacitinib.

Possible risks and uncertainties:

All information provided will be kept strictly confidential. During the treatment period, Telitacicept may cause injection site reactions such as redness, swelling, and pain, increase the risk of infections including respiratory, urinary tract, or opportunistic infections, and may lead to adverse reactions such as dizziness, headache, diarrhea, and abdominal pain. Tofacitinib, on the other hand, may elevate the risk of infections such as herpes zoster reactivation or tuberculosis activation, and long-term use may result in laboratory abnormalities including lymphocytopenia, elevated liver enzymes, and dyslipidemia. Our medical team will closely monitor your condition and adjust the treatment regimen or discontinue therapy if necessary to minimize these risks. Preventive measures, including regular laboratory testing and infection screening, will be implemented to ensure your safety throughout the course of treatment.

Expected benefits:

Testing your specimen will help to diagnose the disease, provide necessary suggestions for your treatment, or provide useful information for disease research.

Alternative treatment:

You can choose to participate in this study or you may not be able to improve your health:

1. Do not participate in this study and continue your routine treatment. There are several conventional treatment methods: oral traditional anti rheumatic drugs or non steroidal anti-inflammatory drugs.

2. Participate in other studies.

3. Do not receive any treatment.

Please consult with your doctor about your decision

Free treatment:

Any expenses incurred by the subjects in participating in the study, including medical expenses, drug expenses and inspection expenses incurred from observation indicators during follow-up, shall be borne by the subjects themselves.

Compensate :

There is no insurance in this study. In case of any damage related to the study, the researcher will compensate the subjects' medical fees, treatment fees, examination fees and mental losses in accordance with the laws and regulations.

Confidentiality:

The information about you obtained in any research will be kept in the scientific research department of the Institute in the form of confidential documents, which will be strictly confidential and only used for this research.

Any public report on the results of this study will not disclose your personally identifiable information. We will make every effort to protect the privacy of your personal medical data to the extent permitted by law.

Voluntary:

You can choose not to participate in this study, or notify the researcher to withdraw from the study at any time. Your data will not be included in the research results, and your medical treatment and rights will not be affected.

If you need other treatment, or you do not comply with the study plan, or you have research-related injuries, or for any other reason, the study physician may terminate your continued participation in the study.

Subject obligations:

As a research subject, you have the following responsibilities: truthfully provide the truth about your medical history and current physical condition; Inform the study doctor of any discomfort he

experienced during the study;

Do not take restricted drugs, food, etc. Tell the study doctor whether he has participated in other studies recently or is currently participating in other studies.

Contact information:

You can keep abreast of the information and research progress related to this study at any time. In case of any new safety information related to this study, we will notify you in time. If you have any questions related to this study, or you have any discomfort or injury during the study, or you have any questions about the rights and interests of the participants in this study, you can contact Dr. huangyanjing at 13857108462.

If you have any questions or demands about the rights and health of participating in this study, you can contact the ethics committee of Zhejiang Provincial People's Hospital at 0571-85893643.

Informed consent signature page

I have read the above introduction about this study, and the research doctor has explained the research content to me in detail. Before signing the informed consent form, I have no more doubts about the study to consult. On this basis, I voluntarily participate in the clinical study introduced in this article, and my decision is based on a full understanding of the possible risks and benefits of participating in this study. In addition, the researcher did not use deception, inducement, coercion and other means to force me to agree to participate in the study, and I knew that I could unconditionally withdraw from the study at any stage.

This informed consent shall be signed by the guardian or legal representative of the subject due to his incapacity or limited capacity.

Subject signature: _____ Signature of legal representative: _____

Date: _____ Date: _____

Contact information of subjects: _____ Contact information of legal representative: _____

I have accurately informed the subject of this document. He / she has accurately read this informed consent form and has the opportunity to ask questions.

Investigator signature: _____

Date: _____

(Note: if the subject is illiterate, the signature of the witness is required; if the subject is incapacitated, the signature of the agent is required)