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 Baricitinib

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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 ≥ 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.

Baricitinib, a selective JAK1/JAK2 inhibitor, belongs to the class of tsDMARDs. It works by blocking the JAK-STAT signaling pathway, inhibiting the intracellular transmission of various pro-inflammatory cytokines (such as IL-6, IFN-γ, IL-23), thereby alleviating inflammatory responses and joint damage in rheumatoid arthritis (RA). Additionally, baricitinib can modulate immune cell functions, for example, by inhibiting the activation of Th17 cells (associated with autoimmune responses) and promoting the differentiation of regulatory T cells, which helps restore immune balance and improve clinical symptoms in patients with difficult-to-treat RA. Furthermore, safety study results indicate that the most commonly reported adverse events for this drug include infections, changes in laboratory parameters, and some gastrointestinal symptoms. Other serious adverse events, such as cardiovascular events, thromboembolism, serious infections, interstitial lung disease, and malignancies, are relatively rarely reported.

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, you will be assigned an identification number and a medical record file will be established. During the study, no additional interventions will be applied to you. This study is an observation of patients with refractory RA who require treatment with the combination of Telitacicept and Baricitinib. Therefore, you will need to be able to attend follow-up outpatient visits on time at the hospital before starting medication and at 4, 8, 12, 16, 20, and 24 weeks after treatment. During these visits, assessments including the DAS28 score and related laboratory indicators (such as DAS28 score, C-reactive protein, erythrocyte sedimentation rate, bone metabolism markers, complete blood count, and liver and kidney function) will be conducted to record changes in your condition and to observe the clinical efficacy and safety of the combination therapy with Telitacicept and Baricitinib. The medication regimen is as follows: Telitacicept, produced by RemeGen Co., Ltd. (Yantai) (National Medicine Permit No. S202110008), is administered at a dose of 160 mg per injection subcutaneously once a week for half a year. Baricitinib (Olumiant), produced by Eli Lilly and Company (National Medicine Permit No. HJ20215001), is administered orally at a dose of 2 mg once daily.

Possible risks and uncertainties:

All information provided by you will be kept strictly confidential. During your course of medication, the use of Telitacicept may lead to adverse reactions such as injection site reactions (e.g., redness, swelling, pain), may increase the risk of infections (such as respiratory, urinary tract, and potential opportunistic infections), and may cause dizziness, headache, diarrhea, abdominal pain, and other side effects. The use of Baricitinib may increase the risk of infections (e.g., herpes zoster reactivation or tuberculosis activation), and long-term use may lead to adverse reactions such as abnormal laboratory parameters (e.g., lymphopenia, elevated liver enzymes, dyslipidemia). During

the treatment process, we will make corresponding adjustments to the regimen or discontinue treatment as necessary to minimize the risk of adverse reactions to the greatest extent possible.

Expected benefits:

By participating in this study, the clinical observations and related examinations you undergo may assist your physician in monitoring changes in your condition more closely, providing reference for evaluating the effectiveness of the Telitacicept combined with Baricitinib treatment regimen in your specific case. Simultaneously, the information you provide through your participation will contribute valuable data to research on the treatment of refractory rheumatoid arthritis, with the potential to benefit future patients suffering from similar conditions. However, it is important to clarify that this is a clinical research study, and its primary purpose is to verify the efficacy and safety of the treatment method. Therefore, participation in this study may not necessarily lead to a direct improvement in your personal health status or treatment outcome, and it may not provide direct personal medical benefit.

Alternative treatmen:

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:

During your participation in this study, expenses related to examinations, treatments, and follow-up visits associated with this research (such as consultation fees, examination and testing fees specified in the study protocol, and the cost of study medications) are generally the responsibility of the participant.

To alleviate your financial burden, the following clarifications and support are provided for this study:

1. The study drug "Telitacicept Injection" is eligible for a "Two Months of Treatment, One Month Free" preferential policy. During the one-month complimentary treatment period, the cost for this medication will be waived.

2. Regarding the study's combination drug "Baricitinib," if its use involves dosages beyond the

conventional regimen, or if the associated costs fall outside the reimbursement scope of medical insurance or are not listed in the insurance catalog, these portions of the expense will need to be borne by you.

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)