Official Title N-Acetylcysteine as Therapy for Transplantation- Associated Thrombotic Microangiopathy

NCT Number NA_____

Version Date: February 5, 2024

Subject Number: Version Number: 1.0

Informed Consent Form for Subjects

(Informed Consent Form)

N-Acetylcysteine as Therapy for Transplantation- Associated Thrombotic Microangiopathy

Dear Madam/Sir:

You are being invited to participate in a clinical study. The following sections describe the research background, objectives, methods, potential benefits, possible discomforts/inconveniences, and your rights related to this study. Please read this carefully before deciding to participate. This informed consent form provides information to help you make an informed decision about participation. If you have any questions, please ask the physician in charge of the study to ensure you fully understand the content. Your participation is voluntary. If you agree to take part in this clinical study, please sign the signature page of this informed consent form.

1. Research Background

Transplant-Associated Thrombotic Microangiopathy (TA-TMA) is a severe complication of hematopoietic stem cell transplantation (HSCT), characterized by microcirculatory hemolytic anemia, peripheral thrombocytopenia, elevated lactate dehydrogenase (LDH), increased serum creatinine, presence of schistocytes in peripheral blood, microcirculatory fibrin deposition, and microvascular thrombosis. The overall incidence of TA-TMA is 17%, with a mortality rate as high as 60–90%.

Current treatments mainly include:

- Discontinuation/withdrawal of calcineurin inhibitors (CNIs) such as Cyclosporine, Tacrolimus, and Sirolimus, and replacement with anti-rejection drugs including Mycophenolate Mofetil (MMF), glucocorticoids, and CD25 monoclonal antibodies;
- Plasma exchange (PE), however, the remission rate of PE for TA-TMA is mostly below 10%;
- Complement blockade therapy, a promising treatment option, includes Eculizumab (a C5 monoclonal antibody) and Narsoplimab (a lectin pathway inhibitor), with remission rates of 71% and 61% respectively. Nevertheless, complement blockers have not been widely used clinically due to their high cost and the fact that some of these drugs have not yet been approved for marketing in China.

N-Acetylcysteine (NAC) is a safe, cost-effective, and easily accessible drug currently used in the respiratory department for the treatment of chronic obstructive pulmonary emphysema. Our previous research results have shown that prophylactic use of NAC can significantly reduce the incidence of TA-TMA, delay the median onset time of TA-TMA, and improve event-free survival (EFS) in transplant patients. Therefore, we aim to further clarify the role of NAC in TA-TMA through this prospective clinical study.

2. Study Name and Objectives

This is a prospective single-arm clinical trial designed to explore the efficacy and safety of N-Acetylcysteine in the treatment of transplant-associated thrombotic microangiopathy (TA-TMA).

3. Study Methods and Content

This is a multicenter, open-label, single-arm, prospective study with an expected duration of 3 years, planning to enroll 44 TA-TMA subjects.

Experimental Group: Intravenous injection of Acetylcysteine Injection at a dose of 16g per day for 14 consecutive days.

4. Study Procedures and Timeframe

The treatment period of this study is 14 days, with a follow-up period of 2 years. The evaluation indicators include:

- Complete blood count (CBC)
- Blood biochemistry
- Peripheral blood smear for schistocytes
- Coombs test
- Haptoglobin
- Routine coagulation tests
- Complement C5b-9
- Urinary protein-to-creatinine ratio
- Blood pressure
- Neurological symptoms and signs

5. Potential Benefits of Participation

Through participation in this study:

- Each patient will receive free detection of complement system activation, circulating endothelial cells, and neutrophil extracellular traps (NETs);

The study may help improve the clinical symptoms of TA-TMA patients and bring clinical benefits.

6. Potential Risks and Discomforts of Participation

During the administration of N-Acetylcysteine, patients may experience adverse reactions such as mild nausea, vomiting, and epigastric discomfort. In most cases, if a small number of patients experience the above reactions, symptoms can be relieved by appropriate dose reduction. In rare cases where symptoms do not fully resolve after drug withdrawal, we will provide supportive treatment.

7. Treatment and Financial Compensation for Study-Related Injuries

All subjects in this trial are covered by insurance. If a subject suffers an injury related to the study, the study sponsor will bear the relevant diagnosis and treatment costs and provide corresponding financial compensation in accordance with the relevant laws and regulations of China.

8. Routine Clinical Treatment Options Outside This Study

Routine treatments (not required for this study) include discontinuation/withdrawal of calcineurin inhibitors (Cyclosporine, Tacrolimus, Sirolimus, etc.), replacement with anti-rejection drugs such as Mycophenolate Mofetil, glucocorticoids, CD25 monoclonal antibodies, and plasma exchange.

9. Rights of Subjects

Subjects participating in the study have the following rights:

- Voluntary participation and right to withdraw at any time;
- Right to be informed, to consent or refuse;
- Right to confidentiality;
- Right to compensation;

- Right to free treatment and compensation in case of injury;
- No discrimination, retaliation, or adverse impact on medical treatment and rights due to withdrawal from the study at any time.

10. Confidentiality of Clinical Study Data

All information and data recorded for subjects participating in the study will be strictly confidential and will not be disclosed publicly. If the study results are published, the identity information of subjects will remain confidential.

11. Collection and Management of Human Biological Samples

Peripheral blood (3ml per time) will be collected from subjects in accordance with the follow-up plan, separated from routine laboratory tests without additional collection times. The samples will be mainly used for immunocellular biological analysis and translational medical research, and will not be used for product development, sharing, or secondary use. Strict compliance with privacy protection and destruction procedures will be ensured. Subjects will receive a financial compensation of ¥200 per blood collection.

12. Contact Information

Researchers:

Depei Wu: 0521-67781856

Yue Han: 0521-67781521

Tingting Pan: 18762936292

Ethics Committee:

Shuangjie Wu: 0512-67972743

Contact persons and information for reporting problems: [to be filled as applicable]

13. Declaration and Signature

Subject's Declaration:

I have carefully read this informed consent form, have had the opportunity to ask questions, and all my questions have been answered. I understand that my participation in this study is voluntary. I may choose not to participate, or withdraw from the study at any time by notifying the researchers, without facing discrimination or retaliation, and my medical treatment and rights will not be affected.

The study physician may terminate my participation in this clinical study if I require other treatments, fail to comply with the study protocol, or for any other reasonable reason.

I voluntarily agree to participate in this clinical study and will receive a signed copy of this informed consent form.

Subject's Full Name (in block letters): _____

Subject's Signature: _____

Date: _____ Year _____ Month _____ Day

Mobile Phone Number: _____

Legal Representative (if applicable):

Legal Representative's Full Name (in block letters): _____

Legal Representative's Signature: _____

Date: _____ Year _____ Month _____ Day

Mobile Phone Number: _____

Relationship with Subject: _____

Reason why the subject cannot sign the informed consent form: _____

Researcher's Declaration:

I have accurately informed the subject of the content of this informed consent form, answered all the subject's questions, and confirmed that the subject is participating in this clinical study voluntarily.

Researcher's Full Name (in block letters): _____

Researcher's Signature: _____

Date: _____ Year _____ Month _____ Day

Mobile Phone Number: _____