Convalescent plasma for the treatment of severe and critical/life-threatening COVID-19: a prospective randomized controlled trial (partial translation)

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1. Study Objectives

In order to actively prevent and control COVID-19, the convalescent plasma of patients with COVID-19 is collected, and the clinical treatment plan of using convalescent plasma to treat patients with COVID-19 is explored.

● Primary Objective

Assess the efficacy of recovery plasma therapy in severe and critical/life-threatening COVID-19 patients.

● Secondary Objectives

o Assess the safety and tolerability of convalescent plasma therapy to severe and critical/life-threatening COVID-19;

o Analyze factors that may affect the effectiveness of plasma treatment during recovery.

2. Treatment programs

2.1 This study is a multicenter, randomized, open, parallel controlled trial. It is planned to recruit 200 patients with severe and critical COVID-19, stratified according to the disease classification (severe or critical/life-threatening), and randomly allocated to the experimental group or control group at a ratio of 1: 1.The treatment group was a conventional treatment combined with a recovery plasma treatment group, and the control group was a conventional treatment group. Subjects who have completed the screening and meet the eligibility criteria begin study treatment. All patients receive conventional treatment, including symptomatic treatment, antiviral treatment, and antibacterial treatment. At any time, if the disease progresses, treatment can be stopped or combined with other interventions. Treatment group on the first day of the study, patients received convalescent plasma therapy to evaluate efficacy and safety indicators. Patients who were discharged or died were reaching the clinical endpoint. All subjects will be followed up to day 28 of the study or reach the clinical endpoint. Patients who completed 28 days of observation or reached the clinical endpoint were considered to have completed the study.

2.2 Principles of convalescent plasma infusion: According to the principle of cross-matching secondary compatibility, blood donors can directly perform ABO-compatible infusion of plasma with negative antibody screening, and ABO homoplasma is preferred.

2.3 Dose of convalescent plasma infusion: Determined by the clinician based on clinical status, patient weight, and new coronavirus antibody titers, patients in the treatment group received intravenous infusions of antibody titers greater than 1: 160 with a volume of 100-600 ml.

2.4 Rate of convalescence plasma infusion: Slow infusion, with a recommended speed of 100 ml/h, not more than 200 ml/ h, and closely monitor for adverse reactions. If any adverse reaction occurs, the adverse reaction can be alleviated by slowing the infusion rate first. If necessary, the plasma infusion can be suspended or terminated, and the adverse reactions after the plasma infusion and the reasons for the interruption of the plasma infusion are recorded in detail.

3. Research population

3.1 Admission criteria for patients

1. The patient signed an informed consent form to participate in the study of convalescent plasma therapy;

2．The age of the patient is 18 or more than18 years old;

3. COVID-19 patients diagnosed by PCR;

4. Nucleic acid positive within 72 hours before blood transfusion;

5. Pneumonia confirmed by imaging;

6. The clinical symptoms reach the standard of severe or critical/life-threatening.

- Severe patients meet any of the following：
  a) respiratory distress, RR ≥ 30 beats / min;
  b) in resting state, oxygen saturation ≤ 93%;
  c) partial pressure of oxygen in arterial blood (PaO2) / oxygen concentration (FiO2) ≤ 300mmHg (1mmHg=0.133kPa)

- Critical/Life-threatening patients meet any of the following：
  a) respiratory failure and need mechanical ventilation;
  b) shock;
  c) patients with other organ failure need ICU monitoring treatment.

7. Accept random grouping into any group;

8. The patient was hospitalized before the end of the clinical study.

9. Willing to participate in all necessary research directions and be able to participate in follow-up;

10. During the period of participating in this study, they will no longer participate in clinical trials such as other antiviral drugs.

3.2 Exclusion criteria for patients

1. The doctor believes that the patient is not suitable to participate in this trial, including those who may not cooperate, do not comply with the requirements of the procedure, or participate in this trial may put the patient in an unsafe situation.

2. Pregnant or lactation period's women;

3. Immunoglobulin allergy;

4. Immunoglobulin A deficiency;

5. There are diseases that may increase the risk of thrombosis, such as cold globulinemia, severe refractory hypertriglyceridemia, clinically defined monoclonal gamma globulinemia, etc.

6. High titer of anti-novel coronavirus antibody RBDIgG (higher than 1) could be detected.

7. Received any experimental treatment for novel coronavirus infection within 30 days before screening;

8. The researchers judged that the patients had the following life-threatening conditions, including, but not limited to, Phammer F < 100mmHg, near-death state or expected survival time less than 24 hours, severe septic shock or disseminated intravascular coagulation ((DIC)), etc

9. Severe congestive heart failure, or other relative contraindications for plasma transfusion determined by researchers.

4. Randomization

The randomization method of this study is as follows: Subjects are randomly assigned to the experimental group (conventional treatment combined with convalescent plasma treatment group) or the control group (conventional treatment group) according to the ratio of 1: 1, and receive according to the treatment plan of this group treatment. In this study, the randomization was stratified based on the severity of COVID-19 (severe or life-threatening) and a randomization schedule was generated for each type of COVID-19 by SAS software. After completing all the screening and evaluation items in this study, the subjects who meet the eligibility criteria will be assigned a random number according to the randomization schedule. This random number will connect the subject to the designated treatment group (experimental group or control group) for treatment. The randomized subject will withdraw the random number of the subject regardless of any reason. Staff responsible for randomization will only be responsible for the assignment of random groups and will not be involved in any specific trial operations.

5. Study endpoint

5.1 Primary endpoint

The 28-day clinical improvement time (TTCI), the number of days after randomization to clinical improvement.

Clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge, the 6-point scale includes:

6 points: Death;

5 points: Hospitalization, requiring extracorporeal membrane oxygenation (ECMO) and/or invasive mechanical ventilation;

4 points: Hospitalization, requiring extracorporeal membrane oxygenation (ECMO) and/or invasive mechanical ventilation;

3 points: Hospitalization, requiring supplemental oxygen (not high-flow or non-invasive ventilation);

2 points: Hospitalization, not requiring supplemental oxygen;

1 point: Discharge.

5.2 Secondary endpoint

• Secondary efficacy endpoint

1. 28-day mortality

2. Hospitalization time (discharge isolation or discharge standards are as follows: the body temperature returns to normal for more than 3 days, respiratory symptoms have improved significantly, acute exudative lesions shows markedly improved by pulmonary imaging, two consecutive nucleic acid tests for respiratory specimens have been negative [sampling interval at least 1 day], can be released from hospital or transferred to the appropriate department according to the condition Treat other diseases.)

3. Proportion of viral nucleic acid negative (3 days after transfusion)

• Safety endpoint

Results of laboratory tests and vital signs

Cumulative incidence of severe adverse events (SAE)

Cumulative incidence of adverse events (AE), grades 3 and 4 AE

Incidence of adverse plasma transfusion reactions

• Exploratory end

1. Evaluation of factors affecting plasma treatment effect during recovery period

According to the outcome and time of discharge of patients treated in groups, the patients' age, gender, medical history, viral load, antibody titer, and different cytokines and chemokines in blood samples before and after treatment (Such as IL-6, IL-10, TNF-α, IL-1β, etc.), analyze the factors that may affect the effect of plasma treatment during recovery.

2. Antiviral mechanism of convalescent plasma

6. The method of statistical analysis

Unless other special statements, all statistical tests were performed using a two-sided 0.05 level test.

Unless otherwise stated, efficacy analysis will be based on FAS and PPS, safety analysis will be based on SS, measurement data will be described using mean ± standard deviation or median (minimum, maximum), and count data will be analyzed using frequency (percent).