A multi-center, open label, randomized controlled clinical study on the efficacy and safety of tocilizumab in patients with novel coronavirus pneumonia

Study Protocol

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Study rationale

A new strain of coronavirus that had never been found in humans was identified by sequencing samples from patients with pneumonia in December 2019. On January 12, 2020, the virus was named as 2019-nCoV by WHO. Now, the disease has been officially named as New Coronavirus Pneumonia (NCP).

NCP common symptoms are fever, cough, more than half of patients with dyspnoea, a small number of patients with muscle soreness or strength, nausea and vomiting, diarrhea. In more severe cases, infections can lead to severe acute respiratory distress syndrome and death due to multiple organ failure.

The "cytokine release syndrome" is an important factor in the progression to critical and critical illness in patients with NCP [1]. However, so far, the mechanism is not clear, and there is no specific treatment in clinical practice, which is an important cause of death in patients with NCP. Thus, the search for effective control "cytokine release syndrome " so that to prevent the development of severe illness is vital to reduce the occurrence of severe, critical illness and mortality rate. The team previously analyzed the immune characteristics of 33 patients with novel coronavirus pneumonia and discovered the key mechanism of severe pneumonia caused by novel coronavirus infection: the rapid activation of inflammatory T cells and mononuclear cells, the production of a large number of cytokines, and the formation of cytokine release syndrome. Granulocyte-macrophage colony-stimulating factor and IL-6 pathway are the key pathways to trigger the inflammatory storm.

IL-6 is a classical multifunctional cytokine involved in inflammatory and febrile responses, with hormone-like properties that affect body. Deregulation of IL-6 production plays an important pathological role in a variety of inflammatory diseases. The IL-6 receptor has two forms, the membrane-bound IL-6 receptor (mIL6R) and the soluble IL-6 receptor (sIL-6R). IL-6 binds to sIL-6R to form a complex that in turn binds to gp130 on the cell membrane, completing trans-signaling and playing a pro-inflammatory role [2-5]. Tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody of the immunIgG1 subtype that binds specifically to sIL-6R and mIL-6R

and bits sIL-6R and mIL-6R-mediated signaling. Tocilizumab is well tolerated in chronic toxicity studies in animals, with no significant abnormalities in other clinical pathology studies or histopathological evaluations [6-8].

Based on these findings, This study establishes a scientific hypothesis that the early use of IL-6 receptor antibodies TCZ (tocilizumab) may block NCP cytokine release syndrome. The research team quickly developed a treatment plan and achieved initial efficacy in the treatment of 14 patients with NCP, without significant adverse events. A multi-center, open-label, randomized controlled study is designed to observe the efficacy and safety of tocilizumab.

Objective of the study

To assess the efficacy and safety of tocilizumab in patients with common NCP (including severe high-risk factors) and severe NCP.

Study methods

A multicenter, randomized, open controlled, competitive study is planned to include a total of 188 patients with novel coronavirus pneumonia.

NCP definition:

(1) Common type of NCP (including severe high-risk factors): common type of patients with bilateral lung disease with or without fever;

(2) Severe NCP: refer to the definition in the New Coronavirus Pneumonia Diagnosis and Treatment Plan (Fifth Edition) issued by the National Health Commission.

Inclusion criteria

- Diagnosis of new type coronavirus pneumonia in common type NCP (including severe high-risk factors), severe patients;

- Age 18-85 years
- IL-6 increased
- The patient or authorized family member voluntarily participated in the study and signed the informed consent form.

Exclusion criteria

- Patients who are participating in other drug clinical trials;
- Pregnant or breast-feeding women;
- ALT/AST > 5 times the UlN, neutrophils < 0.5, platelets less than 50;
- Clear diagnosis of rheumatic immune-related diseases;
- Long-term oral anti-rejection drugs or immunoregulatory drugs;
- Hypersensitivity to tocilizumab or any of the excipients;
- Patients with active pulmonary tuberculosis, combined with clear bacterial infection and fungal infection;
- Patients with history transplantation
- Patients with mental disorders

Treatment regimens

Enrolled patients will be randomized into control group (A) and treatment group (B) according to the randomized controlled table.

- Control group (A): in strict accordance with the "New type of coronavirus pneumonia diagnosis and treatment program (fifth or updated)" routine treatment;
- Treatment group (B): in addition to routine treatment, patients will be given treatment of tocilizumab, the first dose is 4-8 mg/kg, and the recommended dose is 400 mg up to a maximum of 800 mg administered as a 1-hour infusion. In case of fever within 12 hours, an additional dose will be given (same as before), and the cumulative dose could not be more than to two times. The use of corticosteroids shall strictly follow the recommendation in the

diagnosis and treatment of the latest NCP (revision 5 or future updated version). The use of corticosteroids in common type NCP with risk factors is not recommended

Laboratory tests and vital sign

1) Respiratory function index: SaO2 or PaO2/FiO2

A. ordinary type Patients with NCP (including severe risk factors): daily morning after treatment at 9:00 AM, SaO2 shall be monitored until it is back to normal without oxygen

B. severe NCP patients: oxygenation index shall be monitored daily at 9:00 AM after treatment until it is > 300 mmHg

2) Body temperature: Monitor body temperature 12 hours after tocilizumab administration in patients with fever. Measure body temperature twice daily for 3 days after treatment, then once daily until discharge

3） Chest CT: Chest CT to be performed on days 3, 7, and 14 after tocilizumab administration.

4） White blood cells, lymphocytes, CRP, PCT, Liver function (ALT/AST/LDH) and renal function (CR/BUN), muscle enzymes, troponins, Myoglobin, IL-6, PT, APTT, INR to be reviewed on the first day after medication, and then every 3 days until discharge.

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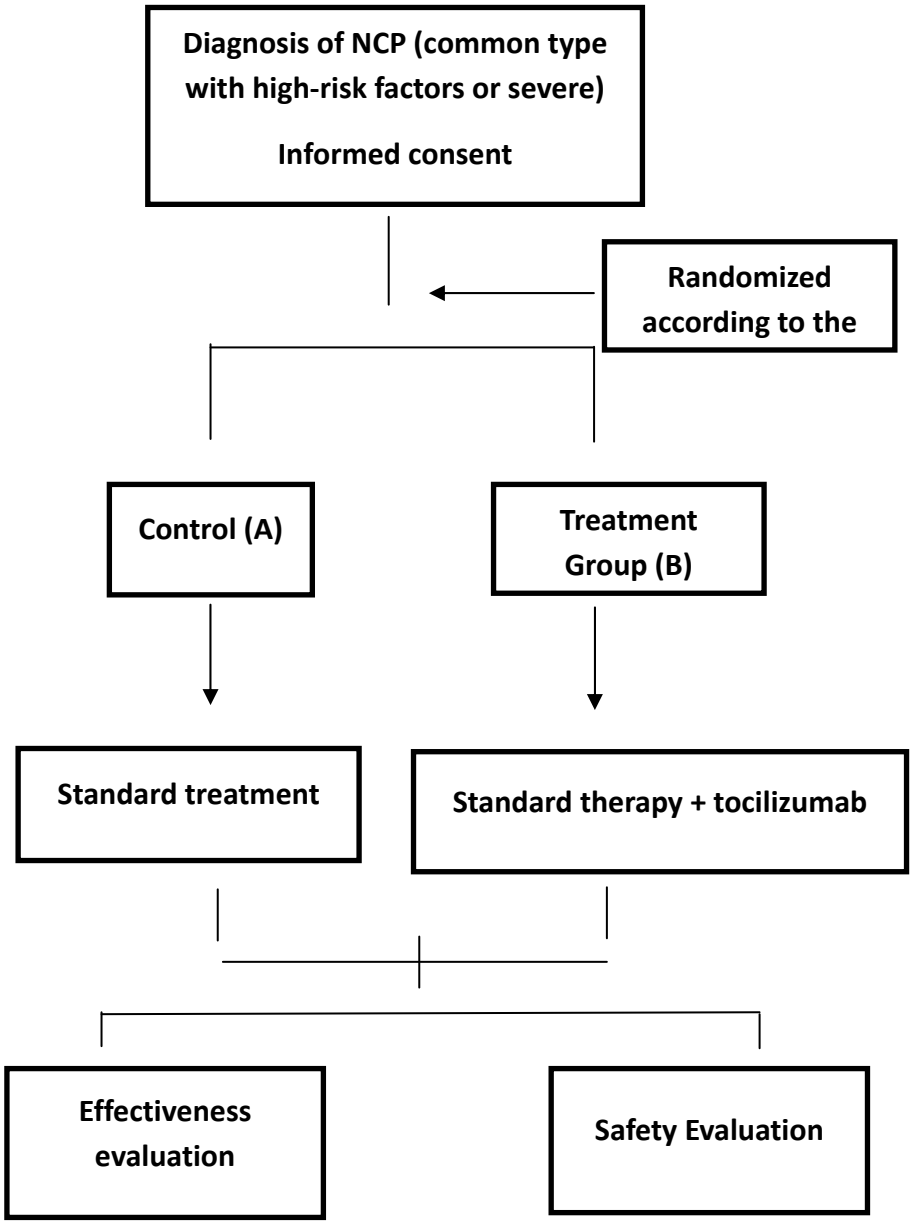
Study flow



Primary and secondary outcome measures

(1) Primary efficacy outcome measure: Clinical Cure rate. Cure is defined according to the fifth edition

of the diagnosis and treatment guidelines issued by NHC

(2) Secondary efficacy outcome measures:

1）Case fatality rate with NCP as the main factor

2）The rate of use of non-invasive or invasive mechanical ventilation in respiratory failure

3）Mean length of hospital stay

(3) Safety outcome measures:

Adverse Events, Serious Adverse Events

Statistical methods

1. Sample Size Determination

The study is a randomized controlled trial. The sample size was calculated based on the comparison of the primary outcome measure, cure rate, randomized in a 1:1 ratio, using a two-sided test, $\alpha = 0.05$, $\beta = 0.1$ (power = 90%). The calculation was based on the assumption that the estimated cure rate is 30% in the test group and 10% in the control group.

2. Statistical Analysis Set

Full Analysis Set (FAS): All randomized subjects with at least one dose and efficacy evaluation will be included in the full analysis set of the trial according to the intention-to-treat (ITT) principle. For subjects prematurely withdrawn from the trial for any reason, missing efficacy measures will be calculated using the most recent observation carried forward (LOCF) method.

Per Protocol Set (PS): Those patients enter the trial and complete the treatment, medication compliance is between 80% and 120%, no concomitant medications influencing the efficacy evaluation. Those patients shall also have completed data on the primary outcome measure and no major protocol violations.

Safety Set (SS) All subjects who received at least one dose of the IMP after randomization and had a safety evaluation will be included.

3. Statistical Analysis

The study is a parallel control design with no specific instructions, and all data used appropriate statistics depending on the type of data. All statistical tests is 2-sided with a statistical significance level of 0.05. The measurement data are mean, standard deviation STD, median, minimum, and maximum, and the count data are frequency and percentage proportion for descriptive statistical summary. The time-event data will be estimated using the Kaplan-Meier method for median survival time.

3.1 Demographic and Baseline Characteristics

All randomized subjects will be statistically summarized for demographic characteristics (gender, age, height, weight, etc.), medical history, and lifestyle habits by randomized medication group based on the FAS.

3.2 Treatment Compliance

If the subject does not receive the planned treatment dose per the clinical study protocol, he/she is considered non-compliant. Treatment adherence (number, mean, SD, median, minimum, and maximum) will be summarized descriptively. The percentage of patients with < 80% compliance will be summarized.

3.3 Efficacy analysis

It will be performed separately in the full analysis set (FAS) and per protocol set (PPS).

(1) Primary Efficacy Outcome

Clinical cure rate: The number and percentage of cures after administration will be calculated and compared between groups using the chi-square test or Fisher's exact probability.

(2) Secondary efficacy outcomes

Mortality rate: The number and percentage of deaths will be calculated and compared between groups using the chi-square test or Fisher's exact probability.

The rate of use of non-invasive or invasive mechanical ventilation in respiratory failure: The number and percentage of patients who experiences respiratory failure after administration will be calculated and compared between groups using the chi-square test or Fisher's exact probability.

Mean length of hospital stay: A descriptive analysis will be used. The two groups will be estimated by Kaplan-Meier curve method, and the time distribution of each group will be analyzed by Log-rank test.

3.4 Safety analysis

All analyses of safety endpoints will be based on the SS set.

All AEs, related AEs, SAEs, and AEs leading to dropout will be summarized separately by System Organ Class (SOC) and Preferred Term (PT) (number, number, and incidence). All adverse events and related adverse events for each system will be summarized separately by severity (mild, moderate, and severe), and a list of all adverse events, related adverse events, serious adverse events, and adverse events leading to dropout will be provided. Safety analyses will be limited to descriptive statistical sum that included, but is not limited to, the following:

- Subject distribution and analysis population;
- Basic characteristics of subjects (including social demographic information, past medical history, and medication history);
- Discontinuation of the trial by the subject;
- Summary of adverse events (all-cause and treatment-related);
- The incidence and severity of adverse events (all-cause and treatment-related);
- Summary of serious adverse event details;
- Analysis of adverse event association;
- Laboratory parameters, vital signs, ECG data and changes from baseline;

- Laboratory parameters, vital signs, ECG data after the test "normal to abnormal" or "abnormal increase."

4. Methods to minimize bias

Randomization is the primary means of ensuring that the study arms are comparable. All parties involved in this study should do everything possible to ensure strict implementation of the randomization scheme. The study will use block randomization and screened eligible subjects will be randomized in a 1:1 ratio to either the test or control arm. This is an open-label, unblinded study.

References

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