The efficacy and safety of carrimycin treatment in patients with novel coronavirus infectious disease (COVID-19) : A multicenter, randomized, open-controlled study

Study protocol

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Study sites:
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Confidentiality

This clinical study protocol is a confidential document for the purpose of this clinical study and shall not be disclosed to anyone other than the investigators involved and members of the institutional review board.

Synopsis

Name of study	The efficacy and safety of carrimycin treatment in patients with novel coronavirus infectious disease (COVID-19): A multicenter, randomized, open-controlled study
Study Objectives	Evaluate the efficiency and safety of Carrimycin in the patients with 2019-nCoV pneumonia, establish the criteria for clinical cure and the early predictive model of COVID-19 progression.
Study design	A randomized, open, positive-controlled and multi-center clinical study
Planned sample size	520 subjects planned.
Inclusion/exclusion criteria	**Subjects shall meet all the following criteria before being included:** **Inclusion criteria** (1) Subjects or their legal representatives have signed the informed consent form(ICF); agree not to participate in other clinical studies within 30 days after the last administration from the first administration of the study drug. (2) Subjects are aged ≥ 18 and ≤ 75; (3) Meet the diagnostic criteria for 2019-nCoV pneumonia (V5.0); (4) SOFA score: 1 ~ 13 points. (5) A retreated patient or the relapsed patient meets any of the following criteria: ① Have fever again or aggravated clinical symptoms; ② 2019nCOVRNA in the throat swabs converts from negative to positive; ③ The clinical symptoms don't improve or 2019nCOVRNA continues to be positive; ④ The chest CT shows pneumonia or fibrosis progression. **Clinical stratification:** 1. Mild type: clinical symptoms mild or asymptomatic, no

	pneumonia performance in CT, but positive 2019-nCoV in throat swabs or gargle. 2. Ordinary type: fever, respiratory symptoms, etc., pneumonia performance visible in CT. 3. Severe type: meeting any of the following criteria: (1) Respiratory distress, RR≥30 times/min; (2) Finger oxygen saturation ≤93% in rest state; (3) Arterial partial pressure of oxygen (PaO2)/concentration of oxygen inhalation (FiO2)≤300mmHg (1mmHg=0.133kPa). 4. Critical type: meeting any of the following criteria: (1) Respiratory failure occurs and mechanical ventilation is required; (2) Patients go into shock; (3) ICU is needed for other organ failure. **Exclusion criteria** (1) Other viral pneumonia (2) Patients who have received tumor immunotherapy (such as PD-1/L1, CTLA4, etc.) in the past 1 month, and inflammatory factor modulators such as Ulinastatin; (3) Patients who have taken anti-bacterial drugs such as macrolide in the past 1 week; (4) Patients who have received organ transplantation or surgery planning in the past 6 months; (5) Patients who can't take food or drugs due to coma or intestinal obstruction; (6) Patients who have severe underlying diseases that affects survival, including uncontrolled malignant tumor with multiple metastases that cannot be resected, blood diseases, dyscrasia, active bleeding, severe malnutrition, etc. (7) Women subjects that are pregnant or lactating, or subjects (including male subjects) having a pregnancy plan (including

	plans for sperm donation or egg donation), or subjects that may fail to take effective contraceptive measures within the next 6 months; (8) Patients with allergic constitution, or patients allergic to macrolides and lopinavir/ritonavir tablets; (9) Patients with contraindications to lopinavir/ritonavir tablets who plan or are using drugs that interact with the drug (including: drugs that are highly dependent on CYP3A clearance and whose elevated plasma concentrations can be associated with severe and/or life-threatening events [with a narrow therapeutic index], CYP3A inducer [see instruction for details]) and cannot stop using or use other drugs instead; (10) Patients whose ALT/AST levels are 5 times higher than the normal upper limit and total bilirubin is 3 times higher than the upper limit of normal, or patients with child-Pugh grade C cirrhosis. (11) ECLS (ECMO, ECCO2R, RRT) (12) Critical patients with expected life＜48 hours (13) Patients who have participated in any other clinical study within 1 month; (14) The investigators conclude that the patients not suitable for the study.
Trial drugs and medication methods	The trail group and the control group were randomized according to 1: 1. (1) Trial group: basic treatment + Carrimycin Mild type: 0.4g of Carrimycin tablets, p.o. after meal once a day for 7 consecutive days, followed up for observation after the end of treatment. Ordinary type: 0.4g of Carrimycin tablets, p.o. after meal once a day for 10 days, followed up for observation after the end of treatment. Severe and critical: 0.4g of Carrimycin tablets, p.o. after meal once a day for 14 consecutive days. If oral administration is not possible,

	the drug should be administered through a nasal feeding tube. For the combination drugs of basic treatment according to the *Diagnosis and Treatment Program for 2019-nCoV* (V5.0,Chinese) (2) Control group: any of basic treatment + lopinavir/ritonavir tablets or Arbidol or chloroquine phosphate: Mild and ordinary type: 400mg/100mg, bid of lopinavir/ritonavir tablets each time; or 500mg bid of chloroquine phosphate; or 200mg tid of Arbidol for 7 consecutive days, followed up for observation after the end of treatment. Severe and critical type: 400mg/100mg, bid of lopinavir/ritonavir tablets each time; or 500mg bid of chloroquine phosphate; or 200mg tid of Arbidol for 10 consecutive days, followed up for observation after the end of treatment. For the combination drugs of basic treatment according to the *Diagnosis and Treatment Program for 2019-nCoV* (V5.0,Chinese)
Therapy/drug combination	**Permitted therapy combination and/or drug combination:** Clinical treatment schemes other than antiviral therapy in the *Diagnosis and Treatment Program for 2019-nCoV* (V5.0,Chinese) are permitted. Acetaminophen (paracetamol), diclofenac sodium suppositories, lyripine (lysisin aspirin) antipyretics are prohibited. **Prohibited therapy combination and/or drug combination:** No other antiviral drugs or antibiotics are allowed during the trial (except retreated or relapsed patients or in severe and critical type cases). Keep a detailed record of the dugs combination, especially the glucocorticoids.
Observation period	Screening period: -2 days~ 0 day; Treatment period: 7-14 days;

	Follow-up observation period: follow up to 30 days after the first administration.
Effectiveness indicators	**Primary efficiency indicators** (1) Fever to normal time (day) (2) Pulmonary inflammation resolution time (HRCT) (day) **(3)** Negative conversion (%) of 2019-nCOVRNA in gargle (throat swabs) at the end of treatment **Secondary efficiency indicators** (1) Negative conversion ratio of 2019-nCOVRNA in gargle (throat swabs), urine and stool on Day 1, 3, 5 and 14 after administration; (2) Progress rate of 2019-nCoV pneumonia (3) Changes in immune-related indicators (lymphocyte count, lymphocyte percentage, counts and percentages of CD4 and CD8, and inflammatory cytokines) from baseline on Day 1, 3, 5 and 7-10 after administration. (4) Changes in SOFA score from baseline on Day 1, 3, 5 and 7-10 after administration; (5) Changes in white blood cell count from baseline on Day 1, 3, 5 and 7-10 after administration; (6) Changes in PCT and C-reactive protein from baseline on Day 1, 3, 5 and 7-10 after administration; (7) Changes in CT features from baseline on Day 7-10 and 14 after administration; (8) Length of stay in hospital and mortality rate. There are currently criteria for release from clinical isolation and discharge on 2019-nCoV pneumonia (V5.0,Chinese), and there is no "gold standard" for clinical cure, and it is difficult to obtain the basis for pulmonary diagnosis. Therefore, the following criteria are currently used clinically (empirical evidence, lack of scientific evidence) and it is not known whether there is a chronic infection or

	virus carrying. Therefore, the following criteria are used for the clinical assessment in this project: Criteria for clinical cure: 1) The clinical symptoms disappear and the quality of life is normal. 2) Lung CT/HRCT is normal. 3) T lymphocyte function and count return to normal. 4) Negative 2019-nCOV in secretions (gargle, urine and stool) Clinical chronic or complications: 1) Gastrointestinal and respiratory symptoms completely disappear, the quality of life is lowered (anxiety, insomnia and other mental disorders) or the lung CT/HRCT lesions exist, or lung fibrosis is formed. 2) Or laboratory abnormalities (blood routine, T lymphocyte count or function). 3) Negative 2019-nCOV in secretions (gargle, urine and stool)
Safety indicators	(1) AE, SAE. (2) Vital signs: breath, blood pressure, heart rate, body temperature. (3) Laboratory examination: blood routine (WBC, RBC, Hb, HCT, PLT, LY and LY%), urine routine (WBC, RBC, Pro), blood biochemical examinations (ALT, AST, TBIL, ALP, GGT, Cr, BUN, Glu) and coagulation function (PT, APTT, TT, FIB). (4) Routine ECG: heart rate, Q-Td, ST segment and T wave changes.
Statistical analysis	**(1) General principle** 1) Description of statistics The primary indicators collected in this study are described with statistical method. Quantitative indicators are described by means of mean, standard deviation, median, quartile, maximum, minimum and the like; qualitative indicators are described by frequency, percentage and the relationship.

2) Statistical test

Unless otherwise specified, the statistical significance level is 0.05 by two-sided test (one-sided 0.025) and the 95% confidence interval shall be provided for the estimation of inter-group variance parameters.

3)Random grouping: The hierarchical random grouping method is adopted

(2) Characteristics of cases

1) Subject distribution

① The population and the number of enrolled and completed cases in each center are listed, and three analysis data sets (FAS, PPS, SS) are determined.

② A detailed list of the data set categories is made.

③ The number and ratio of subjects who are randomly enrolled, complete the trial, and withdraw from the trial early and the reasons are calculated.

④ The subject distribution flow chart is plotted.

2) General information and baseline characteristics

The demographic information, previous medication history and history of other diseases of the patients are described with statistical method. General information and baseline characteristics are described based on FAS.

(3) Analysis of drug exposure and drug combination

Analysis based on SS.

1) Drug exposure, dose intensity and exposure time of each group are calculated.

2) The drug combination is coded by WHO ATC and summarized according to the ATC secondary classification and PT. The number and ratio of cases are calculated.

(4) Efficiency analysis

Analysis based on FAS and PPS.

The primary effective indicator are:(1) Fever to normal time (day),(2)Pulmonary inflammation resolution time (HRCT) (day),(3)Negative conversion (%) of 2019-nCOVRNA in gargle (throat swabs) at the end of treatment on Days 7-10 after administration. The statistical significance level is set to one-sided 0.025. The two-sided 95% confidence interval (95%CI) are calculated. The confidence interval is estimated by Miettinen-Nurminen.

The secondary efficiency indicators include negative conversion ratio of 2019-nCOVRNA from samples, immune-related indicators (lymphocyte count, lymphocyte percentage, counts and percentages of CD4 and CD8), SOFA score, white blood cell count, C-reactive protein, pulmonary imaging improvement indicators and complete antipyresis time on Day 1, 3, 5 and 14 after administration. In-hospital time,clinical cure ration and mortality are also analysed. The secondary efficiency indicators are subject to descriptive statistical analysis according to the data type.

(5) Safety analysis

SS data sets are used for safety analysis.

1) Adverse events are coded according to the MedDRA.
2) The occurrence of adverse events/reactions, serious adverse events/reactions and adverse events/reactions resulting in drop out is summarized and analyzed in the form of a frequency table (number of cases, case, and incidence).
3) The occurrence of varying severity orders of adverse events/reactions, serious adverse events/reactions and adverse events/reactions resulting in drop out is subject to descriptive statistical analysis in the form of a frequency

	table (number of cases, case, and incidence) according to SOC and PT. 4) A detailed list of various adverse events/reactions, serious adverse events/reactions and cases of adverse events/reactions resulting in drop out is made. 5) Changes in the clinical significance determination of laboratory indicators, ECG and physical examination at each visit after administration and baseline test results are described in the form of crosstab. 6) The laboratory indexes and vital signs examination are subject to descriptive statistical analysis according to trial grouping and visits. 7) A detailed list of laboratory indexes, ECG, and clinically significant physical abnormalities.
Expected study time	Study start time: February 2020 Study end time: February 2021

Flow chart of clinical trial

Study stage	Screening period [1]	Medication period					follow-up observation period		Early withdrawal [2]
	Day -2 ~ day 0 (baseline)	Day 1	Day 3	Day 7	Day 10	Day 14	Day 14 ±1 days	Day 28 ±2 days	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Informed consent form	×								
Demographic information	×								
Medical data	×	×	×	×	×	×	×	×	
Vital signs	×	×	×	×	×	×	×	×	×
SOFA score	×		×	×	×	×		×	
Physical examination	×	×	×	×	×	×	×	×	×
Review of inclusion/exclusion criteria	×	×							
Blood routine [3]	×		×	×	×	×	×	×	×
Urine routine [4]	×		×	×	×	×	×	×	×
Blood biochemistry [5]	×		×	×	×	×	×	×	×
Coagulation function [6]	×		×	×	×	×			×
T cell subset and cytokines [7]	×		×	×	×	×	×	×	×
C-reactive protein	×		×	×	×	×			×
2019-nCOVRNA in throat swabs, urine and stool	×	×	×	×	×	×	×	×	×
Chest imaging (CT)	×			×	×	×	×	×	×
12-lead ECG	×			×	×	×			×
Pregnancy test [8]	×							×	×
Enrollment		×							
Administration		×	×	×	×	×			

Study stage	Screening period [1]	Medication period					follow-up observation period		Early withdrawal [2]
	Day -2 ~ day 0 (baseline)	Day 1	Day 3	Day 7	Day 10	Day 14	Day 14 ±1 days	Day 28 ±2 days	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Record of clinical treatment scheme	×	×	×	×	×	×	×	×	×
Trial drug dispensing		×	×	×	×	×			
Trial drug recovery		×	×	×	×	×			×
Combination therapy	×	×	×	×	×	×	×		
Reserve throat swabs	×	×	×	×	×	×	×	×	×
Reserve blood specimens (serum, plasma and cells)	×	×	×	×	×	×	×	×	×
Reserve urine and stool	×	×	×	×	×	×	×	×	×
Adverse event	×	×	×	×	×	×	×	×	×

Notes:

1. Visit 1 (screening period) and visit 2 (baseline) may be on the same day, and Day 0 is the first day of administration;
2. To withdraw from the trial in advance, it is necessary to complete the last visit items; in case of AE at the end of the trial, follow-up should be conducted according to the "AE" requirements of the protocol;
3. Blood routine examinations: including WBC, RBC, Hb, HCT, PLT, LY, LY%;
4. Urine routine examinations: including WBC, RBC, Pro;
5. Blood biochemical examinations: including ALT, AST, TBIL, ALP, GGT, Cr, BUN, Glu;
6. Coagulation function: including PT, APTT, TT, FIB;
7. T cell subset: counts and percentages of CD4+ and CD8+;