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Original Article

Exploring an Integrative Therapy for Treating COVID-19: A Randomized Controlled Trial*

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ABSTRACT **Objectives:** To develop a new Chinese medicine (CM)-based drug and to evaluate its safety and effect for suppressing acute respiratory distress syndrome (ARDS) in COVID-19 patients. **Methods:** A putative ARDS-suppressing drug Keguan-1 was first developed and then evaluated by a randomized, controlled two-arm trial. The two arms of the trial consist of a control therapy (alpha interferon inhalation, 50 μg twice daily; and lopinavir/ritonavir, 400 and 100 mg twice daily, respectively) and a testing therapy (control therapy plus Keguan-1 19.4 g twice daily) by random number table at 1:1 ratio with 24 cases each group. After 2-week treatment, adverse events, time to fever resolution, ARDS development, and lung injury on newly diagnosed COVID-19 patients were assessed. **Results:** An analysis of the data from the first 30 participants showed that the control arm and the testing arm did not exhibit any significant differences in terms of adverse events. Based on this result, the study was expanded to include a total of 48 participants (24 cases each arm). The results show that compared with the control arm, the testing arm exhibited a significant improvement in time to fever resolution (P=0.035), and a significant reduction in the development of ARDS (P=0.048). **Conclusions:** Keguan-1-based integrative therapy was safe and superior to the standard therapy in suppressing the development of ARDS in COVID-19 patients. (Trial registration No. NCT 04251871 at www.clinicaltrials.gov)

KEYWORDS COVID-19, SARS-CoV-2, acute respiratory distress syndrome, Chinese medicine

In December 2019, a number of patients with a new type of pneumonia of unknown etiology were detected in Wuhan, China.[1] It was then soon determined that it was a new severe acute respiratory syndrome (SARS) that was caused by a new coronavirus, the SARS-CoV-2 virus.[2] The new pneumonia was later named the Novel 2019 Coronavirus or COVID-19.[3] In 2002–2003, another SARS-causing coronavirus, the SARS-CoV virus, caused one of the most deadly epidemics in recent history. The outbreak of SARS-CoV caused more than 8,000 reported cases and 774 deaths, with a case-fatality rate (CFR) of 7% in China.[4] Less than a decade later in 2012, another coronavirus, the Middle-East respiratory syndrome (MERS) virus, the MERS-CoV virus, emerged.[5] An outbreak of this virus in 2014 resulted in 662 reported cases and a CFR of 32.97%.[6] Together, these had informed us that coronaviruses represent a new kind of viral pathogens that are characterized by their ability to cause

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respiratory illnesses that can lead to acute respiratory distress syndrome (ARDS). Since ARDS is known to be associated with a very high CFR,[7,8] they had also revealed the propensity of these pathogens in causing epidemics or pandemics with high CFRs.

The emergence of an epidemic or a pandemic that is caused by a new pathogen poses a unique challenge: the rapid accumulation of a large number of patients without any effective treatments. In the cases of a coronavirus epidemic or pandemic that is associated with a high CFR, the challenge could become an unstoppable and rapid accumulation of casualty. In that regard, the rapid development of an effective treatment to reduce the CFR become the utmost important task. Yet, conventional paradigms for developing effective treatments of such a disease, i.e. the development of new antiviral drugs or vaccines, would take months or even years.[9,10] This realization thus prompted us to consider alternative approaches for the rapid development of an effective treatment for COVID-19. Recently, repurposing or off-label uses of pre-existing non-specific antiviral or host modulating drugs have been proposed as a potential effective strategy for the rapid development of anti-viral therapy.[11,12] Such an approach, however, is still facing the issue of a great uncertainty in term of the chance of success. Meanwhile, a collection of Chinese medicine (CM) drugs had been believed to be effective for treating various types of respiratory distress illnesses (RDI) for thousands of years in China and continued to be an integral part of the modern health care system in China.[13-15] This unique situation prompted us to explore the feasibility of using CM drugs as an effective therapy for COVID-19 and/or for other future coronavirus-induced RDI. We report here the development of a novel CM drug and the results of a randomized, controlled trial (RCT) that was designed to assess the safety and effect of a therapy that involves the use of this CM drug.

METHODS

New CM Drug Development for Suppressing ARDS Development in COVID-19 Patients

Since the high CFRs for these coronavirus-causing epidemics are due to the high incident of ARDS, our mission was to develop a new drug that would hopefully be able to reduce the incident of ARDS in COVID-19 patients and/or patients with other RDI. For both SARS and MERS, there exists a great variability with respect to the responses to the viral infections as well as the final outcomes,[4,7,8] signifying the critical role of the host factors in the responses and the prognoses to such virus infections. Therefore, in order to address this unique challenge, we decided to consider taking an alternative strategy that would target the hosts, rather than the pathogens. Furthermore, considering the presumed safety attribute of some CM compounds,[16] we decided to develop a drug that includes as many of the components as possible so that we could enhance the chance of success in suppressing the development of ARDS, providing that the combination is in line with the fundamental principles of CM.

The new formula was derived from 3 different formulae, Yinqiao Powder (银翘散), Sangju Drink (桑菊饮), and Sanren Decoction (三仁汤), named "Keguan-1" (meaning anti-coronavirus 1 in Chinese) with 7 components: *Lonicera japonica* Thunb. (Jinyinhua, lot. 19040301) 30 g, *Forsythia suspensa* (Thunb.) Vahl, (Lianqiao, lot. 19040221) 30 g, *Morus alba* L. (Sangye, lot. 19045321) 15 g, *Chrysanthemum morifolium* Ramat. (Juhua, lot. 19040811) 10 g, *Coix lacryma-jobi* L. var. *mayuen* (Roman.) Stapf, Yiyiren, lot. 19025161) 30 g, *Fritillaria thunbergii* Miq. (Zhebeimu, lot. 19041161) 15 g, and *Prunus armeniaca* L. var. *ansu* Maxim. (Kuxingren, lot. 19045591) 9 g. The powder versions of the drugs for the 7 components of Keguan-1 were obtained from Beijing Tcmages Pharmaceutical Co. Ltd. (Beijing, China) and mixed in the defined ratio.

Quality control assessments were based on the analyses of the relative amounts of the standard compounds by high-performance liquid chromatography tandem mass spectrometry (HPLC-MS), more details are shown in Appendix 1. A random sample of Keguan-1 drug was analyzed both at the beginning and at the end of the study. The results showed that the quality of Keguan-1 was maintained throughout the study (Figure 1).

Study Design

A two-arm, randomized, controlled phase Ⅰ/Ⅱ trial was conducted to assess the safety and the effect of Keguan-1 in suppressing ARDS dvelopment in COVID-19 patients. The two arms consist of a control therapy that is based on the standard of cares recommended by the China National Health Commission (CNHC),[17] and a testing therapy in which the patients

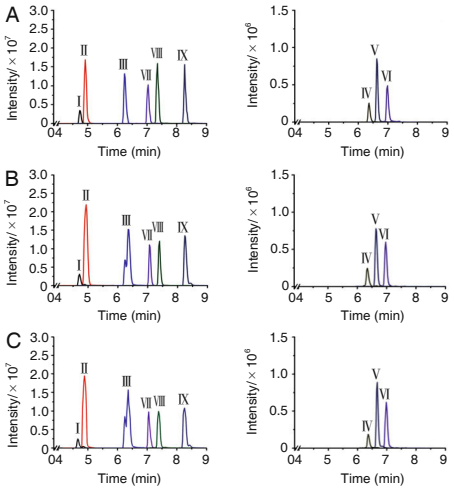

Figure 1. Chromatographs of Mixture of Standard Compounds of Keguan-1

Notes: High-performance liquid chromatography tandem mass spectrometry (HPLC-MS) was used to measure the contents of the 9 control standard compounds for the Chinese medicine components (except for *Coix lacryma-jobi* L.) in the mixture of control standards for Keguan-1 components (A), in Keguan-1 right after it was made (B) and at the end of the study (C). The control standard compounds for individual components are: Jinyinhua-chlorogenic acid (Ⅰ) and galuteolin (Ⅴ); Kuxingren-amygdalin (Ⅱ); Lianqiao-forsythoside A (Ⅲ) and forsythin (IX); Sangye-rutin (Ⅳ); Juhua-chlorogenic acid (I, galuteolin (Ⅴ), and 3,5-dicaffeoyl quinic acid (Ⅵ); Zhebeimu-peimine (Ⅶ) and peiminine (Ⅷ). The standard compound (glyceryl trioleate) in *Coix lacryma-jobi* L. was measured by using a HPLC tandem evaporative light scattering detector. The data were presented in 2 separate graphs with the more abundant ones on the left and the less abundant ones on the right, respectively. Note the difference scales on the Y-axes between the left and the right graphs in each pair of graphs; and that two compounds, chlorogenic acid and galuteolin, are the control standard compounds for more than one component.

were given the new CM drug in addition to the control therapy. A phase Ⅰ analysis based on data from the first 30 participants would be performed; if the therapy was proven safe, the trial would then be expanded into a phase Ⅱ trial to assess the efficacy. The treatment period for each group was 14 days and all the participants were followed-up for 28 days. The trial was approved by the Ethics Board of the Fifth Medical Center of Chinese PLA General Hospital (No. 2020001D), and registered at ClinicalTrials.gov (No. NCT 04251871). The study flowchart is depicted in Figure 2.

Participants Enrollment

Participants were recruited from "suspected COVID-19 patients" in the Fifth Medical Center of Chinese PLA General Hospital who were newly tested positive for SARS-CoV-2. The "suspected COVID-19 patients" were defined as individuals who had contact history with SARS-CoV-2 positive patient(s) and exhibited at least one of the early symptoms of COVID-19, i.e. fever, cough, aspiration, or abnormal findings in chest X-ray radiography or computer

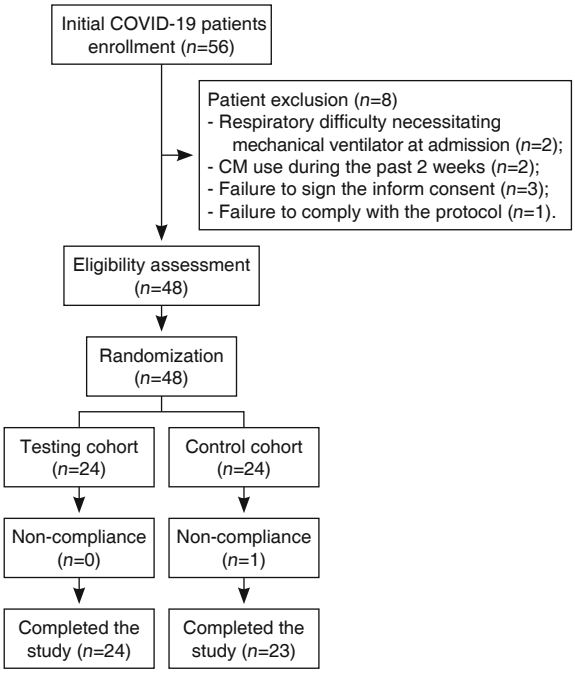

Figure 2. Study Flowchart of Integrative Therapy for COVID-19

tomography (CT) analyses.[17] A reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay for SARS-CoV-2 RNA was used to identify SARS-CoV-2 positive individuals. The assay kits were provided by the Shanghai BioGerm Medical Biotechnology Co., Ltd. Specifically, for each subject, a sputum swab and a throat swab were tested by two independent entities: the Fengtai District Center for Disease Control and the Beijing Center for Disease Control. An individual was considered SARS-CoV-2 positive if both of his/her samples were tested positive by both testing entities.

Individuals with the following specific conditions were exclued: (1) pregnant or lactating women; (2) respiratory failure necessitating mechanical ventilation; (3) liver failure (total bilirubin ⩾10 mg/dL and/or severe coagulation disorders); (4) renal function failure [urine ⩽0.5 $m \cdot kg^{-1} \cdot h^{-1}$, creatinine (Cr) or blood urea nitrogen (BUN) ⩾1.5× upper limits of normal (ULN) although there is adequate circulating blood and cardiac output]; (5) intake of CM or other health supplements during the past 2 weeks; (6) refusal to sign an informed consent form prior to study participation; and (7) unwillingness or inability to comply with the protocol request.

Patient recruitment was initiated on January 22, 2020, right after the completion of the randomization.

Patient enrollment was terminated on February 25, 2020, when it was determined that the COVID-19 epidemic in China had subsided.

Randomization and Masking

Randomization of the cohort assignment for the participants was achieved in the following steps: first, with block = 6 and ratio of 1:1, the random number table (with a total of 150 cases) was generated with SAS (version 9.4). Proc plan statement based on a given seed, by a statistician (who was not involved in data collection or analysis). This led to the arbitrary assignment of the keys into two groups. Following that, patient enrolment was initiated and each eligible participant was given one of these numbers based on the order of being admitted into the participant pool, i.e. the first patient admitted was assigned as 1, the second as 2, and so on. This number was then used to determine the cohort affiliation for each participant. The cohort affiliation and treatment assignment for individual participants were masked. However, due to the limited time in preparing the trial, we could not find proper placebo for the control arm. Thus, no placebo was used in the trial.

Clinical Treatments

Laboratory tests were performed at admission, including a complete blood count and serum biochemistry. All patients were then given the control therapy for 2 weeks. The control therapy was used according to the Directive for the Diagnosis and Recommended Treatments for COVID-19 (version 3)[17] issued by China National Health Commission on January 22, 2020, including the same antiviral treatment (alpha interferon inhalation, 50 μg twice daily; and lopinavir/ritonavir, 400 mg and 100 mg twice daily, respectively) and the other supportive treatments. The chief attending physician decided whether other treatments or interventions were given to individual patients, regardless of their cohort affiliations. For the testing arm, each patient was given the same treatments as in the control therapy plus Keguan-1 19.4 g twice daily. After 2-week treatment, patients were discharged once they were tested negative for the COVID-19 virus. Discharge conditions included: (1) fever resolution persistent for 3 days; (2) recovery of respiratory tract symptoms; (3) recovery of X-ray radiography; and (4) twice negative RT-PCR results taken 24 h apart. Patients remained hospitalized were monitored by the same physicians and might be given additional non-antiviral palliative treatments. For those patients who had not been discharged over treatment of 14 days, palliative treatments were given as needed until discharge. All patients were monitored for 28 days (those who were discharged within 28 days were subjected to follow-up monitoring until day 28 after their admission to the study).

Patient Monitoring and Safety Assessment

During hospitalization, the patients were monitored for a number of parameters by a team of designated nurses who were not aware of the cohort affiliation for the patients for 28 days, starting from the day of admission. Specifically, adverse events, axillary temperature, respiratory distress, and lung injury were monitored. Adverse events were recorded daily in both the treatment period and the follow-up period. The terminologies and grading of severity referred to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).[18] Axillary temperatures were measured at 8 a.m. to 9 a.m.; 12 a.m. to 1 p.m.; 4 p.m. to 5 p.m.; and, 8 p.m. to 9 p.m. on a daily basis.

Outcome Assessment

With the deepening of our understanding of this disease, we realized that the occurrence of ARDS is the most important indicator affecting the fatality rate of COVID-19. Thus, we changed the statistical analysis plan from the original registration as follows: the primary outcome is the incidents of ARDS development; and the secondary outcomes include the time to fever resolution and the recovery of lung injury. These revisions have been updated at ClinicalTrials.gov on May 4, 2020.

Respiratory stress was assessed by monitoring the arterial oxygen tension, inspiratory oxygen fraction, blood oxygen saturation level, continuous positive airway pressure, and positive end-expiratory pressure. ARDS was diagnosed based on Berlin criteria.[19,20] X-ray radiography was used to assess lung injury of the initial 30 patients (phase Ⅰ). CT was used for the rest of the study. Radiography or CT was conducted for all patients at admission, day 7 and 14 after the admission. The data were evaluated by a specialist in a blinded fashion.

The radiological recovery of lung injury on X-ray radiographs was defined as the remission of lung injury to the extent of ill-defined hazy increased density in single/both lungs. The radiological recovery of lung injury on chest CT scans was defined as the remission

of lung injury to the extent of <5% involvement of imaging abnormalities, including ground glass opacity, crazy-paving pattern, and consolidation, in each lung lobe. On X-ray radiographs, any imaging findings of ground glass opacities and focal consolidation in each lung were considered non-recovery; on chest CT, any imaging findings of ≥5% involvement in each lung lobe were considered non-recovery.

Statistical Analyses

The baseline comparison and efficacy evaluation were performed on the per-protocol set. Adverse effects occurred in both the treatment period and the follow-up period were combined to evaluate. Safety was assessed on the safety set. Continuous variables were presented as mean ± standard deviation ($\bar{x} \pm s$) or median (range) when the data conforms to normality or non-normality. Comparison between groups was performed using the *t* test (variance is even) or adjusted *t*-test (variance is uneven) with normality data, and Wilcoxon test with non-normality data. For those categorical variables, the frequencies or proportions of patients in each category were calculated, and χ^2 test was used for comparison between groups. All data were tested on both sides, a *P*-value less than 0.05 was considered statistically significant. Statistics were conducted by a statistician who was blinded to the study grouping. Analyses were done using SAS software, version 9.4.

RESULTS

Baseline Clinical Characteristics of Study Cohorts

All but one of the 48 participants received the treatments as designed. The sole non-compliant participant belongs to the control cohort and was excluded from the study. Thus, the control cohort and the testing cohort each has 23 and 24 participants, respectively. A retrospective analysis did not reveal any significant differences between the two cohorts (*P*>0.05, Table 1). Also, there are no differences with respect to the use of other drugs and treatments between the two cohorts (*P*>0.05, Appendices 2–5).

Table 1. Baseline Demographic and Clinical Characteristics of COVID-19 Participants

Characteristics	Testing cohort (24 cases)	Control cohort (23 cases)	*P* value
Male [Case (%)]	14 (58.3)	12 (52.2)	0.772
Mean age (Year)	46.8 ± 14.4	51.4 ± 17.6	0.332
Body mass index (kg/m^2)	24.8 ± 3.2	25.4 ± 3.0	0.528
Base line temperature (℃)	38.0 (36.2–39.0)	37.9 (36.0–39.1)	0.853
Onset time of symptom to enrollment (d)	6.5 (3.0–17.0)	8.0 (3.0–22.0)	0.779
Baseline symptoms [Case (%)]			
Fever	17 (70.8)	15 (65.2)	0.760
Cough	15 (62.5)	13 (56.5)	0 770
Fatigue	7 (29.2)	7 (30.4)	1.000
Pre-existing chronic diseases [Case (%)]	10 (41.7)	8 (34.8)	0 766
Laboratory indices			
White blood cell count (×10^9/L)	4.2 (2.7–6.8)	5.2 (2.8–7.5)	0.105
Neutrophil count (×10^9/L)	2.7 ± 0.9	3.1 ± 1.2	0.299
Platelet count (×10^9/L)	182.8 ± 54.7	186.7 ± 64.6	0.826
CD 4$^+$ count (μL)	400.0 ± 214.1	462.6 ± 262.5	0.430
ALT (U/L)	26.0 (13.0–173.0)	20.0 (9.0–107.0)	0.096
AST (U/L)	28.5 (14.0–112.0)	27.0 (16.0–81.0)	0.447
Blood urea nitrogen (mmol/L)	3.7 (1.9–7.0)	3.8 (2.4–8.8)	0.317
Creatinine (μmol/L)	76.4 ± 11.2	79.3 ± 13.0	0.419
Prothrombin time (s)	11.9 (10.2–13.5)	12.3 (10.9–18.1)	0.052
D-dimer (mg/L)	0.3 (0.10–1.3)	0.2 (0.1–5.1)	0.798
Procalcitonin (ng/mL)	0.05 (0.02–7.40)	0.05 (0.03–0.53)	0.692
Interleukin-6 (pg/mL)	11.5 (1.5–51.7)	8.4 (1.5–96.1)	0.904
C-reactive protein (mg/L)	8.4 (0.6–56.9)	7.0 (0.4–70.9)	0.874
Abnormality in chest radiology [Case (%)]*	20 (83.3)	16 (69.6)	0.318

Notes: quantitative data are presented as $\bar{x} \pm s$ or median (range). *The chest imaging was performed by either X-ray radiography or CT scan. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

Adverse Events

Several mild adverse effects including diarrhea, anorexia, nausea, stomach pain and vomiting, were observed in the control cohort. The addition of Keguan-1 treatment in the testing cohort did not cause new types of adverse events nor any significant changes in the incidents, duration, or severity of the adverse events compared to those observed in the control cohort (Table 2, Appendix 6). The results of routine blood and biochemical tests at the end of the treatment period did not reveal any significant irregularities for either cohorts (Appendix 7).

Clinical Outcomes

For the primary outcome, no one developed ARDS in the first 3 days after admission. Over the course of the study, 6 of 23 (26.1%) patients of the control arm and 1 of 24 (4.17%) patients of the testing arm developed ARDS, representing a significant difference in the incidents of ARDS development between the two arms (*P*=0.048, Table 3). Furthermore,

Table 2. Adverse Events in Phase Ⅰ Participants with COVID-19 [Case (%)]

Adverse events	Testing cohort (15 cases)						Control cohort (14 cases)						*P* value
	Total	G1	G2	G3	G4	G5	Total	G1	G2	G3	G4	G5	
Diarrhea	9 (60.0)	6 (40.0)	3 (20.0)	/	/	/	8 (57.1)	7 (50.0)	1 (7.1)	/	/	/	1.000
Anorexia	4 (26.7)	4 (26.7)	/	/	/	/	5 (35.7)	5 (35.7)	/	/	/	/	0.700
Nausea	2 (13.3)	2 (13.3)	/	/	/	/	3 (21.4)	3 (21.4)	/	/	/	/	0.651
Stomach pain	2 (13.3)	2 (13.3)	/	/	/	/	3 (21.4)	3 (21.4)	/	/	/	/	0.651
Allergic reaction	/	/	/	/	/	/	1 (7.1)	/	/	/	1	/	0.483
Sepsis	/	/	/	/	/	/	1 (7.1)	/	/	/	/	1	0.483

Notes: G1, mild; G2, moderate; G3, severe; G4, life-threatening; G5, death related

3 of the 6 patients who developed ARDS in the control arm were put on ventilators and 1 of them died on day 24 after admission. The 6 patients in the control arm suffered ARDS for 6, 8, 11, 13, 18, and 20 days, respectively (mean 11.7 days, Table 4). In contrast, the single patient in the testing arm who developed ARDS had ARDS for only 4 days.

Overall, the mean value of time for fever resolution for the control cohort and the testing cohort are 3.0 (1.0–9.0) and 1.5 (1.0–5.0) days, respectively. This represents a significant reduction in the median value of time to fever resolution for the testing arm (1.5 d, *P*=0.035).

At the time of admission, 76.6% of the patients exhibited lung injury. But all of them developed lung injury within 10 days after admission. Over the course of the study, 16 of the 23 (69.6%) patients in control arm and 21 of the 24 (87.5%) patients in testing arm were found to achieve full lung injury recovery judging by the data from X-ray radiography or CT, respectively. Notably, there was a higher (not statistically significant) rate of abnormal radiograph in the testing arm than that in the control arm at baseline; the testing arm achieved higher rate of radiographic recovery after the treatment than the control arm. Thus, the testing arm has a higher rate of lung injury recovery than the control arm, albeit that the difference is not statistically significant (*P*=0.168, Table 3). Typical changes in X-ray radiographs or CT scans are depicted in Appendices 8 and 9.

Table 3. Clinical Courses of COVID-19 Participants [Case (%)]

Indices	Testing cohort (24 cases)	Control cohort (23 cases)	*P*-value
Time to fever resolution (d)	1.5 (1.0–5.0)	3.0 (1.0–9.0)	0.035
Time to negative result for virus (d)	8.0 (4.0–22.0)	10.5 (4.0–23.0)	0.263
Lung radiographic recovery*	21 (87.5)	16 (69.6)	0.168
Occurrence of complications			
Any	1 (4.2)	6 (26.1)	0.048
ARDS	1 (4.2)	6 (26.1)	0.048
Secondary infection	1 (6.7)	3 (21.4)	0.330
Acute kidney injury	2 (8.3)	3 (13.0)	0.666
Acute cardiac injury	0	0	
Septic shock	0	1 (4.3)	0.489
Death	0	1 (4.3)	0.489
Use of mechanical ventilation	1 (4.2)	3 (21.4)	0.348
Day of mechanical ventilation	4.0△	11.7 ± 5.0	N/A
No. of patients transferred to intensive care unit	0	2 (8.7)	N/A

Notes: quantitative data are presented as $\bar{x} \pm s$ or median (range). *The chest imaging was performed by either X-ray radiograph or computer tomography CT scan (Appendices 8–9). △Dada from one patient

DISCUSSION

We have reported here the development of Keguan-1, a new CM drug that was specifically designed for suppressing ARDS development in patients of COVID-19 and/or of other RDI, and the results from

Table 4. Data of COVID-19 Patients Who Developed ARDS

No.	Group	Sex	Age	Pre-existing chronic diseases	Severity of ARDS	Treatment	Duration of ARDS (d)	Outcome
13	A	Female	79	NA	Severe	Invasive mechanical ventilation	18	Death
21	A	Male	33	NA	Mild	High-flow nasal oxygen	11	Discharge
23	A	Male	77	Chronic kidney disease and hypertension	Moderate	Non-invasive mechanical ventilation	13	Discharge
29	A	Female	60	Asthma	Mild	High-flow nasal oxygen	6	Discharge
39	B	Male	34	NA	Moderate	Non-invasive mechanical ventilation	4	Discharge
40	A	Female	74	Atherosclerosis	Moderate	High-flow nasal oxygen	8	Discharge
41	A	Male	78	Hypertension, diabetes and prostatic cancer	Moderate	Non-invasive mechanical ventilation	20	Discharge

Notes: A: control cohort; B: testing cohort. NA: not applicable

a randomized, controlled trial aiming at assessing the safety and efficacy of this new drug. The results of the clinical trial showed that Keguan-1, when used in conjunction with the treatments of a control therapy, did not cause any significant alterations with respect to the types, the incidents, or the severities of adverse events, demonstrating that this new CM-based drug is safe when used under the specific clinical setting. In terms of efficacy, the drug appeared to have beneficial effects for both the primary and the secondary endpoints. Specifically, the addition of Keguan-1 to the control therapy led to: a significant reduction in the incidents of ARDS development (P=0.048); a significant shortening in time to fever resolution (P=0.035); and a trend of improvement (albeit not statistically significant) in the incident of lung injury recovery. Notably, the single case of ARDS in the testing arm had a shorter duration on the ventilator and a shorter time to full recovery than any of the 6 ARDS cases in the corresponding control arm, suggesting a potential beneficial effect in the recovery even after the development of ARDS. Together, these results have shown that Keguan-1 could be used safely to suppress ADRS in COVID-19 patients. In addition, the findings have also provided support for the claims that these CM components are safe for human use and could have beneficial effects for patients experiencing respiratory distress.

Keguan-1 was developed specifically for suppressing the development of ARDS by targeting the host. It was based on an anticipation that SARS-CoV-2 could lead to a respiratory illness that is similar to those caused by SARS-CoV and MERS-CoV, which are characterized by their propensity of outbreak into epidemics with high CFRs and the critical role of the host factor for prognosis.[4-6] Today, COVID-19 has evolved not only in regional epidemics, but a global pandemic.[21] Although its CFR is lower than those of SARS and MERS,[22,23] but it is still terribly high, particularly considering its highly contagious nature and its potential global implication.[24] Significantly, there indeed exists a great variability in the responses and prognosis among COVID-19 patients,[25-27] confirming the suspicion that the host factors paly a very important role in the clinical course of the disease. The mechanism of Keguan-1 in the treatment of COVID-19 may be involved in modulating immune system. Poon, et al[28] found that the Sangju Drink had immunomodulating effects in healthy volunteers, including significant increase of the T-lymphocyte CD4/CD8 ratio. Investigations also found that the herbal ingredients in Keguan-1 and their active components have a potent anti-inflammatory effect. For instance, the major component in *Forsythia suspensa*, forsythiaside, was previously demonstrated to have dose-dependent protective effects on lung injury by attenuating infiltration of inflammatory cells and suppressing tumor necrosis factor α, interleukin-6 and - 1β production through nuclear factor kappa-B.[29] The major component in Lonicera japonica, neochlorogenic acid, could prevent excessive macrophage-mediated inflammatory responses as an activator upregulating AMP-activated protein kinase/nuclear factor erythroid 2-related factor 2 signal transduction.[30] Together, these new information have validated the merit of our original design. Importantly, COVID-19 is still spreading in many places throughout the globe. Yet, no effective treatments or vaccines are in sight.[24,25,31] In the regards, any effective therapy for COVID-19 would potentially have a life-saving value.

In addition, Keguan-1 might suppress ARDS development by targeting the host. Given that ARDS development is the shared key development that leads to a fatal outcome in many respiratory distress illnesses,[23,26] this drug could provide an effective strategy for suppressing ARDS development in respiratory distress illness of other cause and hence a new paradigm for coping with the challenge posed by respiratory distress illnesses due to the newly emerging pathogens. Additionally, the results of this study have lent support for the claim that the components used to make Keguan-1 have excellent safety attributes. Therefore, it is conceivable that its combined use with certain drugs could also be safe. In particular, it may be used to enhance the effect of other anti-SARS-CoV-2 drugs, which should be developed in the future.

The study, however, does have its limitations. First, the cohort sizes are quite small, due to a failure in recruiting a large number of COVID-19 patients before the end of the outbreak in China. The results in this paper should be interpreted for caution. However, it is conceivable that similar studies but with larger scales can be carried out in other countries where COVID-19 cases are still on the rise. Second, X-ray radiography, rather than computer tomography, was used at the early phase of the study to assess the degrees of lung injury due to a logistic issue in setting up the computer tomography system inside the designated confinement unit in a timely manner. In addition, the study did not include a placebo arm due to an ethical consideration.

Conflict of interest

None declared.

Author Contributions

Wang JB, Wang ZX, and Jing J conducted the study and wrote the manuscript, they contributed equally to this work as co-first authors. Wang ZX, Jing J, Zhao P, Dong JH, Zhou YF, Yang G, Jiang TJ, Xu Z, Wu D, Sun YQ, Wang JB, He DC, and Chen Z collected data and provided technical assistance. Jing J, Yu SM, Niu M, Zhao X, Zhang P, Song XA, Bi JF, Bai ZF, Guo YM, Zhao X, Zhao PF, Tang JY, and Li PY analyzed data. Wang JB, Wang RL, Qin EQ, and Xiao XH initiated and oversaw the study.

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Appendix 1. Quality Control for Keguan-1

The quality control markers were selected according to the

Chinese Pharmacopeia (2015 edition). All the standard reference compounds were obtained from the China National Institutes for Food and Drug Control. These compounds were then mixed in a defined ratio to create a quality control standard mixture for the formula. The ratio of mixing was determined based on the relative abundance of each compound in the respective component as well as the relative ratio of the component in the formula.

Determination for the six components (Jinyinhua, Lianqiao, Sangye, Juhua, Zhebeimu and Kuxingren) in Keguan-1

The quality control for the six components (Jinyinhua, Lianqiao, Sangye, Juhua, Zhebeimu and Kuxingren) in Keguan-1 were conducted by the high-performance liquid chromatography tandem mass spectrometry (HPLC-MS). The samples were analyzed using an Eclipse Plus C18 analytical column (2.1 mm i.d. × 100 mm, 1.8 μm i.d., Agilent Technologies, USA). The column temperature was maintained at 30 °C. For the chromatography analysis, separation was achieved with a 25 min linear gradient with the mobile phases of solvent A (water spiked with 0.1% formic acid) and solvent B (acetonitrile spiked with 0.1% formic acid). The flow rate was set as 0.30 mL/min. The gradient was used as follows: a linear gradient of 95% A over initial-1.0 min, 95-

60% A over 1.0–9.0 min, 60–10% A over 9.0–19.0 min, 10–0% A over 19.0–21.0 min, 100% B over 21.0–25.0 min. The eluent was directly introduced into the mass spectrometer.

For mass spectrometry, an Agilent 6550 Q-TOF mass spectrometer with an electrospray ionization source (ESI) was used. The electrospray source parameters were fixed as follows: electrospray capillary voltage was 4 kV in positive ionization mode. The mass range was set from m/z 80 to 1000. Gas temperature was 290°C in positive ionization mode. Gas flow was 13 L/min. Nebulizer was set to 40 pisg (positive). Sheath gas temperature was 350°C and sheath gas flow was 12 L/min. Nozzle voltage was 2000 V in both negative and positive mode. For internal mass calibration during the MS analysis, reference masses 121.0509 (Purine, $[C_5H_4N_4+ H]^+$) and 922.0098 (HP-0921, $[C_{18}H_{18}O_6N_3P_3F_{24}{}^+H]^+$) were used in positive mode, and 112.9856 ($TFANH_4$, $[C_2H_4O_2NF_3{}^- NH_4]^-$) and 1033.9881 $TFANH_4{}^+$ HP-0921, $[C_{20}H_{22}O_8N_4P_3F_{27}{}^- NH_4]^-$) were used in negative mode.

The mixed standards methanol solution was prepared by mixing each of the standard reference compound solution. The Keguan-1 sample solutions were prepared by using methanol to extract the components from the granules through ultrasonic extraction approach followed with filtration by 0.22 μm filters. The final concentration of sample solutions was equivalent to 20.00 mg granules in 1 ml methanol. The fresh-prepared mixed standards solution and the sample solutions were then injected respectively into the Agilent 6550 HPLC-MS system to detect the signature chromatographs of each.

Determination for Yiyiren in Keguan-1

The quality control for Yiyiren was conducted by the high-performance liquid chromatography (HPLC) coupled with evaporative light-scattering detector. The HPLC condition

included: Chromatographic column: Purospher STAR RP-18 endcapped column (4.6 mm i.d.×250 mm, 5 μm i.d.); Column temperature: 25 ℃. Mobile phase: acetonitrile : dichloromethane (65 : 35). Flow rate: 1.2 mL/min; Sample injection size: 5 μl and 20 μl (two-point calibration method). The evaporative light scattering detector condition include: drift tube temperature, 90 ℃; nebulizer temperature, 35 ℃.

The standard reference (glyceryl trioleate) was resolved in the mobile phase (acetonitrile : dichloromethane, 65 : 35) to reach the final concentration of 0.14 mg/ml. The Keguan-1 sample solutions were prepared by using the mobile phase to extract the components from the granules through ultrasonic extraction approach followed with filtration by 0.22 μm filters. The final concentration of sample solutions was equivalent to 8.00 mg granules in 1 ml methanol.

The fresh-prepared mixed standards solution and the sample solutions were then injected respectively into the Waters e2695 HPLC coupled with 2424 ELS Detector to detect the content of glyceryl trioleate.

Appendix 2. Drugs and Biologics Administered

Category	Drug	Testing cohort (n = 24)	Control cohort (n = 23)
Antipyretic	Ibuprofen		
	No. of patients received, n/n	4	4
	Dosing time, days	2.5 (1.0-4.0)	3.0 (1.0-3.0)
Glucocorticoids	Methylprednisolone		
	No. of patients received, n/n	11	11
	Dosing time, days	6 0 (4.0-19.0)	7.0 (3.0-21.0)
	Maximal daily dose, mg/kg	1 78 (0 62-6.80)	2 08 (1.08-5.16)
	Mean daily dose, mg/kg	1 33 (0.56-3.88)	2.30 (0.68-2.75)
Antibacterial	Moxifloxacin		
	No. of patients received, n/n	9	7
	Dosing time, days	9.0 (1.0-13.0)	8.0 (2.0-14.0)
	Piperacillin/Tazobactam		
	No. of patients received, n/n	5	7
	Dosing time, days	9.0 (3 0-21 0)	7 0 (1 0-14 0)
	Linezolid		
	No. of patients received, n/n	1	1
	Dosing time, days	6	2
	Meropenem		
	No. of patients received, n/n	1	2
	Dosing time, days	12	14 and 5
	Amikacin		
	No. of patients received, n/n	1	0
	Dosing time, days	6	N/A
	Vancomycin		
	No. of patients received, n/n	1	1
	Dosing time, days	6	6
	Teicoplanin		
	No. of patients received, n/n	1	0
	Dosing time, days	6	N/A
Antifungal	Caspofungin		
	No. of patients received, n/n	3	3
	Dosing time, days	5.0 (4.0-15.0)	9.0 (7.0-15.0)
	Voriconazole		
	No. of patients received, n/n	1	0
	Dosing time, days	1	N/A
Others	Gamma Globulin		
	No. of patients received, n/n	6	6
	Dosing time, days	4.0 (2.0-20.0)	3 5 (2.0-17.0)
	Human albumin		
	No. of patients received, n/n	3	6
	Dosing time, days	8.0 (6.0-12.0)	7 5 (3.0-20.0)

Notes: Data were presented as: median value (range).

Appendix 3. Drug Use Information

No.	Group	Alpha interferon	Lopinavir/ritonavir	Acyclovir	Ibuprofen	Methylprednisolone	Moxifloxacin	Piperacillin/Tazobactam	Linezolid	Meropenem	Amikacin	Vancomycin	Teicoplanin	Caspofungin	Voriconazole	Gamma Globulin	Human albumin
1	B	+	+	-	-	+	-	+	-	-	-	-	-	-	-	-	-
2	A	+	+	-	+	+	+	-	-	-	-	-	-	-	-	-	-
3	A	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	B	+	+	-	-	-	+	-	-	-	-	-	-	-	-	-	-
6	B	+	+	-	-	-	+	-	-	-	-	-	-	-	-	-	-
7	A	+	+	-	+	-	+	-	-	-	-	-	-	-	-	-	-
8	B	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-
9	A	+	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-
10	B	+	+	-	-	+	+	-	-	-	+	-	+	+	-	-	+
11	B	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	A	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	A	+	+	-	-	+	+	+	-	+	-	+	-	-	-	+	+
14	B	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15	B	+	+	-	-	+	+	+	+	+	-	+	-	-	+	+	+
16	B	+	+	-	+	+	+	-	-	-	-	-	-	-	-	+	-
17	A	+	+	-	+	+	+	-	-	-	-	-	-	-	-	+	+
18	A	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
19	A	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20	B	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-
21	A	+	+	-	-	+	+	+	-	-	-	-	-	-	-	+	+
22	B	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23	A	+	+	-	-	+	+	+	+	+	-	-	-	-	-	+	+
24	B	+	+	-	+	-	+	-	-	-	-	-	-	-	-	+	+
25	A	+	+	-	-	-	+	-	-	-	-	-	-	-	-	+	-
26	B	+	+	-	-	+	+	-	-	-	-	-	-	-	-	+	-
27	B	+	+	-	-	+	+	-	-	-	-	-	-	-	-	+	-
28	A	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
29	A	+	+	-	-	+	-	+	-	-	-	-	-	-	-	+	+
30	B	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
31	B	+	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-
32	A	+	+	-	+	+	-	+	-	-	-	-	-	-	-	-	-
33	A	+	+	-	-	+	-	-	-	-	-	-	-	-	-	+	-
34	B	+	+	-	-	+	-	-	-	-	-	-	-	-	-	+	-
35	B	+	+	-	-	+	-	-	-	-	-	-	-	-	-	+	-
36	A	+	+	-	-	+	-	-	-	-	-	-	-	-	-	+	-
37	B	+	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-
38	A	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
39	B	+	+	-	-	+	-	+	-	-	-	-	-	-	-	+	-

40	A	+	+	-	-	+	-	+	-	-	-	-	-	-	-	-	+
41	A	+	+	-	-	+	-	+	-	-	-	-	-	-	-	-	-
42	B	+	+	-	-	+	+	+	-	-	-	-	-	-	-	-	-
43	B	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44	B	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
45	A	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
46	A	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
47	A	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48	B	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Notes: A: Control cohort; B: Testing cohort; +: used; -: not used.

Appendix 4. Antipyretics Use Information

No.	Group	Dosing information
2	A	300mg, qd, for three days
7	A	300mg, bid, for three days
8	B	300mg, qd, for five days
16	B	300mg, bid, for four days
17	A	300mg, qd, for one day
20	B	300mg, bid, for three days
24	B	300mg, bid, for two days
32	A	300mg, bid, for three days

Notes: A: Control cohort; B: Testing cohort.

Appendix 5. Glucocorticoids Use Information

No.	Group	1st	2nd	3rd	4th	5th	6th
1	B	4.5 mg/kg Seven days	7 mg/kg Four days	3.5 mg/kg Two days	2.25 mg/kg Two days	1.125 mg/kg Two days	1 mg/kg Two days
2	A	1 mg/kg Three days	0.5mg/kg Four days	/	/	/	/
9	A	5.5 mg/kg Three days	4 mg/kg Two days	2.5mg/kg Two days	1.5mg/kg One days	0.75mg/kg Two days	/
12	A	4 mg/kg One days	5.5mg/kg Four days	2.75mg/kg One days	1.33mg/kg One days	0.67mg/kg One days	/
14	B	5.5 mg/kg Two days	2.5 mg/kg One days	4 mg/kg One days	2 mg/kg Two days	1.33 mg/kg Two days	0.67mg/kg One days
15	B	1 mg/kg Five days	0.5 mg/kg Four days	/	/	/	/
16	B	1 mg/kg Three days	/	/	/	/	/
20	B	3.5 mg/kg Six days	4.5 mg/kg One days	2.5 mg/kg One days	1 mg/kg Two days	1 mg/kg One days	/
22	B	4 mg/kg Two days	3 mg/kg Two days	1 mg/kg Two days	/	/	/
25	A	1.33 mg/kg Three days	2.67 mg/kg Three days	5.33 mg/kg Two days	4 mg/kg Two days	0.67mg/kg One days	/
26	B	0.67mg/kg Five days	/	/	/	/	/
28	A	1.33 mg/kg Four days	5.33 mg/kg Three days	4 mg/kg One days	0.67 mg/kg One days	/	/
31	B	0.67 mg/kg One day	1.33 mg/kg Two days	0.67 mg/kg One day			
32	A	2 mg/kg One day	1.5 mg/kg One day	1 mg/kg One day	0.5 mg/kg One day		
33	A	2 mg/kg One day	1 mg/kg Two days				
34	B	1 mg/kg Four days					
35	B	1 mg/kg Three days	0.5 mg/kg Two days				
36	A	1 mg/kg Three days	0.5 mg/kg Three days	0.25 mg/kg One day			
39	B	1 mg/kg One day	2 mg/kg Four days	1.5 mg/kg One day			
40	A	1 mg/kg Two days	0.5 mg/kg Three days	0.25 mg/kg One day			
41	A	1 mg/kg One day	2 mg/kg Two days	1 mg/kg Two days	0.5 mg/kg One day	0.25 mg/kg One day	
42	B	1 mg/kg One day	2 mg/kg Three days	1 mg/kg Two days			

Notes: A: Control cohort; B: Testing cohort.

Appendix 6. Adverse Events of all the Participants

No.	Group	Diarrhea	Anorexia	Nausea	Stomach pain	Allergic reaction	Sepsis
1	B	G1	/	/	/	/	/
2	A	/	/	/	/	/	/
3	A	/	/	/	/	/	/
4	B	/	G1	/	/	/	/
6	B	/	/	/	/	/	/
7	A	G1	G1	/	/	/	/
8	B	G1	/	/	/	/	/
9	A	G1	/	/	/	/	/
10	B	G2	G1	G1	/	/	/
11	B	/	/	/	/	/	/
12	A	G2	G1	/	/	/	/
13	A	G1	/	/	/	G4	G5
14	B	G1	/	/	/	/	/
15	B	G2	/	/	G1	/	/
16	B	G2	/	/	/	/	/
17	A	G1	G1	/	/	/	/
18	A	G1	/	/	/	/	/
19	A	/	/	G1	G1	/	/
20	B	G1	G1	/	/	/	/
21	A	/	/	/	/	/	/
22	B	/	/	/	/	/	/
23	A	G1	G1	G1	/	/	/
24	B	G1	G1	G1	G1	/	/
25	A	/	/	/	/	/	/
26	B	/	/	/	/	/	/
27	B	G1	/	/	/	/	/
28	A	G1	/	/	/	/	/
29	A	/	G1	G1	G1	/	/
30	B	/	/	/	/	/	/
31	B	/	/	/	/	/	/
32	A	/	/	/	/	/	/
33	A	/	/	/	/	/	/
34	B	/	/	/	/	/	/
35	B	/	/	/	/	/	/
36	A	/	/	/	/	/	/
37	B	G2	/	/	/	/	/
38	A	G2	/	/	/	/	/
39	B	/	/	/	/	/	/
40	A	/	/	/	/	/	/
41	A	/	/	/	/	/	/
42	B	/	/	/	/	/	/
43	B	/	/	/	/	/	/

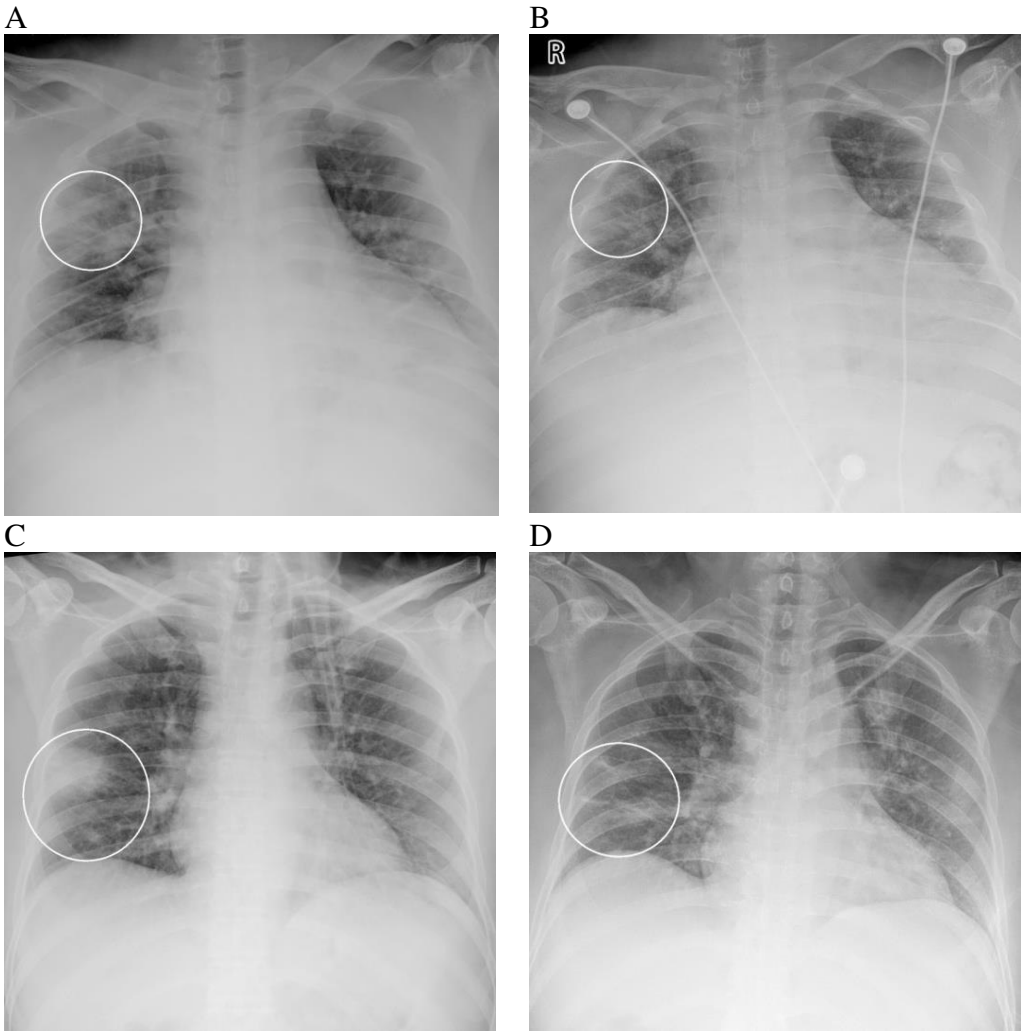
44	B	/	/	/	G1	/	/
45	A	/	/	/	/	/	/
46	A	/	/	/	/	/	/
47	A	/	/	/	/	/	/
48	B	/	/	G1	/	/	/

Notes: A: Control cohort; B: Testing cohort; /: not observed. G1~G5 were the five grades of adverse effects according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) (2). G1, mild; G2, moderate; G3, severe; G4, life-threatening; G5, death related.

Appendix 7. Serum Biochemistry Information

Characteristics	Testing cohort	Control cohort	P value
The 7th day laboratory indices (n=47)	n=24	n=23	
White blood cell count, $\times 10^9$/L	5 7 ± 1 9	6 6 ± 2 5	0.168
Neutrophil count, $\times 10^9$/L	3 2 (0 9-7 7)	3 7 (1 9-12 9)	0.232
Platelet count, $\times 10^9$/L	232 ± 69	227 ± 69	0.813
Alanine aminotransferase, U/L	25 (13-99)	22 (10-78)	0.537
Aspartate aminotransferase, U/L	23 (11-70)	21 (12-41)	0.756
Blood urea nitrogen, mmol/L	4.5 (2.0-8 3)	4.8 (3.2-11.7)	0.157
Creatinine, μmol/L	74 ± 14	71 ± 12	0.488
The 14th day laboratory indices (n=38)	n=17	n=21	
White blood cell count, $\times 10^9$/L	6.2 (3.8-15.1)	6.3 (3.5-21.6)	0.983
Neutrophil count, $\times 10^9$/L	3 9 (1.5-13.4)	4.2 (1.8-19.9)	0.954
Platelet count, $\times 10^9$/L	228 ± 73	210 ± 71	0.431
Alanine aminotransferase, U/L	35 (13-145)	32 (12-135)	0.437
Aspartate aminotransferase, U/L	24 (15-60)	23 (13-52)	0.699
Blood urea nitrogen, mmol/L	4.6 (3.0-7.3)	5 1 (3.7-16.3)	0.363
Creatinine, μmol/L	73 ± 13	71 ± 12	0.505
The 28th day laboratory indices (n=24)	n=14	n=10	
White blood cell count, $\times 10^9$/L	5.2 (2.9-6.5)	5 1 (3.7-13.8)	0.919
Neutrophil count, $\times 10^9$/L	2.7 (0.7-4.3)	2.9 (1.6-13.3)	0 874
Platelet count, $\times 10^9$/L	246 ± 87	234 ± 100	0.764
Alanine aminotransferase, U/L	19 (8-55)	27 (10-90)	0.318
Aspartate aminotransferase, U/L	22 (14-29)	20 (11-236)	0.874
Blood urea nitrogen, mmol/L	4.3 (2.9-7.0)	5 1 (3 6-13.4)	0.138
Creatinine, μmol/L	70 ± 10	78 ± 13	0.112

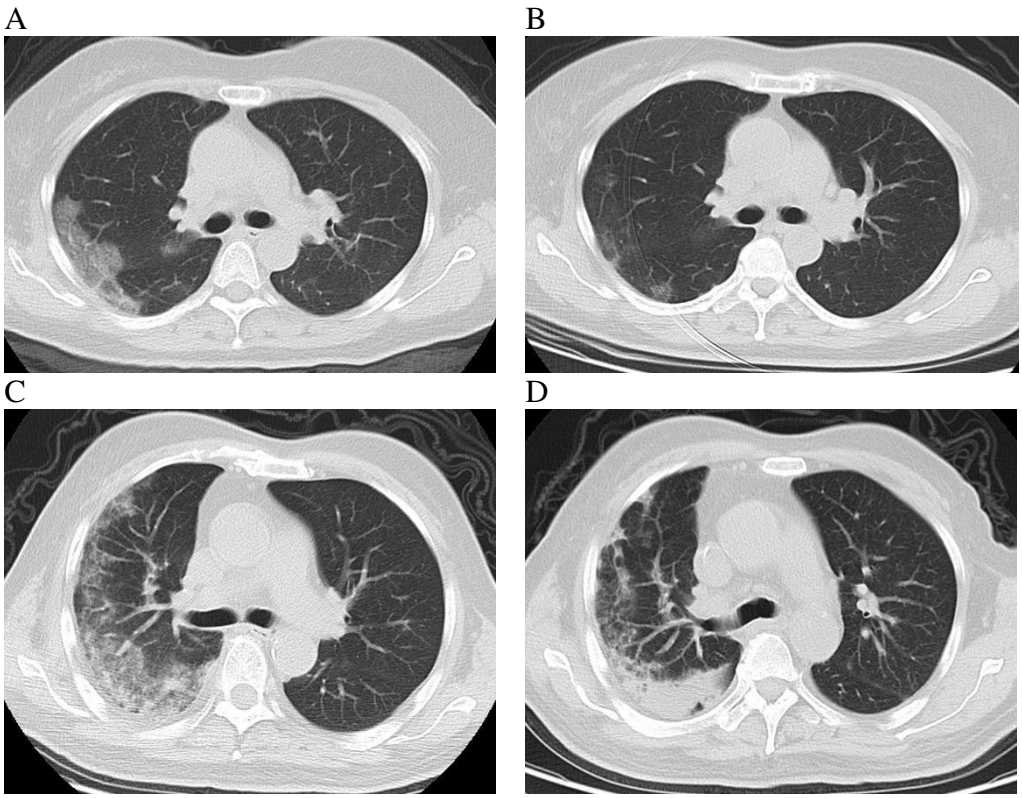
Note: Data were presented as mean ± SD or median (range).



Appendix 8. Representative X-ray Radiographs of COVID-19 Participants

Notes: A and B: X-ray radiographs for Patient 21 of the control cohort before (A) and after (B) the treatment.

C and D: X-ray radiographs for Patient 26 of the testing cohort before (C) and after (D) the treatment. The consolidation area in right lower lobe (indicated by white circle) improved significantly after the treatment of Keguan-1.



Appendix 9. Representative Chest CT of COVID-19 Participants

Notes: A and B: Chest CT for Patient 31 of the testing cohort before (A) and after (B) the treatment. The ground glass opacity (GGO) area in right upper lobe and the lower lobe improved significantly after the treatment of Keguan-1.

C and D: Chest CT for Patient 41 of the control cohort before (C) and after (D) the treatment.

Appendix 10. Data Sharing Statements

Will individual participant data be available (including data dictionaries)?	Yes
What data in particular will be shared?	All of the individual participant data collected during the trial, after de-identification
What other documents will be available?	Study protocol, statistical analysis plan, analytic code
When will data be available (start and end dates)?	Beginning 3 months and ending 5 years following article publication
With whom?	Researchers who provide a methodologically sound proposal
For what types of analyses?	To achieve aims in the approved proposal
By what mechanism will data be made available?	Proposals should be directed to pharm_sci@126.com; to gain access, data requestors will need to sign a data access agreement. Data are available for 5 years and will be send by emails.