Treatment of Covid-19 Patients With High Dose of Ulinastatin

Hai Huang
Changzheng Hospital
Ping-Fang Hu
Changzheng Hospital
Liang-Liang Sun
Changzheng Hospital
Yi-Bin Guo
second military medical university
Qiong Wang
Changzheng Hospital
Zhi-Min Liu
Changzheng Hospital
Ji-Zhong Yin
Changzheng Hospital
Pei-Mei Shi
Changzheng Hospital
Zong-Li Yuan
Changzheng Hospital
Yu Tan
Changzheng Hospital
Chao Zhou
Changzheng Hospital
Ya-Long Liu
Changzheng Hospital
Cheng Chen
Changzheng Hospital
Hui-Hui Song
Changzheng Hospital
weifen Xie (weifenxie@medmail.com.cn)
Changzheng Hospital https://orcid.org/0000-0002-7137-112X

Research

Keywords: Coronavirus disease 2019, Covid-19, protease inhibitor, ulinastatin, inflammation, cytokine storm

Posted Date: June 5th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-32627/v1

Abstract

Background No specific therapeutic agents or vaccines are available for the treatment of Coronavirus disease 2019 (Covid-19) yet. In this study, we aimed to assess the efficacy of high dose ulinastatin for patients with Covid-19.

Methods Twelve patients hospitalized with confirmed SARS-CoV-2 infection were treated with high dose of ulinastatin beyond standard care. The changes of clinical manifestations, laboratory examinations and chest images were retrospectively analyzed.

Results A total of 10 patients with severe Covid-19 and 2 patients with moderate Covid-19 received ulinastatin treatment. The average age of the patients was 68.0 ± 11.9 years, ranging from 48 to 87 years. Nine of 12 patients (75.0%) had one or more comorbidities. The most common symptoms on admission were fever (8/12, 66.7%), cough (5/12, 41.7%) and dyspnea (5/12, 41.7%). The percentage of lymphocytes was decreased in 41.7% of patients (5/12), and 58.3% of patients (7/12) had elevated hypersensitive C-reactive protein (CRP) levels (mean, 49.70 ± 77.70 mg/L). The white blood cell levels and the percentage of lymphocytes returned to normal in all of the patients, and CRP decreased significantly and returned to normal in 83.3% of patients (10/12; mean, 6.87 ± 6.63 mg/L) on the seventh day after ulinastatin treatment. Clinical symptoms were relieved synchronously. The peripheral oxygen saturation improved and 66.7% of the patients (8/12) did not need further oxygen therapy seven days after ulinastatin treatment. No patients required intensive care unit admission or mechanical ventilation. All patients revealed different degrees of absorption of pulmonary lesions after treatment. No obvious adverse events were observed.

Conclusions Our preliminary data revealed that high dose of ulinastatin treatment was safe and showed a potential beneficial effect for patients with Covid-19.

Introduction

Coronavirus disease 2019 (Covid-19) is a respiratory tract infection caused by severe acute respiratory coronavirus 2 (SARS-CoV-2)[1]. It has now become a worldwide pandemic and poses a global health emergency[2]. While the majority of patients with Covid-19 have mild to moderate symptoms, approximately 14% of the patients may progress to severe pneumonia and exhibit considerable fatality[3]. To date, there are no specific therapeutic agents or vaccines available.

Immunologic characteristics of patients with severe Covid-19 exhibit remarkably elevated serum levels of pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-α, IL-1β, characterized as cytokine storm[4, 5]. And the cytokine storm is believed to play a critical role in Covid-19 progression, deterioration, and even death[5]. Strategies to dampen inflammatory responses are therefore proposed[6]. Nafamostat, which is a serine protease inhibitor, had been reported to effectively inhibit Middle East respiratory syndrome coronavirus (MERS-CoV) S protein-initiated membrane fusion[7]. Recently, Hoffmann M. et al.[8] reported that SARS-CoV-2 infection depended on the host cell factors ACE2 and TMPRSS2 could be blocked by camostat mesylate and E-64d, clinically used protease inhibitors.

Ulinastatin is a glycoprotein which extracted and purified from fresh human urine. It inhibits the activity of various proteolytic enzymes and has been widely used for the treatment of acute pancreatitis[9]. Meanwhile, ulinastatin has been demonstrated as an important anti-inflammatory and anti-oxidation agent and has been clinically used as a potential treatment for circulatory shock, severe sepsis and acute respiratory distress syndrome (ARDS)[10–12]. As a protease inhibitor, whether ulinastatin has beneficial effects on Covid-19 or not is unknown to date. In this study, we retrospectively observed the efficacy of high dose of ulinastatin in order to explore an effective therapeutic strategy for patients with Covid-19.

Methods

Patients and ulinastatin administration

This study was conducted at the Optical Valley Branch of Maternal and Child Hospital of Hubei Province, Wuhan, China from February 19, 2020 to April 5, 2020. And the final follow-up date was April 30, 2020. All patients were diagnosed as having Covid-19 according to the guidelines for Diagnosis and Treatment of Covid-19 issued by the National Health Commission of China (version 7.0)[13]. A total of 12 consecutive patients treated with ulinastatin (Techpool Bio-Pharma Co., Ltd, Guangzhou, China) in addition to standard care were enrolled for analysis. Ulinastatin was diluted with 50 ml normal saline and administered via intravenous infusion. The infusion time was within 30 min. The initial dose of ulinastatin was 1 000 000 IU every 8 hours, and tapered down to 500 000 IU every 8 hours after 4 to 7 days. And the total course of ulinastatin administration was around 10 days, depending on the overall status of the patients. This study was

approved by the Ethics Committee from Shanghai Changzheng Hospital and Optical Valley Branch of Maternal and Child Hospital of Hubei Province.

Disease Severity Classification

The illness severity of Covid-19 was assessed in accordance with Guidelines issued by the National Health Commission of China (version 7.0)[13]. Briefly, moderate cases were defined as patients with clinical symptoms and with signs of pneumonia based on CT imaging. Patients with any of the following conditions were considered as severe cases: 1) respiratory distress, respiratory rates (RR) ≥ 30 beats/min; 2) oxygen saturation level less than 93% while breathing ambient air; 3) a ratio of the partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) (PaO2: FiO2) at or below 300 mmHg (1 mmHg = 0.133 kPa).

Data Collection

Clinical information of all patients was retrieved from the hospital's electronic medical record system, including electronic medical records, medication administration records, laboratory results and radiological examinations. Patients' characteristics including age, gender, symptoms, comorbidities including hypertension, diabetes mellitus (DM), cardiovascular and cerebrovascular diseases (CCVD), chronic obstructive pulmonary disease (COPD), malignancy, chronic liver diseases, chronic kidney diseases, neuropsychiatric diseases and infectious diseases were collected. Clinical signs (body temperature, RR, concentration of oxygen inhalation and oxygen saturations (SaO_2)) were recorded daily during hospitalization. For laboratory tests, the following variables including white blood cell count (WBC), haemoglobin concentration (Hb), lymphocyte count (L), hypersensitive C-reactive protein (CRP), total bilirubin (TB), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine (Cr) were obtained on admission and were monitored during hospitalization. And we also quantified the incidence of oxygen-support requirements (ambient air, low-flow nasal cannula oxygen therapy, high-flow nasal cannula oxygen therapy, non-invasive mechanical ventilation and invasive mechanical ventilation), intensive care unit (ICU) admission, the length of hospital stay, the application of extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT).

SARS-CoV-2 RNA was detected by real-time RT-PCR with throat-swab specimens, whereas only qualitative data were available. The viral nucleic acid was closely monitored during hospitalization until discharge or death. The criteria for discharge strictly followed the guidelines issued by the National Health Commission of China (version 7.0)[13], which required two throat-swab samples obtained at least 24 h apart both negative for SARS-CoV-2 RNA.

Statistical analysis

Data were collected with a Microsoft Excel spreadsheet. Continuous variables were described as the mean (± standard deviation, SD) and categorical variables were reported as the subject number with percentage (%). Graphs were conducted using GraphPad Prism 5.0.

Results

General characteristics of the patients

A total of 10 patients with severe Covid-19 and 2 patients with moderate Covid-19 received ulinastatin treatment (Table 1). The average age of the patients was 68.0 ± 11.9 years, ranging from 48 to 87 years. Of the 12 patients, 10 were males (83.3%) and 2 were females (16.7%). The most common symptoms on admission were fever (8/12, 66.7%), cough (5/12, 41.7%) and dyspnea (5/12, 41.7%), followed by fatigue (3/12, 25%) and chest distress (3/12, 25%). Other symptoms including headache, muscle ache, dizziness and anorexia were rare (1/12, 8.3%). Nine of 12 patients (75.0%) had one or more comorbidities. Among them, hypertension was the most common comorbidity (8/12, 66.7%), followed by CCVD (3/12, 25.0%), DM (2/12, 16.7%) and COPD (1/12, 8.3%).

Table 1
Baseline Demographics of the patients receiving ulinastatin treatment.

Patients no.	Sex	Age, y	Principle symptoms	Comorbidity	Disease severity	Days of admission from symptom onset	Days of ulinastatin treatment from hospital admission
1	M	73	Fever, dyspnea, headache	Hypertension	Severe	6	1
2	F	72	Fever, cough	Hypertension, DM, CCVD	Severe	2	10
3	M	74	Fever	COPD, CCVD	Moderate	8	8
4	F	87	None	Hypertension, dementia	Moderate	2	0
5	M	55	Cough, muscle ache, dyspnea, chest distress	Hypertension	Severe	9	0
6	M	72	Cough, dyspnea	Hypertension, CCVD	Severe	1	2
7	M	77	Fever, cough, dyspnea	Hypertension, DM	Severe	4	6
8	M	81	Fever, chest distress, fatigue	Hypertension	Severe	21	6
9	M	57	Fever, cough, chest distress, dyspnea	None	Severe	24	0
10	M	56	Dizziness, fatigue	None	Severe	18	1
11	M	65	Fever, fatigue, anorexia	Hypertension	Severe	19	0
12	M	48	Fever	None	Severe	6	0

M, male; F, female; DM, diabetes mellitus; CCVD, cardio-cerebrovascular diseases; COPD, Chronic obstructive lung disease.

Tables 2 showed the results of baseline laboratory tests on admission. Two patients had an increase of WBC, whereas one patient showed a decrease of WBC in peripheral blood. The percentage of lymphocytes was decreased in 41.7% of patients (5/12), and 58.3% of patients (7/12) had elevated CRP levels (mean, 49.70 ± 77.70 mg/L). Nine patients received arbidol, or lopinavir-ritonavir, or oseltamivir antiviral therapy. Two patients received antifungal treatment (voriconazole) because of coinfection. Five patients (5/12, 41.7%) received short term of intravenous methylprednisolone treatment.

Table 2
Baseline clinical characteristics and other treatments of the patients receiving ulinastatin treatment.

Patients no.	Routine blood test			Oxygen saturation		Drugs administered			
	WBC ($\times 10^9$/L)	L (%)	CRP (mg/L)	Concentration of oxygen inhalation	SaO_2	Antiviral	Antibiotic	Antifungal	Corticosteroids
1	12.6	9.3	274.09	21%	90%	None	Moxifloxacin	None	None
2	3.0	21.1	116.65	41%	94%	Lopinavir-Ritonavir	Piperacillin tazobactam	None	Methylprednisolone
3	4.4	20.8	7.52	21%	95%	None	Moxifloxacin	None	None
4	3.8	18.0	25.97	29%	96%	None	None	None	None
5	4.8	6.3	45.66	41%	92%	Arbidol	Moxifloxacin		Methylprednisolone
6	6.8	21.6	5.5	21%	92%	Ribavirin, Arbidol	Levofloxacin, Cefoperazone Sulbactam Sodium	None	Methylprednisolone
7	5.0	29.4	20.54	21%	89%	Arbidol	Moxifloxacin, Cefoperazone Sulbactam Sodium	Voriconazole	None
8	5.2	20.5	24.36	29%	92%	Arbidol	Moxifloxacin	None	Methylprednisolone
9	6.1	26.2	57.71	21%	86%	Oseltamivir	Moxifloxacin	None	None
10	11.9	7.4	9.51	21%	86%	Arbidol	Moxifloxacin	None	None
11	5.6	20.7	1.92	21%	92%	Arbidol	None	None	None
12	9.0	16.7	6.95	21%	93%	Arbidol	Cefoperazone Sulbactam Sodium	Voriconazole	Methylprednisolone

WBC, white blood cell count; L, lymphocyte; CRP, hypersensitive C-reactive protein; SaO_2, oxygen saturation.

Efficacy Of Ulinastatin Treatment

The WBC levels and the percentage of lymphocytes returned to normal in all of the patients on the seventh day after ulinastatin treatment (Fig. 1A-1C). CRP decreased significantly and returned to normal in 83.3% of patients (10/12; mean, 6.87 ± 6.63 mg/L) on the seventh day after treatment. Clinical symptoms were relieved synchronously in all of the patients. The peripheral oxygen saturation improved and 66.7% of the patients (8/12) did not need further oxygen therapy seven days after ulinastatin treatment (Fig. 1D and 1E). No patients required ICU admission, mechanical ventilation, ECMO therapy or renal replacement therapy. All of the patients were discharged from hospital and the mean hospitalization time was 19.3 ± 6.2 d.

All patients revealed different degrees of absorption of pulmonary lesions after treatment, according to the findings on chest imaging. Figure 2 showed the representative images of patient 5. His chest CT scan showed bilateral, diffuse areas of consolidation and then was transferred to our hospital. The patient complained of severe dyspnea on admission, with RR of 35 beats per minutes. Ulinastatin was administered at a dose of 10 000 000 IU, every 8 h right after admission, in addition to standard therapy. The dyspnea improved considerably the following day and almost disappeared in resting state three days after ulinastatin treatment. The peripheral oxygen saturation reached 100% with low-flow nasal cannula oxygen therapy thereafter. The bedside chest X-ray on the fifth day and the thirteenth day after treatment showed that the lesions were gradually absorbed (Fig. 2).

Meanwhile, we monitored liver and kidney function during hospitalization. Two patients showed slightly elevated TB levels (55.4 μmol/L and 25.8 μmol/L, respectively; normal range 3.4–20.5 μmol/L), two patients showed abnormal ALT levels (69.6 U/L and 109.6 U/L, respectively; normal range 0–55 U/L) and three patients showed abnormal AST levels (52.2 U/L, 51.0 U/L and 37.2 U/L, respectively;

normal range 5–34 U/L) on admission. And those parameters returned to normal after treatment, except one patient with a slightly elevated AST level (70.4 U/L) and one patient with a slightly elevated ALT level (59.2 U/L, Fig. 3A-3C).

Safety

No ulinastatin infusion-related adverse events were observed. And Patients with abnormal liver function on admission were improved instead of deteriorate after treatment. Meanwhile, the creatinine levels were within normal before and after ulinastatin treatment (Fig. 3D).

Discussion

In this study, we retrospectively assessed the efficacy of ulinastatin on patients with Covid-19. Our preliminary observational study revealed that high dose of ulinastatin treatment was safe and had a potential beneficial effect for patients with Covid-19, with rapidly improvement of clinical symptoms, blood parameters and absorption of the pulmonary lesions.

Covid-19 is spreading rapidly around the world and this unprecedented challenge demands clinicians to identify an effective and safe treatment to protect people at high risk[14]. Remdesivir, which shows potent in vitro activity against SARS-CoV-2[15], is considered as the most promising antiviral drug and has been successfully used in several case series of patients with Covid-19[16, 17]. Recently, compassionate use of remdesivir without placebo for 53 patients with severe Covid-19 was reported to have a 68% efficacy [18]. Notably, 23% patients had serious adverse events and 8% patients discontinued remdesivir treatment prematurely. Lopinavir–ritonavir, another antiviral drug, has been showed to have no benefit for hospitalized adult patients with severe Covid-19 according to a recent open-label, individually randomized, controlled trial which conducted in China[19]. Similarly, lopinavir–ritonavir is also related with serious gastrointestinal side effects and 13.8% of patients should be terminated earlier because of the adverse events. Unfortunately, older patients, especially those with comorbidities, were the most vulnerable populations with significantly increased risk of deterioration and fatality [20–22]. Therefore, it is of utmost importance to identify effective therapeutics with high-safety, probably from clinically approved drugs. Ulinastatin, an intrinsic glycoprotein which has been widely used in clinical practice[10], was an ideal candidate. A safety and tolerability study of ulinastatin in adult healthy volunteers revealed that intravenously infused of 8 000 000 IU ulinastatin over 2 h period associated with no severe adverse effects. From our study, patients received 1 000 000 IU ulinastatin every 8 h through intravenous injection, and no adverse effects were noticed.

It is reported that about 14% of the patients will develop into severe cases[23]. Inhibition the deterioration of the illness is of utmost importance during the treatment. Potential risk factors predicting poor prognosis included older age, high Sequential Organ Failure Assessment (SOFA) score and d-dimer greater than 1 μg/mL[20]. Therefore, application of timely, effective and safe supportive therapies seems critical for those patients with high risk factors[23]. Within our study, no patients progressed to more severe cases when received ulinastatin treatment, and no mortality was observed among those patients.

Cytokine storm are believed to play an essential role in the pathogenesis of Covid-19 and might be correlated with disease severity and fatality [4, 5]. Ulinastatin, an intrinsic broad-spectrum protease inhibitor, could effectively inhibit a variety of cell proteolytic enzymes and have multifunctional therapeutic mechanisms [24]. Firstly, ulinastatin has an inhibitory effect on the production of inflammatory cytokines and adhesion molecules [25]. Meanwhile, ulinastatin improves the stability of lysosomal membrane and reduces the synthesis and delivery of lysosomal enzymes, thus scavenging oxygen or hydroxyl radicals [11]. In the present study, we observed the beneficial effect of ulinastatin for patients with Covid-19. Unfortunately, we did not investigate the changes of cytokines during treatment due to limitation of the hospital facility.

There were several limitations in our study. Firstly, the number of patients enrolled was limited. Secondly, it was an observational, retrospective study. And other factors might interfere with the outcomes. However, our preliminary results revealed the promising efficacy of ulinastatin for patients with Covid-19. Thus, further randomized, controlled trials are warranted.

In conclusion, our observational data revealed that administration of high dose ulinastatin showed a potential beneficial effect for patients with Covid-19. Considering the safety of this agent, the sharply rising fatality of Covid-19 and no other approved agent available, timely initiation of ulinastatin treatment is strongly recommended.

List Of Abbreviations

Covid-19, Coronavirus disease 2019; IL-6, interleukin-6; MERS-CoV, Middle East respiratory syndrome coronavirus; ARDS, acute respiratory distress syndrome; RR, respiratory rates; FiO2, fraction of inspired oxygen; CCVD; cardiovascular and cerebrovascular diseases; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; SaO2, oxygen saturations; WBC, white blood cell count; Hb, haemoglobin; L, lymphocyte; CRP, hypersensitive C-reactive protein; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee from Shanghai Changzheng Hospital and Optical Valley Branch of Maternal and Child Hospital of Hubei Province.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was not funded by anyone.

Authors' contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. WX, HH and LS designed the study and revised the manuscript. PH drafted the manuscript. PH and YG did the analysis. QW, ZL, JY, PS, ZY, YT, CZ, YL, CC and HS collected the data.

Acknowledgments

We acknowledge all health-care workers involved in the diagnosis and treatment of patients with Covid-19 in Wuhan.

References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.
2. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020;91(1):157–60.
3. Yang XB, Yu Y, Xu JQ, Shu HQ, Xia JA, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020:doi. 10.1016/s2213-2600(20)30079-5.
4. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. J Clin Invest. 2020. https://doi.org/10.1172/JCI137244.
5. Cao X. COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol 2020:doi. 10.1038/s41577-020-0308-3.
6. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.
7. Yamamoto M, Matsuyama S, Li X, Takeda M, Kawaguchi Y, Inoue J, et al. Identification of nafamostat as a potent inhibitor of Middle East respiratory syndrome coronavirus S protein-mediated membrane fusion using the split-protein-based cell-cell fusion assay. Antimicro Agents Chemother. 2016;60(11):6532–9.

8. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020:doi.10.1016/j.cell.2020.02.052.
9. Lagoo JY, D'Souza MC, Kartha A, Kutappa AM. Role of Ulinastatin, a trypsin inhibitor, in severe acute pancreatitis in critical care setting: A retrospective analysis. J Crit Care. 2018;45:27–32.
10. Karnad DR, Bhadade R, Verma PK, Moulick ND, Daga MK, Chafekar ND, et al. Intravenous administration of ulinastatin (human urinary trypsin inhibitor) in severe sepsis: a multicenter randomized controlled study. Intensive Care Med. 2014;40(6):830–8.
11. Ji M, Chen T, Wang B, Chen M, Ding Q, Chen L, et al. Effects of ulinastatin combined with mechanical ventilation on oxygen metabolism, inflammation and stress response and antioxidant capacity of ARDS. Exp Ther Med. 2018;15(6):4665–70.
12. Zhang X, Zhu Z, Jiao W, Liu W, Liu F, Zhu X. Ulinastatin treatment for acute respiratory distress syndrome in China: a meta-analysis of randomized controlled trials. BMC Pulm Med. 2019;19(1):196.
13. National Health Commission of China. Guideline for diagnosis and treatment for novel coronavirus pneumonia (seventh edition). http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml. Accessed 4 March 2020.
14. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for Coronavirus Disease 2019 (COVID-19): A review. JAMA 2020:doi. 10.1001/jama.2020.6019.
15. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71.
16. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020;382(10):929–36.
17. Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis 2020:doi. 10.1016/s1473-3099(20)30200-0.
18. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020. doi. 10.1056/NEJMoa2007016.
19. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020. doi. 10.1056/NEJMoa2001282.
20. Zhou F, Yu T, Du RH, Fan GH, Liu Y, Liu ZB, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
21. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A nationwide analysis. Eur Respir J 2020:doi. 10.1183/13993003.00547-2020.
22. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 Patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020. doi:10.1001/jama.2020.5394.
23. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed 13 March 2020.
24. Linder A, Russell JA. An exciting candidate therapy for sepsis: ulinastatin, a urinary protease inhibitor. Intensive Care Med. 2014;40(8):1164–7.
25. Kanai T, Ishiwata T, Kobayashi T, Sato H, Takizawa M, Kawamura Y, et al. Ulinastatin, a urinary trypsin inhibitor, for the initial treatment of patients with Kawasaki disease: a retrospective study. Circulation. 2011;124(25):2822–8.

Figures

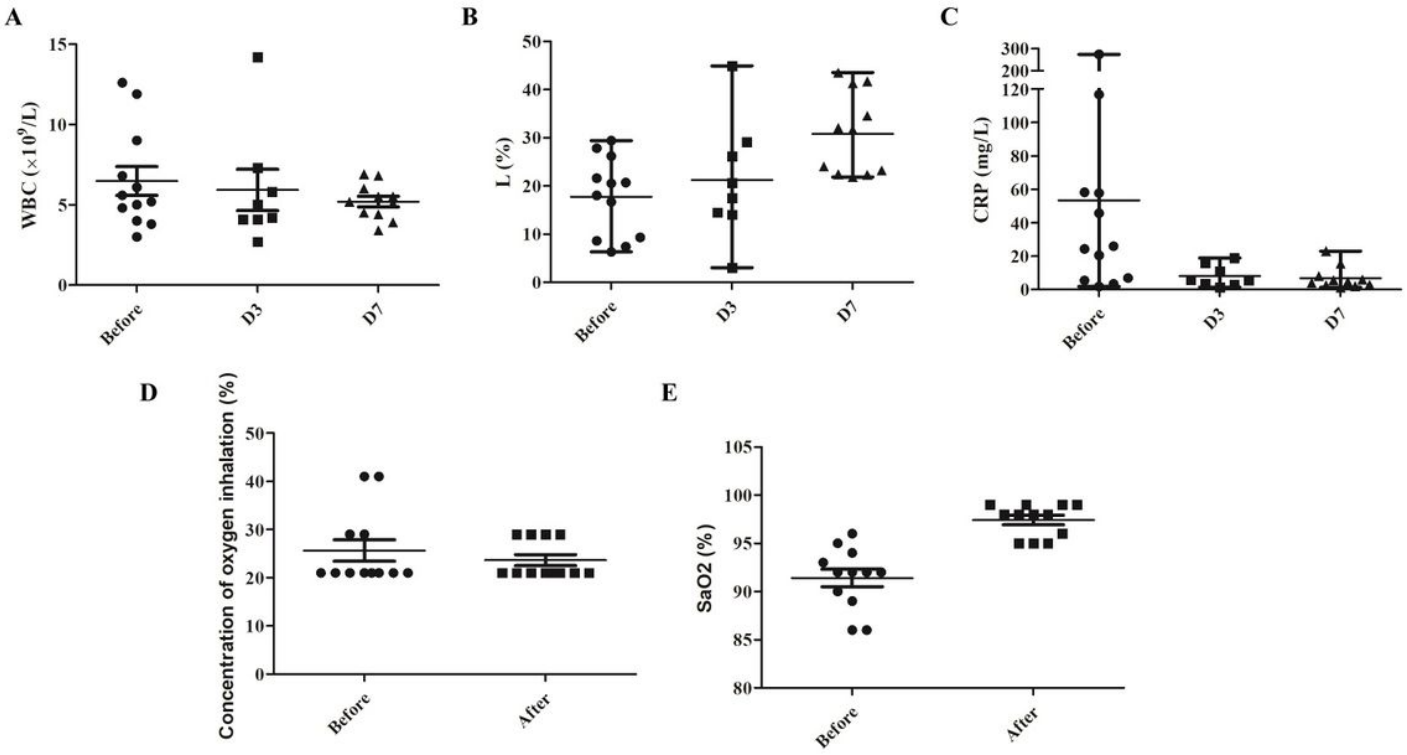

Figure 1

Dynamic changes of clinical parameters in all patients. (A-C) The values of white blood cell count (WBC), percentage of lymphocytes (L%) and hypersensitive C-reactive protein (CRP) before and 3d, 7d post ulinastatin treatment. (D, E) The concentration of oxygen inhalation and oxygen saturation (SaO2) before and after ulinastatin treatment.

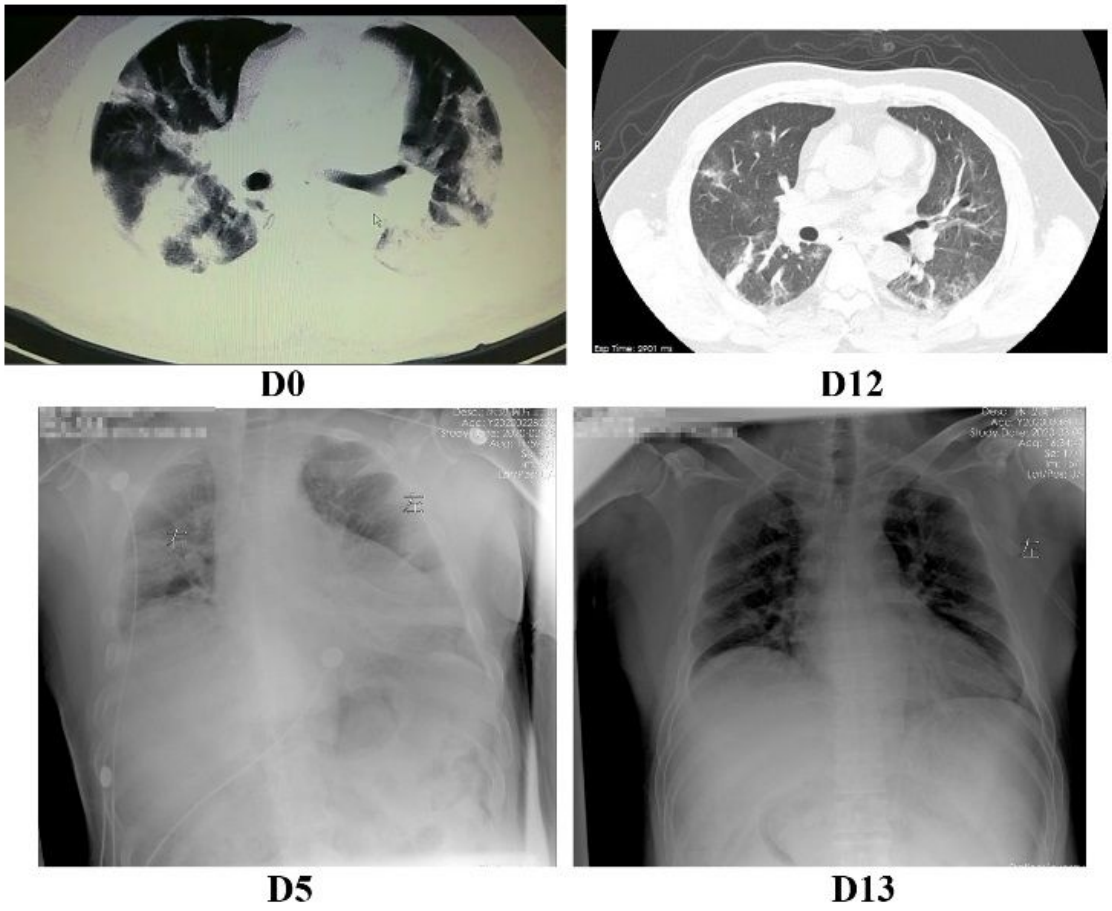

Figure 2

Dynamic changes of chest image of patient 5 showed gradual absorption of the lesions after ulinastatin treatment.

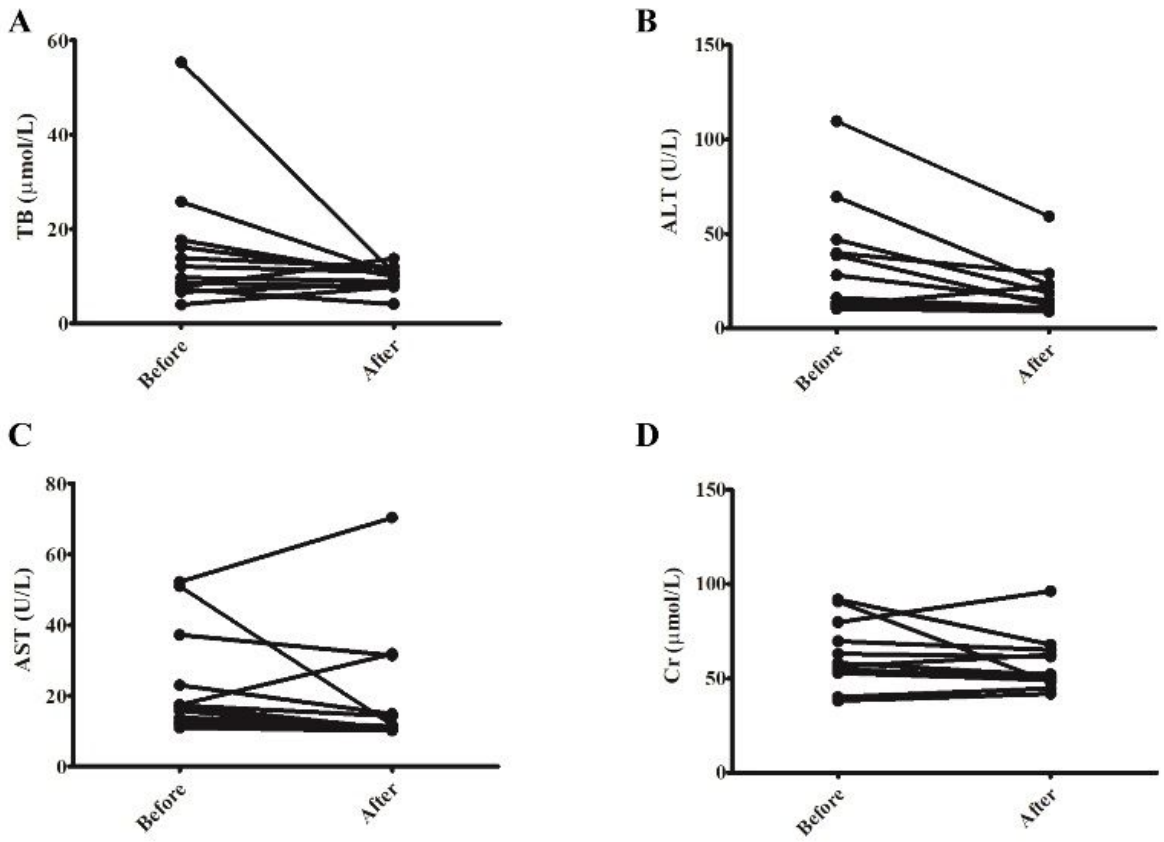

Figure 3

The values of total bilirubin (TB), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine (Cr) before and after ulinastatin treatment for the 12 patients with COVID-19.