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Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19

Zhen Zhu[a,b,1], Zhaohui Lu[c,1], Tianmin Xu[d], Cong Chen[e], Gang Yang[c], Tao Zha[f], Jianchun Lu[a,g], Yuan Xue[a,g,*]

[a] Institute of Hepatology, the Third People's Hospital of Changzhou, No. 300 Lanling North Road, Changzhou 213000, Jiangsu, China
[b] Clinical Laboratory, the Third People's Hospital of Changzhou, Changzhou, Jiangsu, China
[c] Department of Respiratory Diseases, the Second People's Hospital of Wuhu, Wuhu, Anhui, China
[d] Department of Infectious Diseases, the Third People's Hospital of Changzhou, Changzhou, Jiangsu, China
[e] Changzhou Center for Disease Control and Prevention, Changzhou, Jiangsu, China
[f] Wuhu Center for Disease Control and Prevention, Wuhu, Anhui, China
[g] Department of Liver Diseases, the Third People's Hospital of Changzhou, Changzhou, Jiangsu, China

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SUMMARY

Lopinavir/ritonavir and arbidol have been previously used to treat acute respiratory syndrome- coronavirus 2 (SARS-CoV-2) replication in clinical practice; nevertheless, their effectiveness remains controversial. In this study, we evaluated the antiviral effects and safety of lopinavir/ritonavir and arbidol in patients with the 2019-nCoV disease (COVID-19). Fifty patients with laboratory-confirmed COVID-19 were divided into two groups: including lopinavir/ritonavir group (34 cases) and arbidol group (16 cases). Lopinavir/ritonavir group received 400 mg/100mg of Lopinavir/ritonavir, twice a day for a week, while the arbidol group was given 0.2 g arbidol, three times a day. Data from these patients were retrospectively analyzed. The cycle threshold values of open reading frame 1ab and nucleocapsid genes by RT-PCR assay were monitored during antiviral therapy. None of the patients developed severe pneumonia or ARDS. There was no difference in fever duration between the two groups (P=0.61). On day 14 after the admission, no viral load was detected in arbidol group, but the viral load was found in 15(44.1%) patients treated with lopinavir/ritonavir. Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group (P<0.01). Moreover, no apparent side effects were found in both groups. In conclusion, our data indicate that arbidol monotherapy may be superior to lopinavir/ritonavir in treating COVID-19.

Introduction

The emergence of SARS-CoV-2 infection, also known as a 2019-nCoV disease (COVID-19), is continuously increasing. The virus, which can easily be transmitted person-to-person (possibly by people without symptoms) and has already reached 4 continents, currently represents the major public health problem.[1,2]

The SARS-CoV-2 infection causes a spectrum of respiratory illness, from asymptomatic to fatal pneumonia, and the risk factors for exacerbation remain largely unknown. It is speculated that virus replication has an essential role in inflammatory process.[1,3] Based on previous experiences (*SARS outbreak* in 2003), lopinavir/ritonavir might be used for treating SARS-CoV2 replication; however, its effectiveness remains controversial.[4,5]

Arbidol is another antiviral agent that has been approved in China and Russia for treating influenza, SARS, and Lassa viruses.[6,7] A limited number of case reports showed that patients with COVID-19 successfully recovered after receiving lopinavir/ritonavir and arbidol treatment[8,9]; however, it is difficult to prove whether they were cured by the antiviral agent or just a natural course of COVID-19.[5] Recently, Xia reported that combination therapy with lopinavir/ritonavir and arbidol may likely be preferred in a retrospective study with a small sample size.[10]

To date, clinical evidence on lopinavir/ritonavir and arbidol monotherapy in patients with COVID-19 is limited. Herein, we

* Corresponding author at: Institute of Hepatology, The Third People's Hospital of Changzhou, No. 300 Lanling North Road, Changzhou 213000, Jiangsu, China.
E-mail address: xueyuan80908@163.com (Y. Xue).
[1] Zhen Zhu and Zhaohui Lu contributed equally to this work.

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Table 1
Laboratory and radiology findings of patients with COVID-19.

Variables	Lopinavir/ritonavir (n=34)	Arbidol (n=16)	Z or χ^2	P value
Age, years	40.5(34.8–52.3)	26.5(23.3–52.5)	1.395	0.16
Male, n (%)	20(58.8)	6(37.5)	1.982	0.23
Duration of fever, days	2.5(0–5.0)	1.0(0–5.8)	0.510	0.61
Laboratory findings				
ALT, U/L	20.9(12.2–24.1)	15.7(11.0–30.5)	0.499	0.62
C-reactive protein, mg/L	7.7(1.9–26.5)	1.1(0.5–16.0)	2.320	0.02
WBC, E+09/L	5.2(3.9–6.4)	4.5(3.2–6.1)	1.009	0.31
Neutrophils, E+09/L	3.2(2.4–4.5)	2.1(1.4–3.3)	2.174	0.03
Lymphocytes, E+09/L	1.1(0.9–1.5)	1.6(1.1–2.0)	2.184	0.03
D-dimer,μg/mL	0.4(0.3–0.7)	0.3(0.3–0.4)	1.413	0.16
CT findings				
Unilateral pneumonia, n(%)	6(17.6)	3(18.8)	0.009	0.99
Bilateral pneumonia, n(%)	27(79.4)	11(68.8)	0.678	0.49
Ct(*ORF1ab*) <**40 on day 7, n(%)**	26(76.5)	8(50.0)	3.503	0.10
Ct(*ORF1ab*) <**40 on day 14, n(%)**	15(44.1)	0(0)	10.084	<0.01
Duration of positive RNA test, days	11.5(8.8–17.0)	9.5(5.3–11.0)	2.902	<0.01

Data are expressed as median (IQR) and n(%). Comparison was conducted by Kruskal-Wallis test for continuous variables, and Fisher's exact test for categorical values. ALT, alanine aminotransferase; WBC, white blood cells; CT, computer tomography; Ct, cycle threshold.

evaluated the antiviral effects and safety of lopinavir/ritonavir and arbidol in patients with COVID-19.

Method

Patients

Fifty patients diagnosed with COVID-19, according to the Chinese guideline for diagnosis and treatment of COVID-19 [4] were admitted to the Third People's Hospital of Changzhou and the Second People's Hospital of Wuhu. Throat swab was collected upon admission. Besides, all patients underwent a chest computer tomography (CT) scan. All patients received conventional therapy, including oxygen inhalation (2L/min for half an hour, three times a day), atomized inhalation of recombinant human interferon-α2b injection (5 million units, twice a day, [Kawin Technology co. LTD, Beijing, China]). Patients were divided into two groups: including lopinavir/ritonavir group (34 cases) and the arbidol group (16 cases). Lopinavir/ritonavir group received 400mg/100mg of Lopinavir/ritonavir, twice a day for a week (Abbvie Pharmceuticals, Chicago, USA), while arbidol group was given 0.2g arbidol, three times a day, (Wuzhong Pharmceuticals, Suzhou, China).

Data from these patients were retrospectively collected from January 23 to February 29, 2020. Epidemiological history and clinical data were reported to the Chinese Center for Disease Control and Prevention (CDC).

This retrospective study was approved by the Ethics Committee of the Third People's Hospital of Changzhou, according to the Declaration of Helsinki, 2013. Written informed consent was obtained from all patients.

Reverse transcriptase-polymerase chain reaction (RT-PCR) assay

COVID-19 was confirmed based on RT-PCR assay, which was performed by Changzhou CDC and Wuhu CDC using a commercial kit (Biogerm Medical Biotechnology Co., Shanghai, China). The cycle threshold (Ct) values of open reading frame 1ab (*ORF1ab*) and nucleocapsid (*N*) genes by RT-PCR assay were inversely related to viral RNA copy numbers.[11] Duplicate tests at an interval of 24 hours were performed more than once in case the result was negative (Ct≥40).

Statistical analysis

Continuous variables were expressed as median (IQR) and compared using Kruskal–Wallis test. Categorical values were expressed as frequencies and analyzed using Fisher's exact test. All analyses were performed using SPSS 23.0 software (Chicago, IL, USA). A two-sided P<0.05 was considered statistically significant.

Results

Demographics and basal characteristics of patients with COVID-19

As shown in Table 1, 50 patients were divided into two groups, including lopinavir/ritonavir (34 cases) and arbidol (16 cases), according to the antiviral agents. None of the patients developed severe pneumonia or ARDS in the present study. There was no significant difference in age and sex between the two groups (both P>0.05).

Fever was the most common symptom at the onset of illness, and most patients (88.2% and 81.3%) had a short duration of fever (<7 days). There was no difference in fever duration between the two groups (P=0.61). In addition, there were no significant difference in baseline alanine aminotransferase (ALT), white blood cells count and D-dimer (all P>0.05). For patients in lopinavir/ritonavir group, C-reactive protein and neutrophils counts were higher (P=0.02 and 0.03, respectively), while the Lymphocytes count was lower (P= 0.02). For chest CT scans, most patients had bilateral pneumonia in both groups (79.4% and 68.8%).

Efficacy of lopinavir/ritonavir and arbidol in treating COVID-19

For both *ORF1ab* and *N* genes, there was no significant difference in baseline Ct values between the two groups (both P>0.05). On day seven after admission, the viral load was undetectable in half of the patients receiving arbidol and in 23.5% of the patients treated with lopinavir/ritonavir group. Interestingly, on day 14 after the admission, the viral load was undetectable in all the patients in arbidol group, but the viral load was found in 44.1% of patients who received lopinavir/ritonavir (Fig. 1). Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group (P<0.01).

Safety of lopinavir/ritonavir and arbidol in treating COVID-19

One patient in the arbidol group had a slight elevation of ALT (54U/L) on admission. Three patients in the lopinavir/ritonavir group and three patients in the arbidol group showed an elevated level (<125 U/L) of ALT in the first week of admission (χ^2=0.047, P =0.99). One patient in the lopinavir/ritonavir group and two patients in the arbidol group were diagnosed with leucopenia (white

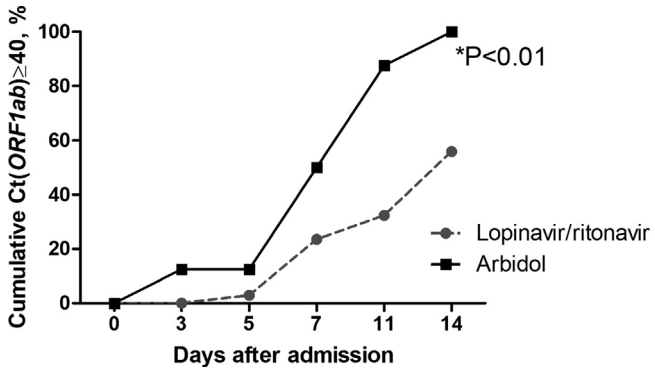

Fig. 1. Dynamic changes of cycle threshold (Ct) values during treatment with lopinavir/ritonavir and arbidol. Ct, cycle threshold.

blood cell count $<4 \times 10^9$/L) on admission. White blood cell counts in the three patients became normal after giving one subcutaneous injection of granulocyte colony-stimulating factors (G-CSF, 150 μg for once, Hangzhou Jiuyuan Genetic Engineering Co. LTD).

Discussion

In the present study, we analyzed the efficacy and safety of lopinavir/ritonavir and arbidol monotherapy in patients with COVID-19. On day 14 after the admission, no viral load was detected in the arbidol group, but the viral load was found in 44.1% of the patients treated with lopinavir/ritonavir. Furthermore, no apparent side effects were found in both groups.

Emerging molecular-based detection methods have been extensively applied in clinical practices. RT-PCR is a rapid, specific, and sensitive method that can be used for the detection of SARS-CoV2. The technique requires two sets of primer-probe pairs, which come from the nucleotide sequence of *ORF1ab* and *N* genes, separately. A commercial kit that has been recommended by China CDC has shown good performance in detecting SARS-CoV2. In the present study, the Ct values, which are inversely related to viral RNA copy numbers,[11] have been used to evaluate the antiviral effects of lopinavir/ritonavir and arbidol.

Currently, no licensed vaccines or antiviral treatments are available for COVID-19. Accurate diagnosis and conventional therapy are crucial for the management of patients with COVID-19.[12] Lopinavir/ritonavir and arbidol have been recently recommended by the National Health Commission and National Administration of Traditional Chinese Medicine for the treatment of COVID-19 [7]; however, the clinical evidence is still very limited. Our data suggest that arbidol monotherapy is more effective than lopinavir/ritonavir in treating COVID-19. Different from Xia's study,[10] our results indicate that patients may benefit from arbidol monotherapy other than combination with lopinavir/ritonavir. It is anticipated that these results will assist clinicians in developing appropriate strategies for managing COVID-19.

The sample size is the major limitation of this study. Regarding the widespread use of lopinavir/ritonavir and arbidol in clinical practice, the effectiveness should be evaluated during the multicenter study with a large sample size.

In conclusion, our data indicate that arbidol monotherapy may be superior to lopinavir/ritonavir in treating COVID-19.

Study design

Yuan Xue. Data collection: Zhen Zhu, Zhaohui Lu, Tianmin Xu, Cong Chen, Gang Yang, Tao Zha, Jianchun Lu and Yuan Xue. Data analysis: Yuan Xue, Zhen Zhu and Zhaohui Lu. Writing: Yuan Xue, Zhen Zhu and Zhaohui Lu. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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