Chloroquine, arbidol (umifenovir) or lopinavir/ritonavir as the antiviral monotherapy for COVID-19 patients: a retrospective cohort study

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Research Article

Keywords: severe acute respiratory syndrome coronavirus-2, coronavirus disease 2019, antiviral monotherapy

Posted Date: April 24th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-24667/v1

Abstract

Background: The severe acute respiratory syndrome coronavirus-2 outbreak was identified in China in December 2019 and spread worldwide, reaching the pandemic levels. However, a specific, effective and proven therapy for the patients with coronavirus disease 2019 (COVID-19) remains elusive. We aim to compare the efficacy and the safety of three antiviral monotherapies (chloroquine phosphate, arbidol (Umifenovir) or lopinavir/ritonavir) in non-severe, hospitalised COVID-19 patients.

Methods: We retrospectively analysed the hospitalised, laboratory-confirmed COVID-19 patients, treated with antiviral monotherapies at Huizhou Municipal Central Hospital between Jan 19 and Mar 16, 2020. Demographic and clinical data were extracted from electronic medical records. The primary outcome of the study was the viral shedding interval.

Results: Twenty-seven patients with COVID-19 were included in the study with 10 receiving chloroquine phosphate, 11 receiving arbidol and 6 receiving lopinavir/ritonavir. Baseline demographics and clinical data were similar between groups. The median viral shedding interval in the lopinavir/ritonavir group was 13.0 days (95% CI: 12.2-23.8), while significantly shorter in the chloroquine group at 5.0 days (95% CI: 0.4-9.6) (p=0.003). A reduced median interval was also observed in the arbidol group, with 8.0 days (95%CI: 4.9-11.1) (p=0.008). Moreover, the hospitalisation duration was shorter in the chloroquine (9.3 ± 1.8 days, p<0.001) and arbidol groups (11.7 ± 3.7 days, p<0.001), and the hospitalisation costs were significantly reduced in the chloroquine (USD 1327 ± 566, p=0.001) and arbidol groups (USD 1167 ± 434, p<0.001), when compared with the lopinavir/ritonavir group (hospitalisation length and costs: 19.7 ± 4.4 days and USD 3806 ± 2262, respectively).

Conclusions: Chloroquine and arbidol could not only shorten the viral shedding interval but also decreased the hospitalisation duration and hospitalisation expenses.

Trial registration: The ethics committee of the Huizhou Municipal Central Hospital approved this study, and the trial was registered with www.chictr.org.cn (ChiCTR2000030931).

Background

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak was identified in China in December 2019 [1]. As of April 5, 2020, a total of 1,133,758 laboratory-confirmed cases of coronavirus disease 2019 (COVID-19) were reported globally, including 62,784 deaths [2]. The SARS-CoV-2 has spread rapidly, reaching the pandemic levels and demanding sustained global attention. However, currently, treatments remain supportive, and clinicians continue to lack a safe and effective antiviral regimen, which is specific to the SARS-CoV-2 and capable of reducing viral load, thus limiting the transmission potential and improving the prognosis. Therefore, identifying a clinically effective drug is considered urgent and essential in the fight against COVID-19.

According to the genome sequences and protein structure analysis, the SARS-CoV-2 is remarkably similar to the SARS-CoV implicated in the 2003 outbreak [3, 4]. Hence, it is reasonable to focus our attention on reviewing existing antiviral drugs which were previously used for SARS-CoV, so as to potentially identify effective drugs for use against the current SARS-CoV-2 [5]. Previous studies reported that chloroquine, arbidol (Umifenovir) or lopinavir/ritonavir could inhibit the activity of the SARS-CoV in-vitro, but their clinical efficacy in-vivo remains unknown [6-8]. In this study, we aim to compare the efficacy and the safety of these three antiviral monotherapies (chloroquine phosphate, arbidol (Umifenovir) or lopinavir/ritonavir) in non-severe, hospitalised COVID-19 patients.

Methods

Study design and participants

This is a retrospective cohort study that included hospitalised, laboratory-confirmed COVID-19 patients at Huizhou Municipal Central Hospital between Jan 19 and Mar 16, 2020. The included patients had been treated with different antiviral monotherapies (chloroquine phosphate, arbidol (Umifenovir) or lopinavir/ritonavir) and were identified from electronic medical records. All patients have already been discharged from hospital. The ethics committee of the Huizhou Municipal Central Hospital approved this study, and the trial was registered with www.chictr.org.cn (ChiCTR2000030931).

Clinical procedures

All patients were diagnosed with COVID-19 in accordance with the Chinese COVID-2019 diagnosis and treatment guidelines [9]. Upper respiratory tract specimens were obtained for a SARS-CoV-2 diagnosis according to the National Health Commission of China's laboratory testing techniques guidelines [10]. A real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay was used to detect the viral RNA of SARS-CoV-2 by targeting an open reading frame 1a/b (ORF1a/b) and nucleocapsid protein (N). Definitive diagnosis is based on both target ORF1a/b and N testing positive [10].

The antiviral monotherapy regimens of the patients included one of the following: 500mg chloroquine phosphate 12-hourly, 200mg arbidol (Umifenovir) 8-hourly or 400mg/100mg lopinavir/ritonavir 12-hourly, not exceeding 10 days of use. Therapy was commenced immediately after the diagnosis with COVID-19 was made. The patients' supportive treatments were in accordance with the Chinese COVID-2019 diagnosis and treatment guidelines [9].

The guideline identifies 4 categories of COVID-19 patients, according to severity [9]. Mild patients demonstrate mild respiratory symptoms without lung infiltration, while common patients demonstrate lung infiltration together with fever or respiratory symptoms. Severe patients demonstrate dyspnoea (respiratory rate $\geq$ 30/min), hypoxia (oxygen saturation $\leq$ 93%, partial pressure of oxygen/ fraction of inspired oxygen $\leq$ 300mmHg), or significant progression of chest imaging lesions >50% within 24-48 hours, while critical-severe patients demonstrate respiratory failure requiring mechanical ventilation, shock, or organ failure, requiring ICU admission [9].

Subsequent hospital discharge criteria includes: 1) Normothermic ≥3 days; 2) Significantly improved respiratory symptoms; 3) Improvement on chest imaging; 4) Two, consecutive respiratory specimens, ≥24 h apart, testing negative for SARS-CoV-2 using RT-PCR [9].

Data collection

Two clinicians (Y.F.X and J.J.Y) independently collected demographic and clinical data from electronic medical records using standardised data collection forms, with any variances or discrepancies being discussed, and the validity of disputed data being moderated and adjudicated by a third clinician (C.Q.L).

Outcomes

The primary outcome of the study was the viral shedding interval, determined by the RT-PCR of the respiratory specimen. Secondary outcomes included the length of hospital stay, hospitalisation expenses, the percentage of patients who still tested positive for SARS-CoV-2 at day 10 and day 14 and the adverse events associated with each therapy. The hospitalisation expenses in this study were expressed in United States Dollars (USD) with an exchange rate of USD1 = Chinese Yuan 7 on April 3, 2020.

Statistical analysis

Data analysis was conducted using SPSS Version 19.0 (IBM SPSS Statistics, Armonk, NY, USA). Data were presented as mean±standard deviation, median (interquartile range [IQR]) or n (%), where appropriate. Continuous variables were compared using one-way analysis of variance for the normally distributed data, with a non-parametric test for data that was not normally distributed. For categorical variables, Pearson's chi-squared test or Fisher's exact test was used. Bonferroni correction was used for the post-hoc multiple comparisons. The viral shedding interval was evaluated using the Kaplan-Meier method and differences were assessed with the log-rank test. Two-tailed *p*-values <0.05 were considered statistically significant.

Results

Sixty-two patients were diagnosed with COVID-19 in Huizhou Municipal Central Hospital before Mar 16, 2020. All patients had already been discharged from the hospital at the time of data gathering. Twenty-seven COVID-19 patients who had received one of the specific antiviral monotherapies of interest, were included in the study, with 10 having received chloroquine phosphate, 11 having received arbidol and 6 having received lopinavir/ritonavir. Patient demographics were similar across the groups [Age: Chloroquine group: 51 years (IQR, 35-63), Arbidol group: 42 years (IQR, 37-57) and Lopinavir/ritonavir group: 47 years (IQR, 42-51), p=0.963; Gender: Chloroquine group: 4 females (40%), Arbidol group: 7 females (63.6%) and Lopinavir/ritonavir group: 4 females (66.7%), p=0.496); Co-morbidities: Chloroquine group: 3 hypertensive patients (30%) and 2 diabetic patients (20%). Arbidol group: 3 hypertensive patients (27.3%). Lopinavir/ritonavir group: 1 hypertensive patient (16.7%). No chronic pulmonary diseases were noted in any group. (p-values were all >0.05)] Moreover, 6 patients (60%) in the chloroquine group, 4

patients (36.4%) in the arbidol group and 4 patients (66.7%) in the lopinavir/ritonavir group, presented with fever (>37.3℃). Based on the National COVID-19 guidelines, 2 patients in the arbidol group were categorised as mild, while the remaining 25 patients across the groups, were classified as the common type (p=0.328). Baseline laboratory test results (Table 1) were also similar across the 3 groups. No patient's severity progressed, and all were discharged according to the relevant discharge criteria.

As for the primary outcome (Fig. 1), the median viral shedding interval in the lopinavir/ritonavir group was 13.0 days (95% CI: 12.2-23.8), while it was significantly shorter in the chloroquine group at only 5.0 days (95% CI: 0.4-9.6) (p=0.003). A reduced median interval was also observed in the arbidol group, at 8.0 days (95% CI: 4.9-11.1) (p=0.008).

After 10 days of treatment, the SARS-CoV-2 testing by RT-PCR was negative for 9 patients (90%) in the chloroquine group (p=0.001) and 8 patients (72.7%) in arbidol group (p=0.009), while comparatively the lopinavir/ritonavir group had no patients testing negative (0/6). Additionally, after 14 days, all the patients in the chloroquine (p=0.036>0.05/3) and arbidol groups (p=0.029>0.05/3) tested negative, while only 3 patients (50%) had tested negative in the lopinavir/ritonavir group. No statistically significant difference in outcome was noted on day 10 or day 14 between the chloroquine and arbidol group.

Additionally, the length of hospital stay was shorter in the chloroquine (9.3 ± 1.8 days, p<0.001) and arbidol groups (11.7 ± 3.7 days, p<0.001), when compared with the lopinavir/ritonavir group (19.7 ± 4.4 days). However, no statistically significant difference could be found between chloroquine and arbidol groups (p=0.316). Furthermore, hospitalisation expenses were significantly reduced in the chloroquine (USD 1327 ± 566, p=0.001) and arbidol groups (USD 1167 ± 434, p<0.001), compared with the lopinavir/ritonavir group (USD 3806 ± 2262). No statistically significant difference could be found between chloroquine and arbidol groups (p=0.943).

Adverse events during the treatment period included: 2 patients (20%) in the chloroquine group reported nausea, vomiting, dysphoria or blurred vision, compared with 1 patient (9.1%) in the arbidol group and 3 patients (50%) in the lopinavir/ritonavir group reported diarrhoea. No statistically significant difference was noted between groups. (p=0.133). Although 1 patient in the chloroquine group required drug withdrawal on day 6 due to dysphoria and blurred vision, all the other cases of adverse effects were relieved with supportive treatment.

Discussion

This is the first study to retrospectively compare the clinical safety and efficacy of antiviral monotherapies (chloroquine, arbidol (Umifenovir) or lopinavir/ritonavir) in non-severe, hospitalised COVID-19 patients. We found that patients treated with lopinavir/ritonavir demonstrated longer viral shedding intervals and hospitalisation durations, as well as increased hospitalisation costs and adverse effects. Additionally, chloroquine and arbidol demonstrated decreased viral shedding intervals and hospitalisation durations, together with reduced hospitalisation costs. The chloroquine group

demonstrated a reduced median viral shedding interval and hospitalisation duration, while the arbidol group showed a lower cost of hospitalisation and rate of adverse effects.

Despite the SARS-CoV-2 outbreak currently being under control in China, the situation remains dire in other countries [2]. Currently, there is no proven, effective antiviral therapy for COVID-19 patients. Identifying a drug that effectively reduces viral load may improve patient outcomes [11]. New drug development takes time, and developing an antiviral drug specifically for COVID-19 over the short term seems highly unlikely. Focusing on the potential of existing antiviral drugs is the most feasible strategy. Hence our willingness to share our experiences, in an effort to determine a potential anti-SARS-CoV-2 therapy.

In previous studies, lopinavir/ritonavir demonstrated in-vitro antiviral activity against SARS-CoV [7]. Additionally, historical control groups demonstrated that compared to ribavirin monotherapy, a ribavirin and lopinavir/ritonavir combination reduced the risk of adverse outcomes in patients with SARS [7]. However, Cao et al. [12] recently advised that no benefit was demonstrated when using lopinavir/ritonavir therapy, compared with other treatments in critical COVID-19 patients. Similarly, in this study, we failed to demonstrate any superiority in outcomes when using lopinavir/ritonavir monotherapy, in non-severe COVID-19 patients. This may be due to lopinavir/ritonavir not being specific enough for COVID-19, or that high blood/tissue concentrations are required to inhibit the virus in-vivo.

Chloroquine has been used for more than 70 years, firstly as an anti-malarial drug and later for autoimmune diseases such as rheumatoid arthritis [13]. Additionally, chloroquine has demonstrated antiviral effects by increasing endosomal pH, thus inhibiting endocytosis [13]. Moreover, it inhibits viral replication by interfering with glycosylation of the angiotensin-converting enzyme 2 receptor of SARS-CoV, which the virus uses to enter the patient's cells [3, 6]. Huang et al. [14] found that COVID-19 patients had higher levels of pro-inflammatory cytokines in their plasma, which might induce a cytokine storm and immunopathological injury [15]. Chloroquine is therefore beneficial in that it can demonstrate immunomodulatory effects, which may reduce complications due to an excessive immune response [16]. In addition, Wang et al. [17] revealed that chloroquine could control SARS-CoV-2 infection in-vitro using a clinically achievable concentration in the plasma, further suggesting that chloroquine may be an effective antiviral therapy during the current outbreak. In our study, we found that chloroquine could reduce the viral load in patients early on, which theoretically should decrease the risk of viral transmission and improve the clinical outcomes of patients. With this being said, 2 patients experienced adverse effects during chloroquine therapy, and concern has previously been raised regarding its toxicity [18]. Therefore, according to the announcements from the National Health Commission of China[9], a patient's electrocardiogram should be normal before commencing chloroquine therapy, and simultaneous administration of quinolone or macrolide antibiotics should be avoided in these patients. Furthermore, for improved safety, the duration of treatment could be shortened to 7 days, with close attention being paid to the patient for the duration of treatment, especially in patients with a lower weight (<50kg).

As a broad-spectrum antiviral agent, arbidol has demonstrated effectiveness in inhibiting certain respiratory viruses (influenza virus, respiratory syncytial virus, etc.) including SARS-CoV in-vitro [8, 19]. Studies comparing arbidol and lopinavir/ritonavir combination therapy to lopinavir/ritonavir monotherapy in hospitalised, COVID-19 patients, found that the combination therapy group demonstrated an increase in negative SARS-CoV-2 tests by day 7 and day 14 with treatment [20]. Similarly, in our study, the arbidol group showed a decreased shedding interval and an increase in negative SARS-CoV-2 tests at day 10 and at day 14. However, the exact mechanism of arbidol against SARS-CoV-2 has not been determined, thus requiring further study.

Some limitations exist in our study. Firstly, it is a single-centred, small sample size study. Secondly, nucleic acid testing was only performed on upper respiratory tract specimens. Finally, the estimated interval of viral shedding is limited by the frequency of respiratory specimen collection, due to the retrospective study design.

In conclusion, our study revealed that chloroquine and arbidol (Umifenovir) could not only shorten the viral shedding interval, but also decreased the hospitalisation duration and hospitalisation expenses of non-severe, COVID-19 patients. Furthermore, we recommend that large randomised, controlled studies be conducted in the future to better understand the efficacy of various antiviral therapies, dosages and usage durations.

Abbreviations

COVID-19 = coronavirus disease 2019;

SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2;

RT-PCR = real-time reverse transcriptase polymerase chain reaction;

ORF1a/b = open reading frame 1a/b;

N = nucleocapsid protein;

USD = United States Dollars;

IQR = interquartile range;

Declarations

Ethics approval and consent to participate

The ethics committee of the Huizhou Municipal Central Hospital approved this study, and the trial was registered with www.chictr.org.cn (ChiCTR2000030931).

Consent for publication

Written consent form was waived due to the rapid occurrence of this infectious disease.

Availability of data and materials

The datasets used and 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

The study was supported by the Project supported by the Chinese National Natural Science Foundation (81700096), the foundation of the First Affiliated Hospital of Guangzhou Medical University (ZH201802) and Guangzhou Medical University (2017[160]).

Authors' contributions

R.C. Chen, L.Q. Zhou and W.J. Huang contributed to the conception and design of the study. H. Huang, L.L. Guan, Y.Q. Yang, J.M. Le Grange and G.Y. Tang contributed to retrieving literature and drafting the submitted article. Y.F. Xu, J.J. Yuan, C.Q. Lin, M.S. Xue and X.L. Zhang contributed to the data acquisition, the interpretation of outcomes and data analysis. All authors contributed to the crucial revision of the draft for important intellectual content, providing final confirmation of the revised version and being responsible for all aspects of the work.

Acknowledgements

Not applicable

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Tables

Table 1. Baseline demographic, clinical and laboratory outcomes of patients with coronavirus disease 2019.

	Chloroquine group n=10	Arbidol group n=11	Lopinavir/ritonavir group n=6	p value
Age (years)	51 (35-63)	42 (37-57)	47 (42-51)	0.963
Female	4 (40%)	7 (63.6%)	4 (66.7%)	0.496
BMI (kg/m^2)	22.9 (22.1-23.3)	23.4 (23.0-24.4)	22.0 (20.8-23.2)	0.199
Hypertension	3 (30%)	3 (27.3%)	1 (16.7)	1
Diabetes	2 (20%)	0	0	0.171
Chronic obstructive pulmonary disease	0	0	0	1
Fever (temperature ≥37·3°C)	6 (60%)	4 (36.4%)	4 (66.7%)	0.424
Cough	7 (70%)	7 (63.6%)	5 (83.3%)	0.866
Clinical classification				0.328
Mild	0 (0%)	2 (18.2%)	0 (0%)	
Common	10 (100%)	9 (81.8)	6 (100%)	
Haemoglobin (g/L)	139.0 (128.0-145.5)	136.0 (126.5-145.5)	137.5 (127.0-142.0)	0.773
White blood cell count (× 10^9/L)	4.2 (3.7-4.9)	4.4 (4.1-5.7)	4.0 (3.7-4.1)	0.194
Lymphocyte count (× 10^9/L)	0.9 (0.8-1.0)	1.1 (0.8-1.2)	0.9 (0.8-1.0)	0.509
Platelet count (× 10^9/L)	238 (226-254)	212 (188-228)	166 (159-254)	0.083
Creatinine (umol/L)	68.2 (56.5-75.3)	55.1 (49.8-59.3)	55.3 (47.5-72.4)	0.224
Alanine aminotransferase (U/L)	23.0 (21.0-41.0)	24.0 (15.0-26.5)	22.5 (14.3-24.8)	0.685
Aspartate aminotransferase (U/L)	27.5 (27.0-36.8)	28.0 (25.5-32.5)	35.0 (28.3-38.8)	0.429
Total bilirubin (umol/L)	17.7 (16.0-20.6)	15.3 (14.4-19.0)	21.8 (13.4-26.3)	0.743
Total protein (g/L)	68.5 (67.9-72.7)	72.1 (65.5-73.3)	67.1 (63.8-69.8)	0.269
Albumin (g/L)	37.4 (33.3-37.9)	38.2 (34.8-39.8)	34.3 (32.8-35.7)	0.172
Lactate dehydrogenase (U/L)	499.5 (487.3-585.0)	507.0 (423.5-539)	477.0 (462.8-598.8)	0.515

Figures

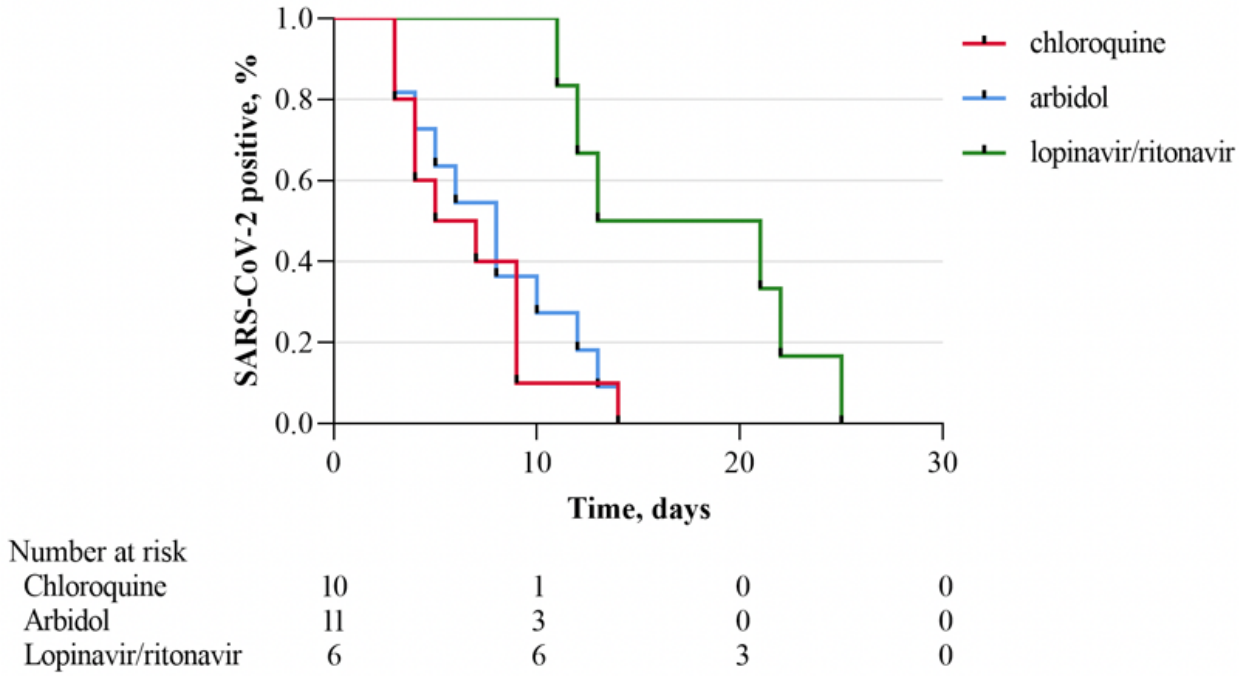

Figure 1

Kaplan-Meier survival curve of the viral shedding interval. SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2;