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Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study

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SUMMARY

Background: Corona Virus Disease 2019 (COVID-19) due to the 2019 novel coronavirus (SARS-CoV-2) emerged in Wuhan city and rapidly spread throughout China. We aimed to compare arbidol and lopinavir/ritonavir(LPV/r) treatment for patients with COVID-19 with LPV/r only.

Methods: In this retrospective cohort study, we included adults (age≥18years) with laboratory-confirmed COVID-19 without Invasive ventilation, diagnosed between Jan 17, 2020, and Feb 13, 2020. Patients, diagnosed after Jan 17, 2020, were given oral arbidol and LPV/r in the combination group and oral LPV/r only in the monotherapy group for 5–21 days. The primary endpoint was a negative conversion rate of coronavirus from the date of COVID-19 diagnosis(day7, day14), and assessed whether the pneumonia was progressing or improving by chest CT (day7).

Results: We analyzed 16 patients who received oral arbidol and LPV/r in the combination group and 17 who oral LPV/r only in the monotherapy group, and both initiated after diagnosis. Baseline clinical, laboratory, and chest CT characteristics were similar between groups. The SARS-CoV-2 could not be detected for 12(75%) of 16 patients' nasopharyngeal specimens in the combination group after seven days, compared with 6 (35%) of 17 in the monotherapy group ($p < 0{\cdot}05$). After 14 days, 15 (94%) of 16 and 9 (52·9%) of 17, respectively, SARS-CoV-2 could not be detected ($p < 0{\cdot}05$). The chest CT scans were improving for 11(69%) of 16 patients in the combination group after seven days, compared with 5(29%) of 17 in the monotherapy group ($p < 0{\cdot}05$).

Conclusion: In patients with COVID-19, the apparent favorable clinical response with arbidol and LPV/r supports further LPV/r only.

Introduction

Since it was first described in December 2019, more than seventy thousand cases of Corona Virus Disease 2019 (COVID-19) have been confirmed, beyond two thousand patients of which were fatal.[1–4] So far, the infection keeps spreading, and more and more exported cases were confirmed in other provinces in China, and other countries. Indicating that the disease is a serious threat to global health.[5,6] The management of patients with COVID-19 consists of a combination of supportive measures, antimicrobial therapy for any associated bacterial or viral infections, and strict implementation of appropriate infection control precautions.[1–4]

The number of this disease is still multiplying, and effective antiviral treatment is therefore required urgently.[5,6] It has been hypothesized that the immunopathological response was triggered by the viral antigen; the most strategic treatment was, therefore, to stop the viral replication at the beginning so that the peak viral load and the subsequent immunopathological damage will be minimised.[7]

We report the findings of Results and outcomes in patients with COVID-19 that compare a combination of arbidol and lopinavir/ritonavir(LPV/r) against LPV/r only. Placebo-controlled studies are difficult to perform in an epidemic of such a life-threatening condition.[7]

Methods

Study design and participants

This single-center, retrospective cohort study included individuals who were diagnosed with laboratory-confirmed COVID-19

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Table 1
Baseline characteristics on day of diagnosis of Corona Virus Disease 2019, by patient group.

	Combination group ($n = 16$)	Monotherapy group ($n = 17$)	p value
Men	7(43·8%)	10 (58·8%)	0·494
Age, years	41·8(14·08)	47·25(17·25)	0·08
Chronic obstructive pulmonary disease	0	1(5·9%)	1·00
Chronic liver disease	1(6·2%)	2(11·7%)	1·00
Diabetes mellitus	2(12·5%)	3(17·6%)	1·00
Coronary heart disease	2(12·5%)	3(17·6%)	1·00
Hypertension	3(18·8%)	2(11·7%)	1·00
Malignant disorder	0	0	
Obesity	2(12·5%)	1(5·9%)	1·00
HIV infection	0	0	
Number of comorbidities	0–2	0–2	
Peripheral white cell count ($\times 10^9$/L)	5·34(1·82)	5·04(1·08)	0·11
Lymphocyte count ($\times 10^9$/L)	1·83(0·82)	1·36(0·52)	0·11
Platelet count ($\times 10^9$/L)	194·8(55·1)	198·6(77·2)	0·69
Serum bilirubin (μmol/L)	9·23(4·97)	9·51(4·86)	0·55
Lung "total severity score" in "4"	5(31·2%)	6(35·3%)	0·875
Tested positive in stool	8(50·0%)	10(58·9%)	0·732

Data are number (%) or mean (SD).

between Jan 17, 2020, and Feb 13, 2020, at The Fifth Affiliated Hospital of Sun Yat-Sen University. Eligible patients were those aged 18 years or older with pneumonia without Invasive or non-invasive ventilation. No other exclusion criteria were applied at this stage.

COVID-19 was diagnosed by real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay for nasal and pharyngeal swab specimens.[7] Only the laboratory-confirmed cases were included in the analysis. All patients with COVID-19 enrolled in this study were diagnosed according to World Health Organization interim guidance.[8]

From Jan 17, 2020, all eligible patients were offered treatment with arbidol and LPV/r in combination group or oral LPV/r only in monotherapy group, after informed consent had been obtained from the patients themselves or their next of kin. The treatment protocol was approved by Pharmacy and Therapeutics Committee. The study was approved by The Research Ethics Committee at the The Fifth Affiliated Hospital of Sun Yat-Sen University to allow retrospective access to patients' records and files (No·ZDWY[2020] Lunzi No·K22-1).

Procedures

Once the nasopharyngeal specimens were positive for SARS-CoV-2 tested by RT-PCR for patients with COVID-19 and patients with abnormal radiological findings, oral drugs were given. We strictly manage all patients, regardless of the severity of the illness, carefully monitor the laboratory examination and chest CT scans. Specifically, arbidol was given at a dose of 200 mg every 8 h and lopinavir (400 mg)/ritonavir (100 mg) orally every 12 h until coronavirus is detected negative by RT-PCR for tree times. The administration period is about 5–21 days. All patients received appropriate supportive care and regular clinical and laboratory monitoring. Normal renal function, liver enzymes, and blood count were assessed at baseline and every other day throughout the treatment course. RT-PCR was performed for nasopharyngeal specimens every other day and daily once negative for SARS-CoV-2′s test after admission to hospital, it was tested daily for stools. In addition to stools were collected from all 33 patients for RT-PCR analysis, and the chest CT scans were performed at days 1, 4, 7,10 and 14 . All patients were monitored for any clinical signs of depression or acute confusion.

Outcomes

The primary endpoint was a negative conversion rate of SARS-CoV-2 from the date of COVID-19 diagnosis(day7, day14), and assessed whether the pneumonia was progressing or improving by chest CT (day7).

Statistical analysis

We used χ^2 and Fischer's exact tests for categorical variables, whereas we used the student's t-test for continuous variables to assess the differences in means of the two groups. The graphical and statistical tests suggested that the proportional hazard assumption was not violated. We did statistical analyses using SPSS software version 13·0(SPSS, Chicago, Illinois). The significance for all statistical analyses was defined as $p < 0{\cdot}050$.

Results

Fifty-six individuals(age≥18years) were diagnosed with COVID-19 infection between Jan 17, 2020, and Feb 13, 2020. Recent research has reported that,[4] 82·1% and 36·2% of patients had lymphopenia and thrombocytopenia, respectively. Overall, leukopenia was observed in 33·7% of patients. Most patients demonstrated high levels of C-reactive protein, but high levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase and D-dimer were less common. Similar characteristics were observed in all patients. Furthermore, we found that stools of 25(45%) in 56 patients were positive for SARS-CoV-2′s test by RT-PCR. In addition to that, 50% of patients' counts of peripheral CD4 and CD8 T cells were reduced by flow cytometric analysis.

Baseline characteristics were generally similar between patients who received oral arbidol and LPV/r therapy, and those who received oral LPV/r only (Table 1), with the exception that organ dysfunction was present in four patients who were admitted and transferred to the ICU, ten patients treated with other antiviral drugs(the data are not yet public)and no abnormal radiological findings was present in nine patients (Fig. 1). After excluding ineligible patients, 33 patients were included in the study. The mean age of all 33 patients was 44·56 years (SD 15·73), and 17 (52%) were men (Table 1). The median number of comorbidities was 0·7 (range 0–2). Mean blood indices on the day of COVID-19 diagnosis include peripheral white cell count $5{\cdot}19 \times 10^9$/L (SD $1{\cdot}47 \times 10^9$/L), lymphocyte count $1{\cdot}59 \times 10^9$/L ($0{\cdot}71 \times 10^9$/L), platelets $196{\cdot}59 \times 10^9$/L ($64{\cdot}76 \times 10^9$/L), bilirubin 9·39 μmol/L (4·76 μmol/L). Overall, 11 (33%) of 33 patients needed a double nasal catheter for oxygen, 24 (73%) of all patients received Immunoglobulin therapy, and 20 (61%) received broad-spectrum antibacterial therapy.

Table 2
Support measures offered and Laboratory indices during the course of Corona Virus Disease 2019, by patient group.

	Combination group ($n = 16$)	Monotherapy group ($n = 17$)	p value
Double nasal catheter for oxygen	5(31·2%)	6(35·3%)	0·72
Immunoglobulin therapy	11(68·8%)	13(76·5%)	0·71
Corticosteroid therapy	1(6·2%)	7(41·2%)	0·04
Number of antibacterial therapy agents	9(56·3%)	12(70·6%)	0·48
Invasive ventilation	0	0	
Vasopressor therapy	0	0	
Peripheral white cell count, minimum ($\times 10^9$/L)	7(43·8%)	10 (58·8%)	0·494
Minimum lymphocyte count, minimum ($\times 10^9$/L)	41·8(14·08)	47·25(17·25)	0·08
Platelet count, minimum ($\times 10^9$/L)	0	1(5·9%)	1·00
Serum bilirubin, maximum (μmol/L)	1(6·2%)	2(11·7%)	1·00

Data are number (%) or mean (SD).

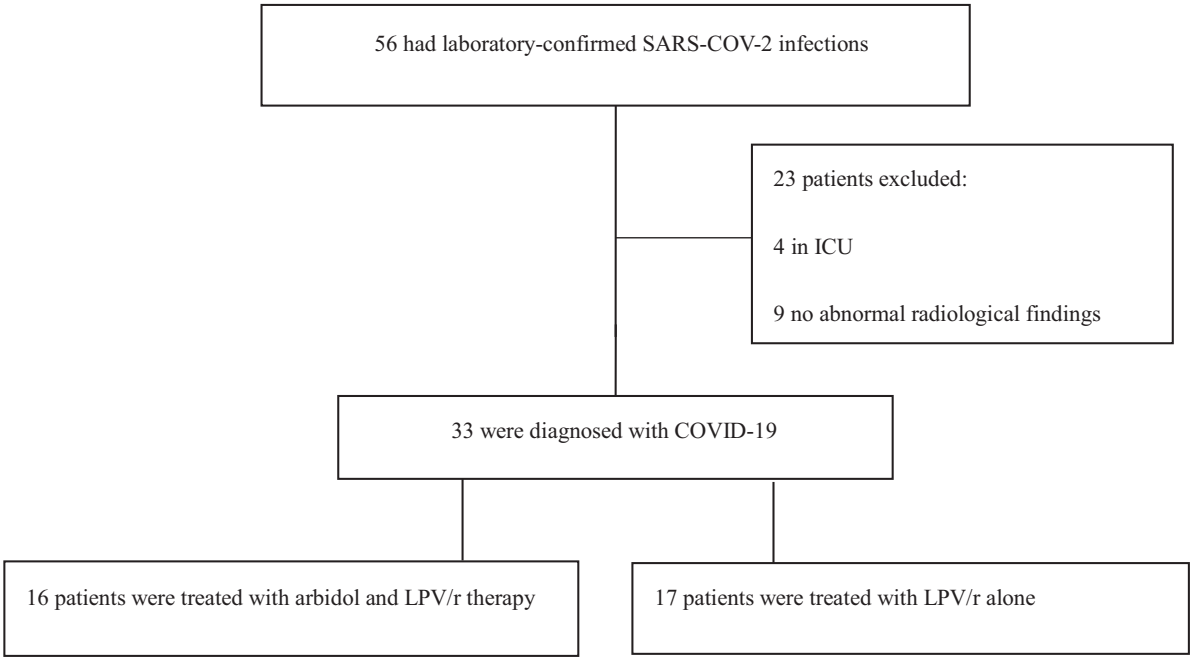

Fig. 1. Study profile.

An overall lung "total severity score" was reached by summing the five lobe scores. Each of the five lung lobes was assessed for degree of involvement and classified as none (0%), minimal (1 - 25%), mild (26 - 50%), moderate (51 - 75%), or severe (76 - 100%). None corresponded to a lobe score of 0, minimal to a lobe score of 1, mild to a lobe score of 2, moderate to a lobe score of 3, and severe to a lobe score of 4.[9,10] 5 (31%) of 16 patients reached a lobe score of 4 in the combination group and 6(35%) of 17 in the monotherapy group in baseline characteristics, and there is no statistically significant differences between two groups (Table 1). However, 1(6%) of 16 received corticosteroid therapy in the combination group compared with 7 (41%) of 17 in the monotherapy group ($p < 0·05$) (Table 2). But, no other statistically significant differences in baseline characteristics or support measures were noted between the two groups (Tables 1 and 2).

After treatment for 7 days, 12 (75%) of 16 patients' nasopharyngeal specimens were negative for SARS-CoV-2's test by RT-PCR in the combination group, compared with 6 (35%) of 17 in the monotherapy group ($p < 0·05$, Fig. 2). After 14 days, 15 (94%) of 16 and 9 (53%) of 17, respectively, coronavirus could not be detected ($p < 0·05$, Fig. 2). Furthermore, the chest CT scans were improving for 11 (69%) of 16 patients in the combination group after 7 days, compared with 5 (29%) of 17 in the monotherapy group ($p < 0·05$, Fig. 3). However, three patients in the monotherapy group were still positive for the stools' test and one in the combination group

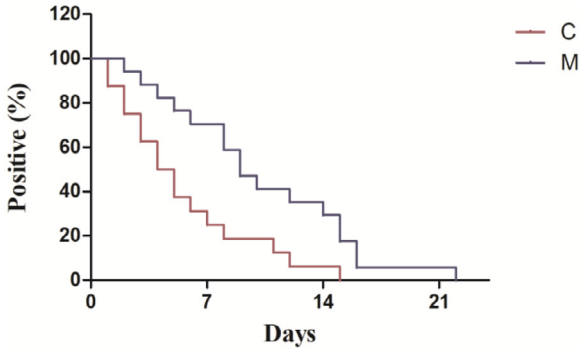

Fig. 2. Nasopharyngeal swab tests of SARS-CoV-2 nucleic acid by RT-PCR between two grous. Note: C refer to combination group; M refers to monotherapy group.

($p > 0·05$, Fig. 3). No other significant differences in laboratory indices between the two groups were noted during the treatment period.

During the treatment period, 68·7% of patients demonstrated elevated levels of bilirubin, mean of top bilirubin was 25·26 μmol/L (10·61 μmol/L) (Table 2). 43·7% of patients demonstrated digestive upsets, such as mild diarrhea and nausea, but all patients had no premature discontinuation secondary to adverse effects.

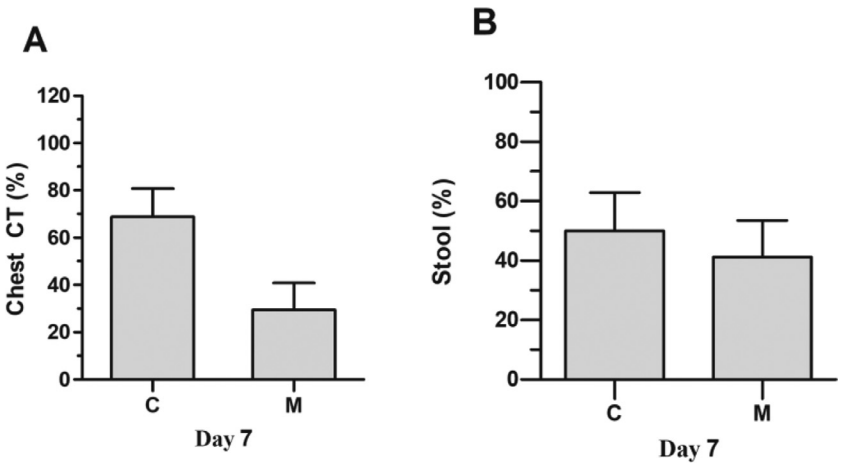

Fig. 3. (A) Chest CT imaging changes between two groups; (B) Stool specimen tests for SARS-CoV-2 nucleic acid . Note: C refers to combination group; M refers to monotherapy group.

Depression or acute confusion was not diagnosed in any of the patients in either group.

Discussion

Effective treatment interventions for patients with severe COVID-19 are still urgently needed. Patients with SARS treated with LPV/r appeared to reduce the viral load, and LPV/r was recommended for patients with MERS-CoV.[7,11] Arbidol and arbidol mesylate were shown to have a direct antiviral effect in early viral replication in vitro for SARS-CoV.[12,13] It has been implied that there was a therapeutic window that could be exploited, provided an active antiviral agent was available.[14] The fundamental strategy in the treatment of coronavirus is, therefore, to find an effective antiviral agent that would decrease the peak viral load and thus, the associated degree of immunopathological damage.[14] In typical patients without Invasive ventilation, our study shows that oral arbidol and LPV/r in the combination group is associated with a significant elevated negative conversion rate of coronavirus' test in 7-day and 14-day, compared with LPV/r only in the monotherapy group. Furthermore, combination therapy is associated with a significantly improved the chest CT scans in 7-day. Fortunately, all the patients did not develop acute respiratory failure during the treatment period, but it was not clear whether it was an effect of antiviral drug.

According to that, we suppose that reducing the viral load as soon as possible could benefit the delay of the progression of lung lesions.Stools of a portion of patients were positive for SARS-CoV-2′s test by RT-PCR. And a few cases, patients in the monotherapy group tested remained positive for SARS-CoV-2 in stools after showing negative in respiratory samples. Chest CT scans may be a better way to assess the effect of treatment compared to nasopharyngeal specimens test for coronavirus.

It has been proved that SARS-CoV-2 uses ACE2 as a viral receptor for entry process.[15,16] ACE2 mRNA is highly expressed in the gastrointestinal system, providing a prerequisite for SARS-CoV-2 infection.[17] About 40% of a total intake dose of arbidol is excreted unchanged within 48 h, mainly with feces (38·9%) and much less with urine (0·12%),[18] and 20% of the LPV/r is found unchanged in the stool.[19] Oral arbidol combine with LPV/r may achieve a high fecal concentration to stop viral replication at this site. Combination therapy may likely be preferred in patients with stool tested positive.

The physical and biochemical examination of main organs and systems did not reveal any significant differences between arbidol-treated and control groups, indicating good tolerability and safety of arbidol in humans.[20] Gastrointestinal symptoms, such as diarrhea and nausea, and elevated levels of bilirubin, are well-recognized complication of LPV/r therapy and was noted previously.[21] Treatment with arbidol and LPV/r was well tolerated in our study.

43% of patients received corticosteroid therapy in the monotherapy group, nevertheless (31%) had improved the chest CT scans in day 7. It is likely that corticosteroids didn't conducive to the recovery of lung injury. The use of corticosteroids is controversial. It had been reviewed that although the glucocorticoid group was younger and had fewer underlying diseases, it had more adverse outcomes, increasing the risk of ICU admission and mortality for patients with SARS receiving hormone therapy.[22] Glucocorticoids could delay the clearance of coronavirus nucleic acids without lower mortality for patients with MERS-CoV infection.[23]

One of the limitations of our study is its small size. Our review, albeit little, is the most significant clinical investigation so far to assess the use of this combination in the treatment of patients with COVID-19. Although baseline characteristics of our treatment and comparator groups seem to be reasonably balanced, substantial differences might not be apparent because of the small number of patients in the study. Our review is also limited by its retrospective, nonrandomized nature, Inevitably, selection and unmeasured confounding bias cannot be excluded entirely. There could be a few alternative interpretations of the results. Undoubtedly, new interventions should ideally be assessed in randomized, controlled clinical trials. However, such an approach is generally accepted to not always be practically feasible in the context of an emerging and relatively uncommon disease such as MERS-CoV infection at the very beginning.[24]

We selected our control group carefully, ensuring that the two cohorts were matched as closely as possible in their clinical characteristics, treatment interventions, and chest CT images other than the receipt of arbidol and LPV/r. We removed four individuals be admitted and transferred to the ICU who had organ dysfunction outlying baseline serum creatinine from the comparator group to minimize the risk of any spurious conclusions driven by clinical characteristics that might be potentially detrimental to clinical outcome. Clinical outcomes for each individual were masked from investigators who selected patients and did matching assessments. Such measurements should be included in any future clinical studies exploring the therapeutic benefit of any antiviral intervention for patients with SARS-CoV-2 infection.

Conclusions

Recent research has suggested that COVID-19 was frequently associated with the presumed hospital-related transmission, 26% of patients required intensive care unit treatment, and mortality was 4·3% in Wuhan, China.[3] The therapeutical emphasis of COVID-19 was, therefore, to antiviral early that would decrease the peak viral load and thus the associated degree of immunopathological damage.[25] This would reduce the need for immunosuppressants, which were often associated with an increased risk of nosocomial infections.[26] One possible implication of this is that, arbidol combine with LPV/r might benefit to delay of the progression of lung lesions and lower the possibility of respiratory and gastrointestinal transmission for decreasing the viral load of COVID-19 and containing a high fecal concentration. Further randomized, prospective studies are still needed, and the mechanism of its antiviral effect to coronavirus remains unclear.

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No external funding was received for this study.

Declaration of Competing Interest

The authors declare no conflict of interest.

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