Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial

Chang Chen, MD[1,2,#], Jianying Huang, MD[1,3,#], Zhenshun Cheng, MD[4], Jianyuan Wu, PhD[1,3], Song Chen, MD[5], Yongxi Zhang, MD[6], Bo Chen, PhD[1,3], Mengxin Lu, MD[5], Yongwen Luo, MD[5], Jingyi Zhang, MD[7], Ping Yin, PhD[8], Xinghuan Wang, MD[1,3,5,9,*]

Author affiliations:

[1]Clinical Trial Center, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, 430071, China

[2]Department of Anesthesiology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, 430071, China

[3]Wuhan Leishenshan Hospital, Wuhan, Hubei, 430000, China

[4]Department of Respiratory Medicine, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, 430071, China

[5]Department of Urology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, 430071, China

[6]Department of Infectious Diseases, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, 430071, China

[7]Department of Cardiology, The Third People's Hospital of Hubei Province, Wuhan, Hubei, 430033, China

[8]Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, 430030, China

[9]Center for Evidence-Based and Translational Medicine, Zhongnan Hospital of

Wuhan University, Wuhan, Hubei, 430071, China

[#]Contributed equally.

***Corresponding author:** Dr. Xinghuan Wang, Clinical Trial Center, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, China. Tel: +86-27-67813104. E-mail: wangxinghuan@whu.edu.cn

Manuscript word count: Key points 57; Abstract 336; Full text 3678

Key points

Question: How about the efficacy and safety of favipiravir to treat COVID-19 patients?

Findings: In ordinary COVID-19 patients untreated with antiviral previously, favipiravir has higher 7 day's clinical recovery rate and more effectively reduced incidence of fever, cough except some antiviral-associated adverse effects.

Meaning: Favipiravir can be considered as a preferred treatment approach to ordinary COVID-19 pneumonia.

Abstract

Importance: WHO has made the assessment that coronavirus disease 2019 (COVID-19) can be characterized as a pandemic. But there is no effective antiviral drug for COVID-19 so far.

Objective: To compare the efficacy and safety of favipiravir and arbidol to treat COVID-19 patients on 7 day's clinical recovery rate.

Design: Prospective, multicenter, open-label, randomized superiority trial in February, 2020.

Setting: Multicenter study.

Participants: Patients with confirmed COVID-19 admitted to 3 hospitals from Feb 20, 2020 to Mar 12, 2020.

Interventions: Conventional therapy + favipiravir or arbidol.

Main Outcomes and Measures:

The primary outcome was 7 day's clinical recovery rate. Duration of fever, cough relief time and auxiliary oxygen therapy or noninvasive mechanical ventilation rate were the secondary outcomes. The patients with chest CT imaging and laboratory-confirmed COVID-19 infection, aged 18 years or older were randomly assigned to receive favipiravir or arbidol. Safety data were collected for a further 1 weeks' follow-up.

Results: 120 patients were assigned to favipiravir group (116 assessed) and 120 to arbidol group (120 assessed). In FAS cohort, for ordinary patients with COVID-19, 7 day's clinical recovery rate was 55.86% in the arbidol group and 71.43% in the

favipiravir group (P = 0.0199). For ordinary COVID-19 patients and COVID-19 patients with hypertension and/or diabetes, the time of fever reduction and cough relief in favipiravir group was significantly shorter than that in arbidol group (both P < 0.001), but there was no statistical difference was observed of auxiliary oxygen therapy or noninvasive mechanical ventilation rate (both P > 0.05). The most possible adverse events were abnormal LFT, psychiatric symptom reactions, digestive tract reactions and raised serum uric acid (3 [2.50 %] in arbidol group vs 16 [13.79%] in favipiravir group, P < 0.0001).

Conclusions and Relevance: In ordinary COVID-19 patients untreated with antiviral previously, favipiravir can be considered as a preferred treatment because of its' higher 7 day's clinical recovery rate and more effectively reduced incidence of fever, cough except some antiviral-associated adverse effects.

Trial Registration: This study is registered with Chictr.org.cn, number ChiCTR200030254.

Introduction

December 2019, an outbreak of pneumonia caused by a novel coronavirus occurred in Wuhan, Hubei province, followed has spread rapidly throughout China. As of 14 March, the WHO reported 146,181 confirmed cases across more than 130 countries [1]. But there are still no effective antiviral drugs for COVID-19 so far. The global mortality rate of COVID-19 is 3.4% [2], Wang *et al.* indicated the mortality rate in Wuhan is 4.3% [3], as the proportion of critical cases in Wuhan is relatively high. A study has demonstrated that patient with hypertension and/or diabetes had a higher risk of contracting COVID-19 [4]. It is of great significance to carry out effective antiviral treatment in 80% of the ordinary patients with COVID-19, which can reduce the progress of ordinary patients to critical cases.

SARS-CoV-2 and influenza viruses have a similar disease presentation. The clinical manifestations both are dominated by respiratory symptoms, which present as a wide range of illness from asymptomatic or mild through to severe disease and death, yet there are important differences between the 2 viruses. which approaches and treatment are most appropriate to control its transmission and limit potential consequences of the epidemic remain unclear. There is no specific treatment for this disease, so healthcare providers treat the clinical symptoms (e.g. fever, difficulty breathing) of patients. Supportive care (e.g. fluid management, oxygen therapy, etc.) can be highly effective for patients with symptoms. There are currently no antiviral drugs recommended or licensed by the U.S. Food and Drug Administration for COVID-19. Arbidol is an antiviral treatment for influenza infection used in Russia and China and

has been renewed as a result of the SARS-CoV-2 outbreak [5]. Favipiravir is converted to the ribofuranosyl triphosphate derivative by host enzymes and is a promising antiviral drug targeting the influenza viral RNA-dependent RNA polymerase (RdRP) [6]. Although arbidol is the most widely used of antiviral, there are no randomized comparative study data to show that one antiviral is better than another for SARS-CoV-2. The clinical studies of some drugs (human interferon alfa-2b, ribavirin, chloroquine phosphate, lopinavir and arbidol) were currently undergoing to test the efficacy and safety of these drugs in the treatment of COVID-19 [7].

Approximately, 80% of laboratory confirmed patients have had mild to moderate disease, which includes non-pneumonia and pneumonia cases in China. Cough and fever were the most typical symptoms of COVID-19 [8]. Favipiravir was approved in Japan for stockpiling against influenza pandemics. In this study, we hypothesized that favipiravir would be non-inferior to arbidol in terms of efficacy for moderate symptoms, and improves outcomes clinical recovery of fever, cough, and breathing difficulties compared with antiviral efficacy of arbidol. We therefore assessed the clinical efficacy and safety of favipiravir versus arbidol as treatment for SARS-CoV-2.

Methods

Study design and participants

We conducted a prospective, multicenter, open-labelled, randomized superiority trial in 240 patients with COVID-19 pneumonia at three hospitals (120 patients from Zhongnan Hospital of Wuhan University, 88 patients from Leishenshan Hospital, 32 patients from The Third People's Hospital of Hubei Province). Patients were prospectively enrolled and followed-up from Feb 20, 2020 to Mar 12, 2020. In this study, according to the proportion of 1:1 between the experimental group (favipiravir) and the control group (arbidol), the randomized open label was produced by professional statistical software SAS9.4. The Ethics Committee at Zhongnan Hospital of Wuhan University approved the trial protocol (approval number: 2020040) and written informed consent was obtained from all participants or their authorized representatives.

Patients were eligible if they met all the following criteria: (1) aged 18 years or older; (2) voluntarily signed informed consent; (3) the initial symptoms were within 12 days; (4) diagnosed as COVID-19 pneumonia.

Patients meeting any of the following criteria were excluded: (1) were allergic to fabiravir or arbidol; (2) ALT/AST increased 5 times higher than the upper limit of normal, or with child Pugh C; (3) critical patients whose expected survival time < 48 hours; (4) childbearing age women with positive pregnancy test; (5) with HIV infection; (6) were considered unsuitable by researchers.

Procedures

Arbidol is the recommended drug in The Novel Coronavirus Pneumonia Diagnosis and Treatment Scheme (6th trial version, February 19th) which formulate by the National Health Commission of P.R.C. and the National Administration of Traditional Chinese Medicine [9]. The experimental group (famiravir) was treated with routine treatment + famiravir tablets (1600 mg/time on the first day, twice a day; 600 mg/time from the second day to the end of the experiment, twice a day). The control group (arbidol) was treated with routine therapy + arbidol (200 mg each time, 3 times a day, from the first day to the end of the trial). The course of treatment in both groups was 7-10 days. If necessary, the treatment time could be extended to 10 days according to the judgment of researchers. Except arbidol and famiravir, some other drugs were used for conventional therapy and symptomatic treatment to improve adverse reactions. The details of drugs use were listed in Supplementary Table S1.

Definitions

The primary outcome was the clinical recovery rate at 7 days or the end of treatment, which was stratified as ordinary patients with COVID-19, critical patients with COVID-19, COVID-19 patients with hypertension and/or diabetes. The recovery of fever, respiratory rate, oxygen saturation and cough relief after treatment were defined as clinical recovery, and the recovery state lasted no less than 72 hours. It needs to meet several conditions: axillary temperature $\leq$ 36.6 °C; respiratory frequency $\leq$ 24 times/min; Oxygen saturation $\geq$ 98% without oxygen inhalation; mild or no cough. The armpit temperature, respiratory rate, oxygen saturation without oxygen, oxygen therapy and noninvasive positive pressure ventilation (NPPV) were recorded in daily

follow-up. Repeated measurements were made at least twice in each follow-up. The measurements were taken after 15 minutes rest at room temperature (23±2 °C).

Secondary outcomes included the time from randomization to fever reduction (patients with fever at the time of enrollment), the time from randomization to cough relief (patients with moderate or severe cough at the time of enrollment), the rate of auxiliary oxygen therapy or noninvasive mechanical ventilation during the trial, the all-cause mortality during the trial, the rate of respiratory failure during the trial (defined as $SPO_2 \leq 90\%$ or $PaO_2/FiO_2 < 300$ mmHg without oxygen inhalation, and requires oxygen therapy or higher respiratory support).

Blood biochemistry, urine routine, coagulation function, C-reactive protein, nucleic acid and CT were examined on the third day (D3±1 day) and the seventh day (D7±1 day) after taking the drug, and the adverse events and concomitant medication were observed.

Classification criteria of ordinary COVID-19 patients and critical COVID-19 patients: (1) Ordinary COVID-19 patients: has a fever, respiratory symptom, can be observed by imageology methods. (2) Critical COVID-19 patients: meeting any of the following case: a. dyspnea, RR > 30 times/min; b. the $SpO_2 < 93\%$ in the resting state; c. $PaO_2/FiO_2 < 300$mmHg (1 mmHg = 0.133 kPa). PaO_2/FiO_2 should be corrected according to the formula: $PaO_2/FiO_2 \times$ [atmospheric pressure (mmHg)/760]. The pulmonary imaging showed that the lesions progressed more than 50% within 24-48 hours, and the patients were classified as critical patients.

Statistical Analysis

Sample size estimation: the expected clinical recovery rate of the experimental group is 70%, the clinical recovery of the control group is 50%, $\alpha = 0.025$ (single side), $\beta = 0.20$, power = 0.80. According to the distribution ratio of 1:1 between the experimental group and the control group, the statistical sample size is 92 participants in each group. The sample size increased about 20% considering factors such as shedding/elimination. The trial was designed to include 240 participants in the group, including 120 in the experimental group and 120 in the control group.

SAS9.4 software was used for statistical analysis. For the main efficacy indicator/primary outcome (clinical recovery rate after 7 days or the end of treatment), the comparison between the experimental group and the control group adopts the optimal test. We calculated the bilateral 95% CI of the difference between the clinical recovery rate of the experimental group and the control group. If the lower limit was > 0, it was considered the experimental group (favipiravir) is superior to the control group (arbidol). Log rank test was used to compare the “time” between the two groups. For the secondary efficacy indicators/secondary outcomes, t test or Wilcoxon rank sum test (if t-test was not applicable) was performed for safety indicators and continuous variables, Wilcoxon rank sum test was used for grade variables. Frequency or composition (%) were used for statistical description of classification indexes, and Chi-square test test or Fisher’s exact test was used for comparison between groups. For all statistical tests, P value < 0.05 (bilateral) were considered as statistically significant.

Results

Basic characteristics of patients in the 2 groups

Total 236 patients with COVID-19 were enrolled in the full analysis set (FAS), 116 in the experimental group (favipiravir) and 120 in the control group (arbidol). The characteristics of patients in the 2 groups were shown in table 1. In the experimental group, 59 were males and 57 were females, 87 (75.00%) were < 65 years and 29 (25.00%) were ≥ 65 years, 36 (31.03%) were with hypertension and 14 (12.07%) with diabetes. In the control group, 51 were males and 69 were females, 79 (65.83%) were < 65 years and 41 (34.17%) were ≥ 65 years, 30 (25.00%) were with hypertension and 13 (10.83%) with diabetes.

At the time of enrolled, the main signs and symptoms were fever (64 [55.17%] in favipiravir group vs 61 [50.83%] in arbidol group, P = 0.5911), fatigue (40 [34.48%] in favipiravir group vs 27 [22.50%] in arbidol group, P = 0.0579), dry cough (70 [60.34%] in favipiravir group vs 64 [53.33%] in arbidol group, P = 0.3393), myalgia (2 [1.72%] in favipiravir group vs 3 [2.50%] in arbidol group, P = 1.0000), dyspnoea (9 [7.76%] in favipiravir group vs 4 [3.33%] in arbidol group, P = 0.2285), expectoration (13 [11.21%] in favipiravir group vs 11 [9.17%] in arbidol group, P = 0.7619), sore throat (9 [7.76%] in favipiravir group vs 17 [14.17%] in arbidol group, P = 0.1726), diarrhoea (22 [18.97%] in favipiravir group vs 15 [12.50%] in arbidol group, P = 0.2354), dizziness (1 [0.86%] in favipiravir group vs 5 [4.17%] in arbidol group, P = 0.2306), insomnia (16 [13.79%] in favipiravir group vs 29 [24.17%] in arbidol group, P = 0.0426) and conjunctivitis (6 [5.17%] in favipiravir group vs 7

[5.83%] in arbidol group, P = 1.0000). No significant difference of basic characteristics of patients between the two groups was observed.

Comparison of 7 day's clinical recovery rate of favipiravir and arbidol in COVID-19 patients

Of 116 cases in favipiravir group, 98 were classified as ordinary COVID-19 patients and 18 were critical COVID-19 patients, 42 COVID-19 patients were with hypertension and/or diabetes. Of 120 cases in arbidol group, the ordinary and critical COVID-19 patients were 111, 9 respectively; 35 were with hypertension and/or diabetes.

The clinical recovery rate was 51.67% (62/120) in the arbidol group and 61.21% (71/116) in the favipiravir group after a 7 day's antiviral treatment (P = 0.1396), with the difference of recovery rate between two groups (95% CI) was 0.0954 (-0.0305, 0.2213). Concretely, for ordinary patients with COVID-19, 7 day's clinical recovery rate was 55.86% (62/111) in the arbidol group and 71.43% (70/98) in the favipiravir group (P = 0.0199), with the difference of recovery rate between two groups (95% CI) was 0.1557 (0.0271, 0.2843); for critical patients with COVID-19, clinical recovery rate was 0 (0/9) in the arbidol group and 5.56% (1/18) in the favipiravir group (P = 0.4712), with the difference of recovery rate between two groups (95% CI) was 0.0556 (-0.0503, 0.1614); for COVID-19 patients with hypertension and/or diabetes, clinical recovery rate was 51.43% (18/35) in the arbidol group and 54.76% (23/42) in the favipiravir group (P = 0.7704), with the difference of recovery rate between two groups (95% CI) was 0.0333 (-0.1904, 0.2571) (Table 2).

Comparison of duration of fever, cough relief time and auxiliary oxygen therapy or noninvasive mechanical ventilation rate between 2 groups

Table 3 displayed duration of fever, cough relief time and auxiliary oxygen therapy or noninvasive mechanical ventilation rate between the favipiravir and arbidol groups. Of 98 ordinary COVID-19 patients in the favipiravir group, 57 had a fever and 60 had a cough; of 111 ordinary COVID-19 patients in the arbidol group, 65 had a fever and 64 had a cough. For ordinary COVID-19 patients, the time of fever reduction and cough relief in the favipiravir group was significantly shorter than that in the arbidol group ($P < 0.0001$).

Of 42 COVID-19 patients with hypertension and/or diabetes in the favipiravir group, 28 had a fever and 25 had a cough; of 35 COVID-19 patients with hypertension and/or diabetes in the arbidol group, 24 had a fever and 23 had a cough. For COVID-19 patients with hypertension and/or diabetes, the time of fever reduction and cough relief in the favipiravir group was also significantly shorter than that in the arbidol group ($P < 0.0001$).

For ordinary patients with COVID-19, auxiliary oxygen therapy or noninvasive mechanical ventilation rate was 17.12% (19/111) in the arbidol group and 8.16% (8/98) in the favipiravir group ($P = 0.0541$), with the difference of recovery rate between 2 groups (95% CI) was -0.0895 (-0.1781, -0.0009); for critical patients with COVID-19, auxiliary oxygen therapy or noninvasive mechanical ventilation rate was 88.89 (8/9) in the arbidol group and 72.22% (13/18) in the favipiravir group ($P = 0.3261$), with the difference of recovery rate between 2 groups (95% CI) was -0.1667

(-0.4582, 0.1248); for COVID-19 patients with hypertension and/or diabetes, auxiliary oxygen therapy or noninvasive mechanical ventilation rate was 28.57% (10/35) in the arbidol group and 21.43% (9/42) in the favipiravir group (P = 0.4691), with the difference of recovery rate between two groups (95% CI) was -0.0714 (-0.2658, 0.1230). There was no statistical difference was observed of auxiliary oxygen therapy or noninvasive mechanical ventilation rate between 2 groups (both P > 0.05). Of all cases enrolled in this study, the all cause mortality was 0. The rate of new dyspnea in arbidol group was 11.67% (14/120) and in favipiravir group was 3.45% (4/116) with the P value = 0.0174. The cases of respiratory failure in the two group were both 4.

Comparison of antiviral-associated adverse effects between two groups

In the whole process of trial, we detected some antiviral-associated adverse effects. 37 adverse effects cases in the favipiravir group and 28 cases in the arbidol group were observed. The most common adverse events were raised serum uric acid (3 [2.50 %] vs 16 [13.79%], P = 0.0014), more common in patients of the favipiravir group than those in the arbidol group. But no statistical difference was observed for abnormal LFT (ALT and/or AST were elevated) (12 [10.00%] in the arbidol group vs 9 [7.76%] in the favipiravir group, P =0.5455), psychiatric symptom reactions (1 [0.83%] vs 2 [1.72%]; P = 0.6171) and digestive tract reactions (nausea, anti-acid, flatulence [10]) (14 [11.67%] vs 16 [13.79%]; P = 0.6239) (Table 4). These adverse reactions disappeared when most patients were discharged from hospital.

Discussion

COVID-19 pneumonia has rapid development into a global pandemic [1]. For the infected patients, it is an urgent matter to improve the cure rate and reduce the death rate, but there are no effective antiviral drugs for COVID-19 so far. In China, although arbidol has been recommended in The Novel Coronavirus Pneumonia Diagnosis and Treatment Scheme (6th trial version) [8]. The efficacy and safety of arbidol were not very optimistic. Favipiravir was approved in Japan for stockpiling against influenza pandemics, the efficacy of it in the treatment of COVID-19 pneumonia is unclear. We conducted a prospective, multicenter, open-labelled, randomized superiority trial and hypothesized that favipiravir would be non-inferior to arbidol in terms of efficacy for moderate symptoms, and improves outcomes clinical recovery of fever, cough, and breathing difficulties compared with arbidol antiviral.

Among the 236 cases enrolled in the study, 66 (27.9%) were combined with hypertension, 27 (11.44%) were with diabetes, 13 (5.5%) with conjunctivitis and 45 (19.06%) with insomnia. There was no significant difference between the favipiravir and arbidol groups. Patients with hypertension and diabetes may be at high risk of COVID-19 pneumonia, which depends on epidemiological data to confirm. Conjunctivitis may be caused by seasonal eye allergy, or the invasion of conjunctiva by COVID-19. There was no evidence to prove that the nucleic acid test of eye secretion was positive. Insomnia was mainly caused by anxiety and cough at night. It was possible that isolation time and external environment of patients with COVID-19

may cause psychological problems, which deserved further attention.

In ordinary COVID-19 patients, favipiravir has higher 7 day's clinical recovery rate (71.43%) than arbidol (55.86%), and the time of cough relief and fever reduction of fabiravir was significantly shorter than that of arbidol. for COVID-19 patients with hypertension and/or diabetes, the clinical recovery rate was 54.76% in the favipiravir group, no remarkably different with that 51.43% in the arbidol group (P = 0.7704). It may be related to SpO_2 in the 7 day's clinical recovery without oxygen inhalation. Hypertension and diabetes are chronic diseases, which have a certain impact on the recovery of lung function. Therefore, it needed more time (> 7 days) that SpO_2 were recovered to more than 98% without oxygen inhalation. It indicated that fabiravir could be used in the treatment of ordinary COVID-19 patients, which may inhibit the development of the course of disease. For ordinary patients with COVID-19, auxiliary oxygen therapy or noninvasive mechanical ventilation rate was 17.12% in the arbidol group and 8.16% in the favipiravir group (P = 0.0541); for COVID-19 patients with hypertension and/or diabetes, auxiliary oxygen therapy or noninvasive mechanical ventilation rate was 28.57% in the arbidol group and 21.43% in the favipiravir group (P = 0.4691). It was suggested that the lung tolerance to hypoxia was low in patients with hypertension and diabetes. Patients with hypertension and diabetes were more likely to progress. Once the virus started causing the disease, these patients would be treated with antiviral therapy after the lung progress was intensified, which may only shorten the course of disease or the detoxification period, and could not recover other damages caused by the virus (myocardial, kidney, sepsis). Therefore, for the patients

with hypertension and diabetes, the early improvement of symptoms is the key. Because the “spike protein” attacked by COVID-19 attacked the ACE2 target protein on the surface of pulmonary epithelial cells [4], and the patients with hypertension and/or diabetes accounted for 32.6% of all cases, we analyzed the primary outcome and secondary outcomes of the patients with hypertension and/or diabetes, and evaluated the clinical efficacy of fabiravir in the treatment of COVID-19.

Inevitably, our study has some limitations. First, it was difficulty to select the drug of control group. For the COVID-19 pneumonia, there is no effective antiviral drug was reported. Chinese doctors had recommended antiviral drugs in the sixth edition of the guidelines: recombinant human interferon alfa-2b, ribavirin, chloroquine phosphate, lopinavir and arbidol. The clinical studies were currently undergoing to test the efficacy and safety of these drugs in the treatment of COVID-19. Despite the antiviral effect of arbidol, there is no exact data in the literature to support its effectiveness. Arbidol was widely used by Chinese doctors in the initial stage of antiviral epidemic of COVID-19 (Jan. 1 to Jan. 30, 2020) [11]. For ethical reasons, we chose arbidol as the positive control, and adopted the optimal experimental design. Second, due to the limitation of the observation period, it lacked the safety and effectiveness judgment as long as 1 month. Besides, it also lacked the evidence tracking of relapse (including nucleic acid conversion to positive, fever and cough again) in the next month in the discharged patients with negative nucleic acid test and normal CT imaging lung test. Third, in the inclusion criteria, we did not include the positive nucleic acid test. The accuracy of nucleic acid kit and throat swab sampling would affect the judgment of

results. We collected the number of nucleic acid positive cases in the screening period, 54 (46.55%) in favipiravir group and 46 (38.33%) in arbidol group. The clinical diagnosis and CT results suggested that there might be negative nucleic acid in patients with COVID-19 pneumonia. In the screening period, the patients with contact history, typical CT imaging results of COVID-19 and obvious clinical symptoms had negative nucleic acid test, which was related to the previous treatment, onset time, sampling and detection kit. Fourth, among all the participants, there were 18 critical patients in the favipiravir group and 9 critical patients in the arbidol group. Because of the imbalance of the proportion of critical patients between the two groups, it had an important impact on the primary outcome (7 day's clinical recovery rate), secondary outcomes and combined medication. According to the severity of COVID-19 and whether it is combined with hypertension and/or diabetes, a stratified analysis was conducted.

Conclusions

In ordinary COVID-19 patients untreated with antiviral previously, favipiravir can be considered as a preferred treatment because of the higher 7 day's clinical recovery rate and more effectively reduced incidence of fever, cough except some antiviral-associated adverse effects.

Author contributions

Dr. Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: C. Chen, Huang, Cheng, Wu, Wang.

Acquisition, analysis, or interpretation of data: C. Chen, Huang, Cheng, Wu, Y. Zhang, Yin, Wang.

Drafting of the manuscript: C. Chen, Huang, S. Chen, Lu, Luo, B. Chen, J. Zhang, Yin, Wang.

Critical revision of the manuscript for important intellectual content: C. Chen, Huang, Wu, S. Chen, Lu, Luo, J. Zhang, B. Chen.

Statistical analysis: C. Chen, S. Chen, Yin.

Obtained funding: Wang.

Administrative, technical, or material support: C. Chen, Huang, Wang.

Study supervision: Huang, Yin, Wang.

Declaration of Interest

All authors have no conflicts of interest to declare.

Data sharing Statement

With the permission of the corresponding author, we can provide participant data, statistical analysis.

Acknowledgments

This work was supported by the National Key Research and Development Program of China (2020YFC0844400).

References

1. Coronavirus disease 2019 (COVID-19) Situation Report. World Health Organization. 2020.3.14. *https://www.who.int/*

2. Max Roser, Hannah Ritchie and Esteban Ortiz-Ospina. Coronavirus Disease (COVID-19)-Statistics and Research. *https://ourworldindata.org/coronavirus*

3. Wang D, Hu B, Hu C, *et al*. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020; published online Feb 07. doi: 10.1001/jama.2020.1585.

4. Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020; published online Mar 11. doi: 10.1016/S0140-6736(20)30566-3.

5. Hulseberg CE, Fénéant L, Szymańska-de Wijs KM, *et al*. Arbidol and Other Low-Molecular-Weight Drugs That Inhibit Lassa and Ebola Viruses. *J Virol*. 2019; 93(8). pii: e02185-18. doi: 10.1128/JVI.02185-18.

6. Goldhill DH, Te Velthuis AJW, Fletcher RA, *et al*. The mechanism of resistance to favipiravir in influenza. *Proc Natl Acad Sci USA*. 2018; 115(45): 11613-11618. doi: 10.1073/pnas.1811345115.

7. Dong L, Hu S, Gao J, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. published online Mar 11. 2020; doi: 10.1016/S0140-6736(20)30566-3.

8. Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395(10223). doi: 10.1016/S0140-6736(20)30183-5.

9. Chinese diagnosis and treatment plan of COVID-19 patients (The sixth edition). *http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2.shtml*.

10. Zhang H, Kang ZJ, Gong HY, *et al*. The digestive system is a potential route of 2019 nCoV infection: a bioinformatics analysis based on single-cell transcriptomes. *bioRxiv* 2020.01.30.927806; doi: https://doi.org/10.1101/2020.01.30.927806.

11. Li Q, Guan X, Wu P, *et al*. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020; published online Jan 29. doi: 10.1056/NEJMoa2001316.

Figure legend

Figure 1. Flow Diagram of the Study.

Table 1. Basic characteristics of the participants.

Variables	Favipiravir group (N = 116)	Arbidol group (N = 120)	P value
Gender			
Female, n (%)	57 (49.14)	69 (57.50)	0.2473
Male, n (%)	59 (50.86)	51 (42.50)	
Age (years)			
< 65, n (%)	87 (75.00)	79 (65.83)	0.1232
≥ 65, n (%)	29 (25.00)	41 (34.17)	
Hypertension	36 (31.03)	30 (25.00)	0.3018
Diabetes	14 (12.07)	13 (10.83)	0.7656
Insomnia	16 (13.79)	29 (24.17)	0.0426
Conjunctivitis	6 (5.17)	7 (5.83)	1.0000*
Signs and symptoms			
Fever	64 (55.17)	61 (50.83)	0.5911
Fatigue	40 (34.48)	27 (22.50)	0.0579
Dry cough	70 (60.34)	64 (53.33)	0.3393
Myalgia	2 (1.72)	3 (2.50)	1.0000*
Dyspnoea	9 (7.76)	4 (3.33)	0.2285
Expectoration	13 (11.21)	11 (9.17)	0.7619
Sore throat	9 (7.76)	17 (14.17)	0.1726
Diarrhoea	22 (18.97)	15 (12.50)	0.2354
Dizziness	1 (0.86)	5 (4.17)	0.2306
Nucleic acid tests			
Positive	54 (46.55)	46 (38.33)	0.4202
Suspected	6 (5.17)	6 (5.00)	
CT (N = 235 with data)	N = 116	N = 119	0.7635
COVID-19 pneumonia	112 (96.55)	114 (95.80)	

*t test was performed for continuous variables, frequency or composition (%) were used for statistical description of classification indexes, and Chi-square test or Fisher's exact test was used for comparison between groups.

Table 2. Comparison of 7 day's clinical recovery rate of favipiravir and arbidol in COVID-19 patients.

Variables	Favipiravir group	Arbidol group	Rate ratio (95% CI)	P value
Total patients	**(N = 116)**	**(N = 120)**		0.1396
Recovered, n (%)	71 (61.21)	62 (51.67)	0.0954 (-0.0305, 0.2213)	
Ordinary patients	**(N = 98)**	**(N = 111)**		
Recovered, n (%)	70 (71.43)	62 (55.86)	0.1557 (0.0271, 0.2843)	0.0199
Critical patients	**(N = 18)**	**(N = 9)**		
Recovered, n (%)	1 (5.56)	0 (0.00)	0.0556 (-0.0503, 0.1614)	0.4712
Patients with hypertension and/or diabetes	**(N = 42)**	**(N = 35)**		
Recovered, n (%)	23 (54.76)	18 (51.43)	0.0333 (-0.1904, 0.2571)	0.7704

Table 3. Comparison of duration of fever, cough relief time and other secondary outcomes between two groups.

Variables	Duration of fever		Cough relief time	
	Favipiravir group	**Arbidol group**	**Favipiravir group**	**Arbidol group**
Ordinary patients	**N = 57**	**N = 65**	**N = 60**	**N = 64**
Day 1	12 (21.05)	2 (3.08)	1 (1.67)	3 (4.69)
Day 2	23 (40.35)	8 (12.31)	1 (1.67)	1 (1.56)
Day 3	16 (28.07)	16 (24.62)	21 (35.00)	7 (10.94)
Day 4	4 (7.02)	15 (23.08)	18 (30.00)	11 (17.19)
Day 5	0 (0.00)	13 (20.00)	9 (15.00)	12 (18.75)
Day 6	0 (0.00)	4 (6.15)	7 (11.67)	10 (15.63)
Day 7	0 (0.00)	2 (3.08)	2 (3.33)	3 (4.69)
Day 8	-	-	1 (1.67)	4 (6.25)
Day 9	-	-	0 (0.00)	1 (1.56)
Censored	2 (3.51)	5 (7.69)	0 (0.00)	12 (18.75)
Log-rank P value	< 0.0001		< 0.0001	
Patients with hypertension	**N = 28**	**N = 24**	**N = 25**	**N = 23**
Day 1	7 (25.00)	0 (0.00)	1 (4.00)	2 (9.09)
Day 2	13 (46.43)	4 (16.67)	0 (0.00)	0 (0.00)
Day 3	5 (17.86)	5 (20.83)	6 (24.00)	3 (13.64)
Day 4	3 (10.71)	2 (8.33)	7 (28.00)	2 (9.09)
Day 5	0 (0.00)	7 (29.17)	2 (8.00)	2 (9.09)
Day 6	0 (0.00)	3 (12.50)	5 (20.00)	3 (13.64)
Day 7	-	-	1 (4.00)	0 (0.00)
Day 8	-	-	2 (8.00)	2 (9.09)
Day 9	-	-	0 (0.00)	1 (4.55)
Censored	0 (0.00)	3 (12.50)	1 (4.00)	7 (31.82)

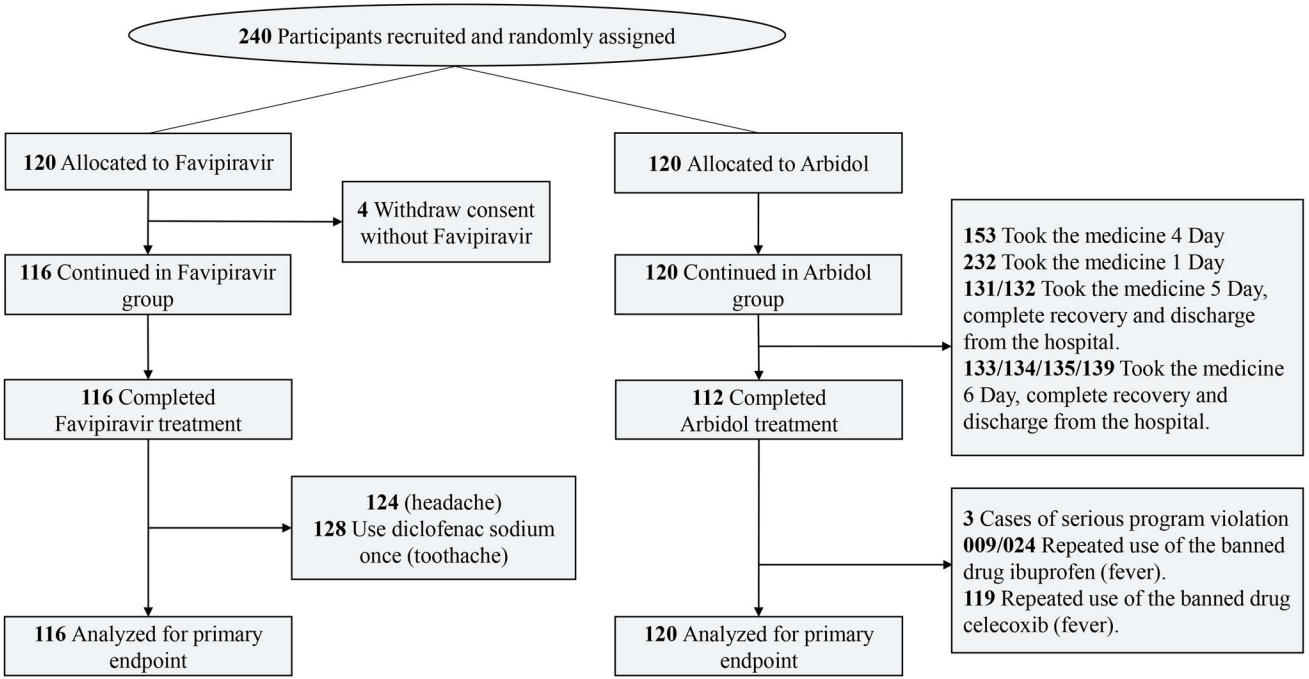
Log-rank P value	< 0.0001		0.0053	
Other secondary outcomes				
AOT or NMV*	**Favipiravir group**	**Arbidol group**	**Rate ratio (95% CI)**	**P value**
Ordinary patients	N = 98	N = 111		
With auxiliary, n (%)	8 (8.16)	19 (17.12)	-0.0895 (-0.1781, -0.0009)	0.0541
Patients with hypertension and/or	N = 42	N = 35		
With auxiliary, n (%)	9 (21.43)	10 (28.57)	-0.0714 (-0.2658, 0.1230)	0.4691
All-cause mortality	0 (0.00)	0 (0.00)	/	/
Dyspnea after taking	4 (3.45)	14 (11.67)	/	0.0174
Respiratory failure, n (%)	1 (0.86)	4 (3.33)	/	0.3700*

*Fisher's exact test was used for comparison between groups.

Table 4. Comparison of antiviral-associated adverse effects between two groups.

Adverse effects	Favipiravir group (N = 116)		Arbidol group (N = 120)		P value
	Frequency	Cases, n (%)	Frequency	Cases, n (%)	
Total	43	37 (31.90)	33	28 (23.33)	0.1410
LFT abnormal	9	9 (7.76)	12	12 (10.00)	0.5455
Raised serum uric acid	16	16 (13.79)	3	3 (2.50)	0.0014
Psychiatric symptom reactions	2	2 (1.72)	1	1 (0.83)	0.6171*
Digestive tract reactions	16	16 (13.79)	17	14 (11.67)	0.6239

*Fisher's exact test was used for comparison between groups.


240 Participants recruited and randomly assigned
120 Allocated to Favipiravir
4 Withdraw consent without Favipiravir
116 Continued in Favipiravir group
116 Completed Favipiravir treatment
124 (headache)
128 Use diclofenac sodium once (toothache)
116 Analyzed for primary endpoint
120 Allocated to Arbidol
120 Continued in Arbidol group
153 Took the medicine 4 Day
232 Took the medicine 1 Day
131/132 Took the medicine 5 Day, complete recovery and discharge from the hospital.
133/134/135/139 Took the medicine 6 Day, complete recovery and discharge from the hospital.
112 Completed Arbidol treatment
3 Cases of serious program violation
009/024 Repeated use of the banned drug ibuprofen (fever).
119 Repeated use of the banned drug celecoxib (fever).
120 Analyzed for primary endpoint