Favipiravir, camostat, and ciclesonide combination therapy in patients with moderate COVID-19 pneumonia with/without oxygen therapy: An open-label, single-center phase 3 randomized clinical trial

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Summary

Background The effectiveness of combination therapy for COVID-19 pneumonia remains unclear. We evaluated favipiravir, camostat, and ciclesonide combination therapy in patients with moderate COVID-19 pneumonia.

Methods In this open-label phase 3 study, hospitalized adults who were positive for SARS-CoV-2 and had COVID-19 pneumonia were enrolled prior to official vaccination drive in Japan. Participants were randomly assigned to favipiravir monotherapy or favipiravir + camostat + ciclesonide combination therapy. The primary outcome was the length of hospitalization due to COVID-19 infection after study treatment. The hospitalization period was calculated from the time of admission to the time of patient discharge using the clinical management guide of COVID-19 for front-line healthcare workers developed by the Japanese Ministry of Health, Labour, and Welfare (Version 3). Cases were registered between November 11, 2020, and May 31, 2021. Japan Registry of Clinical Trials registration: jRCTs031200196.

Findings Of 121 enrolled patients, 56 received monotherapy and 61 received combination therapy. Baseline characteristics were balanced between the groups. The median time of hospitalization was 10 days for the combination and 11 days for the monotherapy group. The median time to discharge was statistically significantly lower in the combination therapy vs monotherapy group (HR, 1·67 (95% CI 1·03−2·7; P = 0·035). The hospital discharge rate was statistically significantly higher in the combination therapy vs monotherapy group in patients with less severe COVID-19 infections and those who were ≤60 years. There were no significant differences in clinical findings between the groups at 4, 8, 11, 15, and 29 days. Adverse events were comparable between the groups. There were two deaths, with one in each group.

Interpretation Combination oral favipiravir, camostat and, ciclesonide therapy could decrease the length of hospitalization stays without safety concerns in patients with moderate COVID-19 pneumonia. However, lack of hard clinical primary outcome is one of the major limitations of the study.

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Keywords: COVID-19; Camostat; Ciclesonide; Combination therapy; Favipiravir; Hospital stay; Randomized controlled trial; SARS-CoV-2

Introduction

Health authorities across the globe have approved repurposed drugs for treatment of ongoing coronavirus disease 2019 (COVID-19) pandemic and there are other strategies being employed for clinical management.[1] These therapeutic approaches include treatment with antivirals (lopinavir/ritonavir, favipiravir, remdesivir), anti-inflammatory agents (dexamethasone, hydroxychloroquine, colchicine),

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Research in context

Evidence before this study

We searched PubMED on June 2021 for studies using free text and related MeSH terms for hospital discharge following COVID-19 vaccination, using the terms "COVID-19 infections", "favipiravir (MeSH)", and drug combinations (MeSH)". We only considered studies published in English.

Added value of this study

Although combination regimens have been shown effective for COVID-19 infection, evidence is lacking for oral medications in combination form. This open-label phase 3 randomized study found that median discharge is significantly shorter with favipiravir, camostat, and ciclesonide combination therapy vs favipiravir monotherapy. We also found discharge rate was significantly higher in the combination therapy vs monotherapy group in patients with less severe COVID-19 infections and those who were ≤60 years.

Implications of all the available evidence

The overall safety and efficacy of favipiravir, camostat, and ciclesonide combination therapy make it a potential addition to the treatment arsenal for moderate COVID-19 infection. However, the lack of the hard clinical primary outcome in the study should be kept in mind.

and immuno-modulators (tocilizumab, sarilumab, siltuximab, anakinra, baricitinib, ruxolitinib, mavrilimumab, and itolizumab). Currently, combination treatment with the antiviral remdesivir and anti-inflammatory drugs, such as dexamethasone and immune therapies, are considered the optimal treatment strategy.[2] However, most of the treatments for COVID-19 are administered intravenously, which poses a significant challenge to treatment access for out-patients as well as for in-patients. This may result in poor treatment compliance rates impacting the overall treatment outcomes. Therefore, new and effective oral/inhaled treatments for COVID-19 are urgently needed.

Favipiravir is one of the repurposed oral antiviral drugs that was previously approved for a new and re-emerging influenza pandemic caused by SARS-CoV-2 by the Japan Pharmaceuticals and Medical Devices Agency in 2014. Favipiravir showed rapid viral clearance, radiological improvements, and was safe and effective in patients with moderate pneumonia in previous studies.[3-5] Favipiravir has now emerged as a potential antiviral drug for COVID-19 in China, Russia, and Japan, and more studies are underway in the USA, UK, and India.[3,6] Alternatively, corticosteroids have been recommended by the treatment guidelines to prevent inflammation that can lead to lung injury and multisystem organ dysfunction in patients with COVID-19 infections.[7] Ciclesonide is an inhaled corticosteroid that was previously shown to reduce local inflammation in the lungs and inhibit antiviral activity against SARS-CoV-2 in *in vitro* studies and clinical trials are being conducted to demonstrate the efficacy in mild COVID-19.[8,9] A recently phase 2 trial has shown that ciclesonide inhalation shortened SARS-CoV-2 viral shedding duration, and can potentially inhibit disease progression.[10] Camostat mesylate is a well-known oral serine protease inhibitor of the human transmembrane surface protease TMPRSS2, and it is a potential antiviral drug against COVID-19.[11] Previous studies have shown some beneficial effect of camostat mesylate administration in treating COVID-19 infections.[12] Multiple clinical trials are being conducted to assess the efficacy of camostat mesylate in decreasing viral load, hospitalization days, and mortality in patients with COVID-19 infections.[13]

The aforementioned drugs favipiravir, ciclesonide, and camostat have been approved for other indications without any substantial safety concerns. Blocking host receptors and enzymes involved in SARS-CoV-2 replication has been identified as a potential novel treatment strategy. SARS-CoV-2 entry and activation can occur via TMPRSS2 if it is co-expressed on the surface of target cells with ACE2.[14] Inhaled corticosteroids may also be useful in COVID-19 treatment because they reduce the expression of key proteins involved in virus entry into host cells.[15] COVID-19 genes have also been shown to be downregulated by inhaled corticosteroids. Because SARS-CoV-2 uses host proteases as its entry activators, inhibitors of these enzymes may provide therapeutic benefits against COVID-19 and SARS-CoV infections. Although evidence from randomized trials is not completely supportive, TMPRSS2 inhibitors administered in higher doses or during the very early phase of Covid-19 may be effective in hospitalized with COVID-19.[16] Among non-hospitalized patients who were treated with ciclesonide were less likely to have a subsequent emergency department visit or hospital admission for reasons related to COVID-19 by day 30 vs placebo.[17]

Although ciclesonide and camostat have been shown to be potentially effective against COVID-19, there are no well-established outcomes on the efficacy of these drugs in combination with favipiravir. Theoretically, the combination of these drugs may provide synergistic effects due to different mechanisms of action. The purpose of this randomized phase 3 clinical study was to evaluate the potential clinical benefits and safety of combining favipiravir with camostat and ciclesonide in patients with moderate COVID-19 pneumonia (Trial Registration: jRCTs031200196).

Methods

Study design

This was an investigator-initiated, single-center, prospective, parallel-group, open-label, exploratory,

randomized controlled trial assessing the safety and efficacy of combination therapy in hospitalized patients with COVID-19 pneumonia who were not receiving mechanical ventilation. The study was registered under trial registration rctportal.niph.go.jp Identifier: jRCTs031200196. The study included registered cases between November 11, 2020, and May 31, 2021 at the International University of Health and Welfare Narita Hospital in Japan.

This study was designed and conducted according to the protocol (Appendix 1) and Declaration of Helsinki; Clinical Trials Act Enforcement Regulations; Ordinance of the Japanese Ministry of Health, Labor, and Welfare; and Japanese Good Clinical Practice (GCP). Prior ethical approval for the protocol and the informed consent document was obtained from the Tokyo Medical and Dental University, Certified Review Board (CRB; Approval No NR2020-003), and each participating hospital investigator received permission from the administrator to conduct the study, after which the representative physician submitted the explanatory and consent documents to the Ministry of Health, Labor, and Welfare (MHLW) in Japan. This trial is registered and recorded in the Japan Registry of Clinical Trials (jRCT; jRCTs031200196), and research only commenced after the jRCT release. All patients provided written informed consent for participation in the study.

Participants (inclusion and exclusion criteria)

Patients (≥20 years of age) who were hospitalized during the study drug administration period were eligible for enrolment. Other inclusion criteria included patients who were positive for SARS-CoV-2 according to polymerase chain reaction (PCR) or loop mediated isothermal amplification methods, diagnosed with COVID-19 by other tests approved by the MHLW, and high-resolution computer tomography (HRCT) confirmed clear pneumonia due to COVID-19. The severity criteria are based on the Japanese government's official clinical guide.[18] The severity is divided into four categories: mild, moderate I, moderate II, and severe. A moderate participant (with pneumonia) was included in this study. No patients received a vaccination for COVID-19 as they were enrolled prior to the start of a vaccination program in Japan. Premenopausal female patients were included if they were able to confirm a negative pregnancy test before administration of the study drug. Patients were excluded if they received systemic administration of a drug suggested to have an antiviral inhibitory effect on SARS-CoV2 within 28 days before the date of consent acquisition. Patients who were using inhaled or oral steroids and those who could not inhale ciclesonide using an inhalation assist device were also excluded. Recurrence or reinfection of COVID-19 with evident respiratory infection complications other than COVID-19 (chronic infections, mycobacteriosis, mycosis, etc.), and those suspected of having congestive heart failure, severe liver dysfunction equivalent to Grade C in the Child-Pugh classification system, with renal dysfunction requiring dialysis, suspected of having immunodeficiency diseases such as HIV infection, impaired consciousness such as disorientation, with hereditary xanthinuria, with hyperuricemia (<1 mg/dL) or xanthine urolithiasis, with uncontrolled gout or hyperuricemia, with a history of hypersensitivity to favipiravir, camostat, or ciclesonide were also excluded as well as severe cases requiring ICU admission, artificial respiration, and extracorporeal membrane oxygenation (ECMO) support. Patients who were deemed inappropriate as subjects by the study investigators, such as those who are not cooperative, do not obey directions, and/or do not follow rules (e.g., do not take medication on time), were excluded. Patients were withdrawn from the study if they had a very high risk of deterioration or if there was a need for mechanical ventilation as predefined in the rescue protocol.

The patients who were not able to use inhaled or oral medicine due to disease progression during the study period were permitted to drop out and per the rescue protocol could use intravenous medications such as remdesivir and dexamethasone.

Randomization and masking

Eligible participants were randomly assigned in a 1:1 ratio using a stratified block randomization method to receive either monotherapy (favipiravir) or combination therapy (favipiravir + camostat + ciclesonide). Favipiravir was administered to all participants in both groups for 10 days, or until the patient was discharged. Factors that randomization was stratified by (50 years or older, less than 50 years), gender, severity of disease, and presence or absence of complications (with or without any of the following complications: diabetes, ischemic heart disease, chronic respiratory disease). Co-author R.F determined the randomization scheme (Stratified block randomization), block size, and allocation adjustment factors, which were then implemented into the Electronic Data Capture (EDC) system by an assigned data manager in the independent data center. The allocation result was displayed on the system [EDC; REDCap (Research Electronic Data Capture; 10.0.20 (https://www.project-redcap.org/)] by inputting and confirming the necessary items such as the allocation adjustment factor in the EDCAs this was an open-label study, no blinding or masking was used. Accounts with the ability to perform data entry and allocation were only given to investigators who had been approved by the ethics committee. The Investigators used a web browser to access and use the EDC because we used an Application Service Provider.

Procedures

Patients in both groups received favipiravir 200 mg tablets at a loading dose of 1,800 mg (9 tablets) twice daily

on day 1 (9 tablets) followed by 800 mg (4 tablets) twice daily. This dosage was higher than the approved dosage for influenza virus infections considering that systemic side effects are less likely to occur.

Patients randomized to the combination therapy group received camostat 200 mg orally thrice a day and ciclesonide 400 μg (two inhalations of 200 μg) thrice daily for 10 consecutive days.

The date of hospitalization was considered as day 0 and the day starting study drug administration was day 1. Day 0 and day 1 were the same for the majority of patients. However, they were not the same in some patients because such patients were admitted to the hospital at night (e.g., 11:00 p.m., day 0 and agreed to participate in the study), but such patients did not begin the study (e.g., take medication at next 8:00 am, day 1). The study period was divided into a 10-day administration period and a post-observation period. The medical history, baseline, demographic and other characteristics, and vital signs were collected on day 0 or day 1. Blood samples were also collected for laboratory tests on day 0 or day 1. Vital signs such as body temperature, blood pressure, pulse, oxygen saturation (SpO_2), oxygen usage, and respiratory rate were assessed at day 0 or days 1, 4, 8, 11, 15, and 29. Hematological, coagulation function assessments, biochemical tests and immunological assessments, SARS-CoV2 viral genome load, chest X-ray (day 0 or days 1, 4, 8, 11, 15, 29) and HRCT day 0, or days 1, 8, 15, and 29 (or at the time of cancellation) were carried out.

Clinical outcomes

The primary outcome of this study was the length of hospitalization duration due to COVID-19 pneumonia; the monotherapy and combination therapy groups were compared.

The hospitalization period was calculated from admission to patient discharge based on the clinical management guide of COVID-19 for front-line healthcare worker by the Japanese Ministry of Health, Labour and Welfare in Japan (MHLW) (used version at the time, version 3·0; current latest version, version 6·0) including "Criteria for release from accommodation facility care" for patient with symptoms discharge is possible: 1) 10 days after the date of onset and 72 hours after the resolution of symptoms (he definition of "the resolution of symptoms": when fever subsides without any antipyretics and respiratory symptoms such as cough, difficulty in breathing, improve); 2) 24 hours after the resolution of symptoms if the patient has tested negative with the PCR test twice within at least 24 hours between tests; 3) if the patient could not be discharged due to social reasons, the number of days until the discharge criteria were met were used for evaluation. At the time this study was conducted in Japan, the MHLW required that patients be discharged from hospital in accordance with the above discharge criteria, and these criteria was strictly followed in our medical institutions as well as most of hospitals in Japan. As a result, we designed the study with these discharge criteria in mind, as well as length of hospitalization as an objective endpoint consistent with the patient's interests.

The secondary endpoints included changes in the clinical, laboratory, and imaging findings overtime at 4, 8, 11, 15, and 29 days after treatment. The changes in clinical findings included changes in body temperature, oxygen usage, respiratory rate, oxygen saturation, severity, ventilator attachment, ECMO use, ICU management, and other concomitant medications. The changes in laboratory findings included changes in Alb, lymphocyte count, C-reactive protein (CRP), D-dimer, PIC, turnaround time (TAT), white blood cell count, platelet count, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatinine kinase (CK), creatinine, blood urea nitrogen (BUN), sodium, potassium, glucose, uric acid, procalcitonin, ferritin, and interleukin-6 (IL-6). The SARS-CoV2 virus genome amount (days 8, 15, 29, or the day before discharge or the day of discharge) was assessed. The presence or absence of antibody (IgM, IgG) production (only on days 8, 15, and 29) was also evaluated.

The exploratory endpoints were changes in scored severity, SpO_2, and evaluation of changes on chest CT. The following scoring method was employed for evaluation of severity: computation of severity scores on days 4, 8, 11, 15, and 29, improvement of 2 grades = +2 points, improvement of 1 grade = +1 point, no change = 0 points, deterioration of 1 grade = 3 points, and deterioration of 2 grades = 5 points; for severity assessments, the criteria of the novel coronavirus Infection Medical Practice Guideline guide version 3·0 was used.[18] For evaluation of SpO_2 changes, the following scoring method was used: if $SpO_2 \geq 96\%$ in room air = 0 points, $93\% \leq SpO_2 < 96\%$ in room air = 1 point, $90\% \leq SpO_2 < 93\%$ in room air = 2 points, $SpO_2 \geq 90\%$ maintained with the use of an oxygen cannula at 1−2 L/min= 3 points, $SpO_2 \geq 90\%$ maintained with the use of an oxygen at 3 −4 L/min = 4 points, oxygen therapy with a mask, reservoir bag = 5 points, non-invasive positive pressure ventilation, high flow nasal oxygen = 6 points and artificial ventilation, and ECMO = 7 points.

For evaluation of pneumonia based on HRCT, the following scoring was used: marked improvement = +2 points, slight improvement = +1 point, no change = 0 points, slight exacerbation = 3 points, and marked exacerbation = 5 points.

The safety endpoint was the incidence of adverse events (AEs), including abnormal changes in vital signs, laboratory test values, and physiological function tests.

Sample size

We determined that 118 patients (favipiravir monotherapy: 59 patients, and favipiravir combination therapy group: 59 patients) would provide greater than 80% power to detect a hazard ratio (HR) of 1·8 as a target effect for the combination therapy group vs the monotherapy group using a 2-sided significance level of 0·05, assuming a 15% dropout. A total of 97 events was expected. As no prior data were available on the effect on the length of hospitalization in the combination therapy group, we assumed that the median length of hospitalization with combination therapy would be shorter at 2·22 days than the median length with favipiravir monotherapy. As one of the discharge criteria of the MHLW included 10 days having passed since onset, 10 days were subtracted from the assumed median length of hospitalization of 15 days in the monotherapy group to obtain 5 days, and 10 days were subtracted from the assumed median length of hospitalization of 12·78 days in the combination therapy group to obtain 2·78 days (HR 1·8). However, even with a slightly smaller effect size (HR=1.67; 2 days shorter), we still have 70% power for the primary analysis (as noted in the protocol). Intention-to-treat analysis was used for evaluation of the primary endpoint.

Statistical Analysis

Regarding the length of hospitalization, survival curves were created for each group using the Kaplan–Meier (KM) method. To calculate the 95% confidence interval (CI) for the median number of days of hospitalization, the Brookmeyer and Crowley method was used.[19] Patients with a length of hospitalization of >1 month (28 days) were censored at 28 days. Furthermore, censoring of death was considered as 28 days as per McCaw's et al.[20] An intergroup comparison was conducted with a stratified log-rank test with an allocation factor [age (≥60 years, <60 years)], sex (male, female), severity (moderate I, pneumonia without oxygen usage; moderate II, pneumonia with the requirement of additional oxygen support), and complications (presence or absence) as a stratum. Similarly, with the allocation factor as the covariate, the HR of the combination therapy group versus the monotherapy group was calculated along with the associated 95% CI using Cox's proportional hazard model. Subgroup analyses were conducted for allocation factors that were pre-defined, as well as for body mass index (BMI) and smoking history, which were considered as post-hoc. We conducted a landmark analysis starting from days 2, 3, and 5 and an analysis that censored patients at the time of progression to evaluate the delayed effect of combination therapy.

Significance testing for the primary endpoint was performed at the 2-sided 0·05 level. No significance testing and no adjustment for multiple testing for secondary outcomes was performed. SAS version 9·4 (SAS Institute Inc.) was used for analyses, tabulations, and chart output.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. J.T, Y.T, and K.T had full access to the all data of each subject in the hospital. J.T and K.T took the decision to submit for publication.

Results

Subjects

Between November 11, 2020 and May 31, 2021, the study enrolled 121 patients and assessed them for eligibility. A total of 119 were randomized into two groups. Two of the screened patients were excluded for not meeting the study criteria. A total of 57 patients were randomized to monotherapy and 62 patients were randomized to combination therapy. One patient from the monotherapy group was excluded as the study treatment was not administered, and one patient from the combination therapy group was excluded due to duplicate registration. During the study, there were two deaths, one each in the monotherapy and combination therapy groups. In the combination therapy group, three patients were lost to follow-up. Overall, 56 patients received monotherapy and 61 patients received combination therapy and were included in the intent-to-treat (ITT) population (Figure 1). A total of seven patients (12·5%) from the monotherapy group and eight patients (13·1%) from the combination therapy group were withdrawn based on the investigator's judgment of the patient's condition and were treated per the rescue protocol.

The baseline characteristics were balanced between the monotherapy and combination therapy groups (Table 1). The mean age of the ITT population across the study was 57 to 59 years and the majority were male in both treatment groups (64%, 66%). The duration from onset of symptoms to hospitalization was about six days in both groups. All patients had moderate COVID-19 disease at baseline.

Time to hospital discharge in patients receiving combination therapy vs. monotherapy

The summary of time to hospital discharge in patients receiving monotherapy and combination therapy is shown in Table 2. The monotherapy group showed a median time to discharge of 11 days (95% CI of 11–12) and the combination therapy group showed a median time of 10 days (95% CI of 9–11). The time to discharge was statistically significantly lower in the combination therapy group compared to the monotherapy group (HR, 1·67 (95% CI 1·03–2·7; P = 0·035; Table 2).

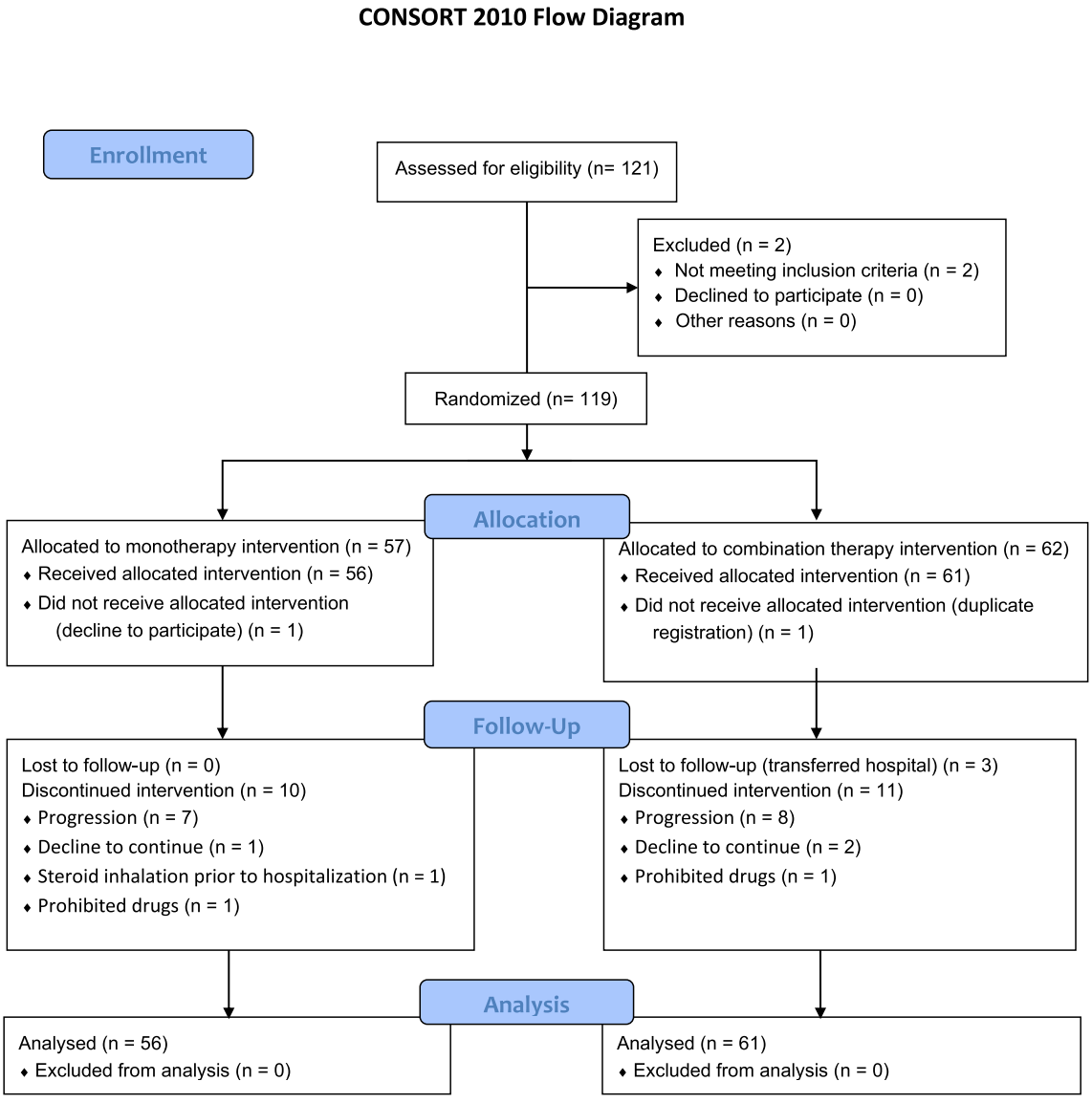

Figure 1. Flow diagram for the patients enrolled.

Landmark analysis without early withdrawal effects revealed no significant difference in estimated hazard ratio. Both FAS/ITT (full analysis set/intention to treat) and PPS (per protocol set) produced comparable results (Supplementary Table 1 and 2). The rates of hospital discharge were higher in the combination therapy group compared to the monotherapy group between days 7 and 14 as shown by the KM plot (Figure 2). Subgroup analyses based on baseline factors, such as age, severity, and smoking status, showed the combination therapy group as compared to monotherapy group had a statistically significantly higher hospital discharge rate in patients aged ≤60 [HR, 2·92 (95% CI 1·37–6·19)], with less severe disease [Moderate I, HR, 2·01 (95% CI 1·13–3·61)], and among non-smokers [HR, 1·99 (95% CI 1·04–3·81); Figure 3]. Supplementary Figure 1 presents the HRs for all subgroups. Also, the proportion of patients discharged after complete recovery was higher in the combination therapy group compared to the monotherapy group (Figure 4).

On day 4, 20 patients (37·7%) in the monotherapy group and 24 patients (41·4%) in the combination therapy group received supplemental oxygen. There was a general decrease in the proportion of patients reported with oxygen administration in both the treatment groups on days 8,11, and 15, and by day 29 no patients required supplemental oxygen (Table 3).

	Monotherapy (n=56)	Combination therapy (n=61)
Characteristics		
Age (years)	57.2 (13.6)	59.5 (13.7)
median (Q1, Q3)	57.5 (49.0, 67.5)	62.0 (49.0, 70.0)
<= 40	7 (12.5%)	5 (8.2%)
>40, <=50	8 (14.3%)	13 (21.3%)
>50, <=60	15 (26.8%)	11 (18.0%)
>60, <=70	15 (28.6%)	18 (29.5%)
>70, <=80	9 (16.1%)	12 (19.7%)
>80, <=90	1 (1.8%)	2 (3.3%)
Sex (male)	37 (66.1%)	39 (63.9%)
BMI	25.7 (4.2)	26.0 (4.4)
median (Q1, Q3)	25.7 (22.3, 28.1)	25.4 (22.7, 28.3)
Ethnicity		
Japan	56 (100%)	61 (100%)
Duration of the symptom to admission to hospital, days	6.4 (2.6)	6.3 (2.3)
Severity of disease at baseline		
Mild (pneumonia-)	0 (0%)	0 (0%)
Moderate I (pneumonia+, respiratory failure-)	38 (67.9%)	39 (63.9%)
Moderate II (pneumonia+, respiratory failure+)	18 (32.1%)	22 (36.1%)
Severe (artificial ventilation or ECMO in ICU)	0 (0%)	0 (0%)
Comorbid disease		
Diabetes Mellites	11 (19.6%)	18 (29.5%)
Cardiovascular disease	3 (5.4%)	0 (0%)
Chronic pulmonary disease	7 (12.5%)	4 (6.6%)
Smoking history		
Never smoker	34 (60.7%)	44 (72.1%)
Currently or former smoker	22 (39.3%)	17 (27.9%)
(Brinkman index)	695.7 (616.8)	523.6 (713.3)
Laboratory findings		
C-reactive protein (mg/dL), median (Q1, Q3)	5.88 (1.35, 9.86)	4.87 (1.73, 7.45)
Procalcitonin (ng/ml), median (Q1, Q3)	0.07 (0.05, 0.10)	0.07 (0.05, 0.11)
Lactate dehydrogenase (U/dL), median (Q1, Q3)	289.5 (240.0, 333.0)	274.5 (248.5, 343.0)
D-dimer (μg/ml), median (Q1, Q3)	0.69 (0.48, 0.82)	0.60 (0.42, 0.89)

***Table 1*: Baseline characteristics of participants (ITT).**
Data are means (±SD) or n (%) otherwise stated. BMI, body-mass index is the weight in kilograms divided by the square of the height in meters; ECMO: extra-corporeal membrane oxygenation; ICU: Intensive care unit; ITT: Intent-to-treat; SD: Standard deviation.

Clinical and laboratory findings in patients receiving combination therapy vs. monotherapy

No significant differences at study days 4, 8, 11, 15, and 29 were observed between the monotherapy and combination therapy groups regarding changes in clinical findings such as body temperature, oxygen usage, respiratory rate, oxygen saturation, severity, ventilator attachment, ECMO use, ICU management, and other concomitant medications. There were no significant differences in the laboratory findings; that is, Alb, lymphocyte count, CRP, D-dimer, PIC, TAT, white blood cell count, platelet count, bilirubin, AST, ALT, LDH, ALP, CK, creatinine, BUN, sodium, potassium, glucose, uric acid, and procalcitonin between the groups at days 4, 8, 11, 15, and 29. The majority of patients had negative test results for the SARS-CoV2 virus genome in both groups and there was no significant difference between the groups. Severity scores and pneumonia scores did not show any significant difference between the groups.

Adverse effects with combination therapy vs. monotherapy

The number of AEs were comparable in the monotherapy and combination therapy groups (57·1% and 55·7%, respectively; Table 4). The overall rate of serious adverse events (SAEs) was low; there was one SAE reported in the monotherapy group and no SAEs were reported in the combination therapy group. Overall, two deaths were reported, with one in each group. The patient who died in the monotherapy group experienced an acute pulmonary thromboembolism on day 7, as shown by pathological anatomy. The patient was stable and had no respiratory failure at that time. As per the

	Monotherapy (n = 56)	Combination therapy (n = 61)	Hazard ratio (95% CI)	P value**
Primary endpoints				
Primary analysis				
Time to hospital discharge, median (95%CI) (days)	11 (11-12)	10 (9-11)	1.672 (1.034-2.704)	0.035
Death, n (%)	2 (4%)	1 (2%)		
Secondary analysis				
Landmark analysis (2 days)			1.634 (1.008, 2.650)	–
Landmark analysis (3 days)			1.772 (1.076, 2.919)	–
Landmark analysis (5 days)			1.954 (1.166, 3.275)	–
Time to hospital discharge without progression, median (95%CI) (days)	11 (11-12)	10 (9-11)	1.567 (0.961-2.555)	–
Progression or death, n (%)	8 (14%)	8 (13%)		
Safety endpoints				
Any adverse event, n (%)	32 (57.1%)	34 (55.7%)		–
Blood uric acid increased*	28 (50.0%)	30 (49.2%)		–
Liver function abnormal*	4 (7.1%)	1 (1.6%)		–
Serious adverse event, n (%)	1 (1.8%)	0 (0.0%)		–

***Table 2*: Time to hospital discharge who received combination therapy as compared with monotherapy (ITT).**
CI, confidence interval.
* Adverse events occurred in > 5% are shown.
** Stratified log-rank test.

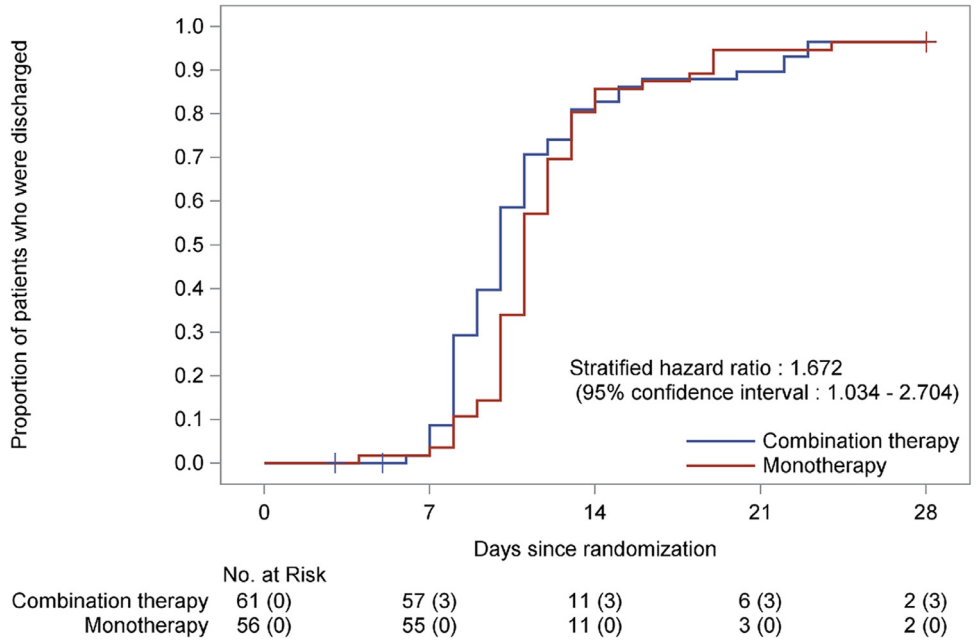

Figure 2. Proportion of Patients Who Were Discharged in the Monotherapy and Combination Therapy Groups.
Numbers at risk at day 14, 21 and 28 include one death in each treatment group as per the statistical analysis. The combination therapy group as compared to monotherapy group had a statistically significantly higher hospital discharge rate.

investigator's assessment, the event was not related to the study treatment. The patient who died in the combination therapy group was 73-years-old and had a heavy smoking history, hypertension, COPD, and a medical history of brain infarction. At day 3, respiratory failure had progressed severely (the patient was not able to use an inhaler and take medicine), and the patient was withdrawn from the study and received non-study treatments. The patient was reported to have died on day 12.

Most of the AEs reported in the study were related to laboratory test abnormalities (51·8% in monotherapy and 52·5% in combination therapy groups). Liver

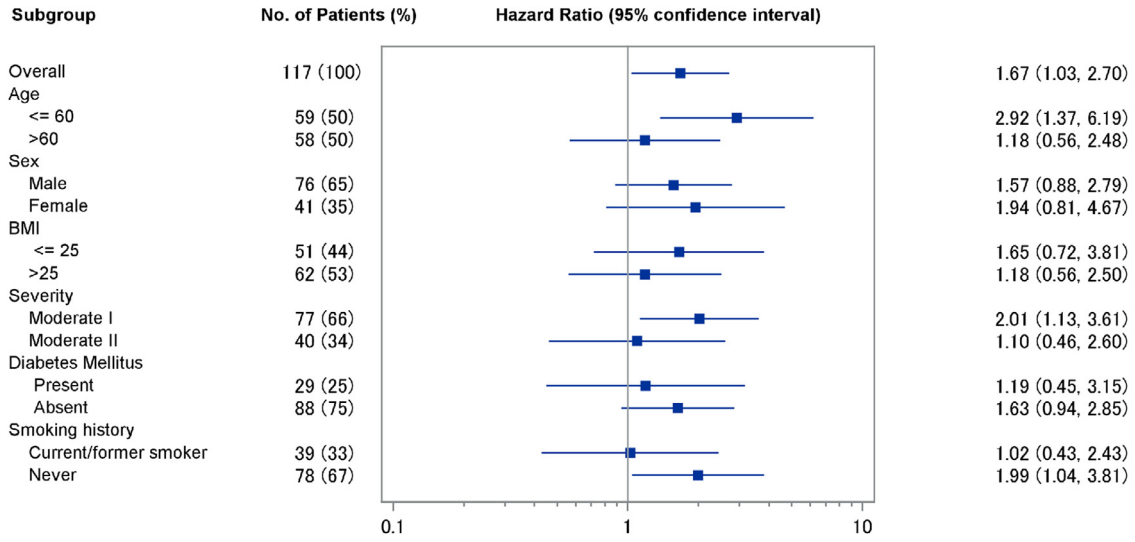

Figure 3. Hazard Ratio of Hospital Discharge Rates in the Treatment Groups Stratified by Subgroups.

The combination therapy group as compared to monotherapy group had a statistically significantly higher hospital discharge rate in patients aged ≤60 [HR, 2·92 (95% CI 1·37—6·19), with less severe disease [Moderate I, HR, 2·01 (95% CI 1·13—3·61)], and among non-smokers [HR, 1·99 (95% CI 1·04—3·81)].

dysfunction was reported in a higher percentage of patients in the monotherapy group compared to the combination therapy group (7·1% versus 1·6% in monotherapy and combination therapy groups, respectively). Oral candidiasis, generally associated with ciclesonide, was observed in one patient in the combination therapy group, and no such cases were reported in the favipiravir monotherapy group (Supplementary Table 3).

Discussion

In this study, the efficacy of favipiravir + camostat + ciclesonide inhaler combination therapy for the aggravation of COVID-19 pneumonia was evaluated as compared to favipiravir therapy alone. Since antivirals are only likely to have any effect if started within the first few days of symptom onset, both groups adopted antivirals-favipiravir to prevent patients with pneumonia in the early stages from disease progression or minimize deterioration. This study showed that administration of the combination therapy resulted in a statistically significantly shorter length of hospital stay compared to the favipiravir monotherapy. Although the primary outcome was "hospitalization," we did analyze the time (duration) from the onset to discharge for all patients. The median difference was the same (not statistically significant, partly because some patients were unable to be admitted to hospitals due to the pandemic situation in Japan at the time). Further, a higher proportion of patients were discharged between day 7 to day 14 of treatment in the combination therapy group compared to the monotherapy group. The hospital discharge rate was statistically significantly higher in the combination therapy for overall group and also in the subgroups of patients with lesser disease severity (i.e., pneumonia without oxygen demand) and younger age group (≤60 years). The overall safety profile of the combination therapy was comparable to that of monotherapy and the combination therapy was safe and tolerated well by the combination therapy group. However, the efficacy of both monotherapy and combination therapy seems limited for patients with greater disease severity, as a total of seven patients (12·5%) from the monotherapy group and eight patients (13·1%) from the combination therapy group did not show any improvement in their clinical condition and were withdrawn from the study. All withdrawn patients were treated per the rescue protocol. Among these patients, three were transferred to another hospital in another medical region as a result of the Governor's instructions/adjustment to accommodate many returnees and foreigners with COVID-19, which was not our intention. We contacted the patients and/or each hospital at the time, and two of these three patients were transferred to another hospital twice due to regional reasons, indicating the difficulty in scientifically precise follow-up. As long as they were followed, they were all included in the ITT analysis; the three patients who were truly withdrawn were censored at the time of withdrawal in the time-to-event analyses. Due to the aforementioned reasons, these transfers occurred quite coincidentally in only one combination group. Such patients, however, were found in both groups and

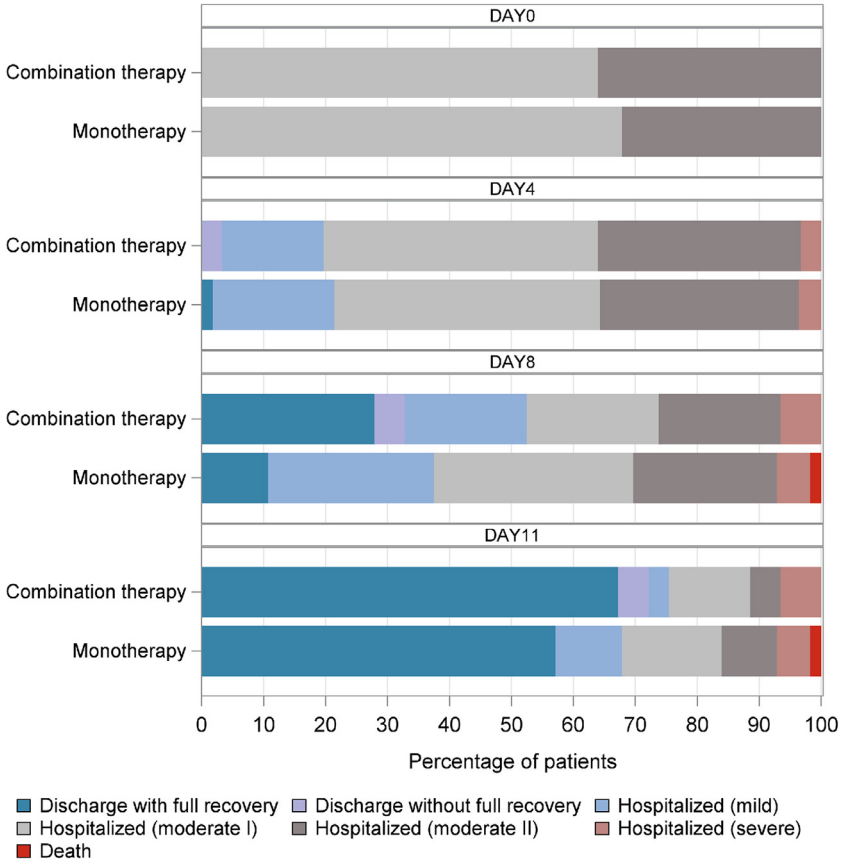

Figure 4. Proportion of Patients Discharged After Complete Recovery in Patients Receiving Monotherapy or Combination Therapy. The higher proportion of patients discharged after complete recovery was observed in the combination therapy group compared to the monotherapy group at Day 8 and 11.

were subjected to a rescue (withdraw) protocol. In this study, landmark analysis without early withdrawal effects revealed no significant difference in estimated hazard ratio. In addition, both FAS/ITT and PPS produced comparable results.

Multiple studies have demonstrated the efficacy of combination therapies compared to the monotherapy approach.[21] In this study, we used a combination therapy that included the oral/inhaled drug combination of favipiravir, camostat, and ciclesonide. To the best of our knowledge, oral medications in a combinatorial form have not been studied extensively for treatment of patients, although some oral monotherapies are being studied.[22] The development of oral treatment is expected to increase the ease of administration and increase compliance and decrease the burden on healthcare systems.

A previous study analyzed the clinical course of 1,099 patients diagnosed with COVID-19 throughout China, and the results indicated the median length of hospital stays was 12·0 days.[23] In this study, the median time to discharge was 11 days in the favipiravir monotherapy group, while the combination therapy group had a median time to discharge of 10 days, with the difference being statistically significant. These numbers differed probably due to differences in the severity and presence or absence of pneumonia, in addition to the number of cases and discharge criteria.

Previous studies on favipiravir monotherapy have shown a clinical benefit and reduction in clinical deterioration rates compared to standards of care.[4] In this study, favipiravir monotherapy showed a shorter time to discharge from hospitalization in patients with moderate COVID-19, compared to the previous studies, while the combination therapy was found to be slightly more effective in decreasing the length of hospital stay. The combination therapy group also showed statistically significantly higher discharge rates among the subgroups with moderate COVID-19 infections (with pneumonia and without respiratory failure; Moderate I group) and in the younger age subgroup of patients ≤65-year-old. Although the favipiravir monotherapy and combination therapy were shown to decrease the hospitalization duration in the overall study population, the disease progression was observed in 12·5%–13·1% patients. Therefore, even when favipiravir or combination therapy is

Point in time		Monotherapy N = 56		Combination Therapy N = 61		Risk difference (95% CI)*
		N	Percentage (%)	N	Percentage (%)	
Day 4	With administration	20	37·7	24	41·4	3.6 (-15.4 to 22.2)
	No administration	33	62·3	34	58·6	
Day 8	With administration	16	32·7	14	25·9	-6.7 (-24.9 to 11.2)
	No administration	33	67·3	40	74·1	
Day 11	With administration	4	10·5	8	23·5	13.7 (-3.5 to 32.3)
	No administration	37	90·2	26	76·5	
Day 15	With administration	2	22·2	1	10·0	-12.2 (-51.4 to 25.6)
	No administration	7	77·8	9	90·0	
Day 29	With administration	0	0·0	0	0·0	0.0 (NE)
	No administration	35	100·0	34	100·0	

***Table 3*: Summary of Oxygen Administration in the Monotherapy and Combination Therapy Groups (ITT).**
CI: Confidence interval; NE: Not evaluable.
*CI of risk difference was calculated using exact method.

	Monotherapy N = 56	Combination Therapy N = 61
Any adverse event, n (%)	32 (57·1%)	34 (55·7%)
Blood uric acid increased*	28 (50·0%)	30 (49·2%)
Liver function abnormal*	4 (7·1%)	1 (1·6%)
Oral candidiasis	0 (0·0%)	1 (1·6%)
Serious adverse event, n (%)	1 (1·8%)	0 (0·0%)
Death	1 (2%)	1 (2%)

***Table 4*: Summary of Adverse Events in the Monotherapy and Combination Therapy Groups (Safety Population).**

administered, the administration of standard therapies, including remdesivir and dexamethasone, should not be delayed.

There was no substantial impact of add-on therapy on other clinical parameters such as body temperature, oxygen usage, respiratory rate, oxygen saturation, severity, ventilator attachment, ECMO use, and ICU management. No impact of add-on therapy was found on laboratory findings, such as Alb, lymphocyte count, CRP, D-dimer, PIC, TAT, white blood cell count, platelet count, bilirubin, AST, ALT, LDH, ALP, CK, creatinine, BUN, sodium potassium glucose, uric acid, procalcitonin levels.

The overall rate of adverse event rates was similar in the monotherapy and combination therapy groups. There was no indication of add-on therapy leading to higher rates of AEs. In this study, an increase in blood uric acid levels and liver function abnormalities were frequently reported AEs in both study groups. These results are similar to previous studies on favipiravir (package insert for favipiravir). Notably, the AEs commonly associated with the add-on treatment were not reported at a substantial rate in this study (package inserts for camostat and ciclesonide). No anaphylactic reactions were reported in the monotherapy and combination therapy groups. Therefore, the combination therapy treatment regimen was well tolerated.

There were a few limitations in this study including lack of hard clinical primary outcome, no standard care, lack of multiple endpoints and multiple comparisons, and relatively small sample size. We recognize that the double-blind placebo control study is the appropriate study design to accurately evaluate the efficacy of drugs. Since many Japanese physicians and patients recognized Favipiravir as potential effective treatments (not approved; off-label use or clinical trials with informed consent and patients' signature) at the timing of the study, we thought it difficult to conduct placebo-controlled trials. Although it was very important to accurately measure the efficacy of individual drugs, it was deemed more important to evaluate the superiority of the three-drug combination over the monotherapy in this study. Our primary interest was to evaluate the effect of combining three different modes of action and to determine the outcome of combining camostat with the two drugs. We could not assess data on the subtypes alpha or delta and have no plan to assess omicron further. The safety profiles for monotherapy and combination therapy were generally similar. The use of polytherapies has been generally reported to be associated with higher toxicity.[24] The reason for the lack of

difference in the adverse event rate in the study could be due to the study not being powered to detect a difference in adverse event rates between treatment groups, resulting in a smaller sample size. Also, the shorter study duration and small sample size could be another factor. Further larger studies are needed to confirm the findings.

Overall, administration of oral favipiravir along with the add-on therapy of oral camostat and inhaled ciclesonide could be beneficial in decreasing the duration of hospitalization, leading to faster discharge rates, without any major safety concerns. The adoption of oral/inhaled combination treatment of favipiravir + camostat + inhaled ciclesonide can increase treatment access with better outcomes and decrease the strain on healthcare systems. Although the efficacy of these oral/inhaled treatments was suboptimal for patients with progression to severe disease, the treatments are likely more beneficial for younger age groups (≤60 y) and in patients with less severe COVID-19 pneumonia who do not require oxygen therapy.

Contributors

JT, TK, and KT wrote the manuscript. JT, RF, TK, and KT designed, planned the study, and verified the underlying data. TK and RF managed data and analyzed data. JT, YH, TK, YT, YI, TK, HT, YT, and KT contributed to data collection or characterization of samples. All authors had full access to all the data in the study and accept responsibility for the decision to submit this manuscript for publication.

Declaration of interests

J.T has received funding from Teijin Pharma Ltd as part of a collaborative research project with Chiba University and Teijin Pharma Ltd. Other authors declare that they have no conflict of interest.

Data sharing protocol

Study protocol and informed consent form were shared. We do not plan to share the original data because we obtained the consent from the participants that their data be used solely for this study but not for other purposes.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101484.

References

1 Saber-Ayad M, Saleh MA, Abu-Gharbieh E. The rationale for potential pharmacotherapy of COVID-19. *Pharm Basel Switz*. 2020;13:96.
2 Cantini F, Goletti D, Petrone L, Najafi Fard S, Niccoli L, Foti R. Immune therapy, or antiviral therapy, or both for COVID-19: a systematic review. *Drugs*. 2020;80:1929–1946.
3 Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. *Int J Infect Dis*. 2021;102:501–508.
4 Shrestha DB, Budhathoki P, Khadka S, Shah PB, Pokharel N, Rashmi P. Favipiravir versus other antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis. *Virol J*. 2020;17:141.
5 Shinkai M, Tsushima K, Tanaka S, et al. Efficacy and safety of favipiravir in moderate COVID-19 pneumonia patients without oxygen therapy: a randomized, phase III clinical trial. *Infect Dis Ther*. 2021;10:2489–2509. https://doi.org/10.1007/s40121-021-00517-4.
6 Arab-Zozani M, Hassanipour S, Ghoddoosi-Nejad D. Favipiravir for treating patients with novel coronavirus (COVID-19): protocol for a systematic review and meta-analysis of randomised clinical trials. *BMJ Open*. 2020;10: e039730.
7 COVID-19 treatment guidelines panel. Coronavirus disease 2019 (COVID-19) treatment guidelines [Internet]. National Institutes of Health. Available from: https://www.covid19treatmentguidelines.nih.gov/. Accessed on 1 December 2021.
8 Deokar K, Agarwal M, Dutt N, et al. A review of Ciclesonide in COVID-19. Still a long way to go. *Adv Respir Med*. 2021;89:79–81.
9 Terada-Hirashima J, Suzuki M, et al. Efficacy and safety of inhaled ciclesonide in treating patients with asymptomatic or mild COVID-19 in the RACCO trial: protocol for a multicenter, open-label, randomized controlled trial. *JMIR Res Protoc*. 2020;9:e23830.
10 Song J-Y, Yoon J-G, Seo Y-B, et al. Ciclesonide inhaler treatment for mild-to-moderate COVID-19: a randomized, open-label, phase 2 trial. *J Clin Med*. 2021;10:3545.
11 Hoffmann M, Hofmann-Winkler H, Smith JC, et al. Camostat mesylate inhibits SARS-CoV-2 activation by TMPRSS2-related proteases and its metabolite GBPA exerts antiviral activity. *EBioMedicine*. 2021;65: 103255. https://doi.org/10.1016/j.ebiom.2021.103255.
12 Hofmann-Winkler H, Moerer O, Alt-Epping S, et al. Camostat mesylate may reduce severity of coronavirus disease 2019 sepsis: a first observation. *Crit Care Explor*. 2020;2:e0284.
13 Breining P, Frølund AL, Højen JF, et al. Camostat mesylate against SARS-CoV-2 and COVID-19—Rationale, dosing and safety. *Basic Clin Pharmacol Toxicol*. 2021;128:204–212.
14 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020;181:271–280.e8.
15 Finney LJ, Glanville N, Farne H, et al. Inhaled corticosteroids downregulate the SARS-CoV-2 receptor ACE2 in COPD through suppression of type I interferon. *J Allergy Clin Immunol*. 2021;147:510–519.e5.
16 Gunst JD, Staerke NB, Pahus MH, et al. Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial. *EClinicalMedicine*. 2021;35: 100849.

17 Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA Intern Med*. 2022;182:42–49.

18 Clinical management of patients with COVID-19. A guide for front-line healthcare worker version 3.0 Issued by Ministry of Health, Labour and Welfare in Japan. (in Japanese. current latest version: version 6.0) [Internet]. 2021. Available from: https://www.mhlw.go.jp/content/000829136.pdf. Accessed on 1 December 2021.

19 Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*. 1982;38:29–41.

20 McCaw ZR, Tian L, Vassy JL, et al. How to Quantify and Interpret Treatment Effects in Comparative Clinical Studies of COVID-19. *Ann Intern Med*. 2020;173:632–637.

21 Coppock D, Baram M, Chang AM, et al. COVID-19 treatment combinations and associations with mortality in a large multi-site healthcare system. *PLOS ONE*. 2021;16: e0252591.

22 [preprint] Fischer W, Eron JJ, Holman W, et al. Molnupiravir, an oral antiviral treatment for COVID-19. *MedRxiv Prepr Serv Health Sci*. 2021. 2021.06.17.21258639.

23 Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382: 1708–1720.

24 Doi Y, Hibino M, Hase R, et al. A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. *Antimicrob Agents Chemother*. 2020;64: e01897.