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High-dose methylprednisolone therapy in combination with favipiravir for COVID-19 patients with respiratory failure

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Abstract

Objective : Medication with corticosteroids has been reported to reduce mortality in COVID-19 patients with respiratory failure. However, systemic corticosteroid therapy has been reported to delay the clearance of SARS-CoV-2 RNA, and persistence of the virus is associated with poor prognosis. In terms of preservation of antiviral activity, simultaneous administration of corticosteroids and antiviral agents is an attractive strategy to cope with COVID-19. The aim of this study was to evaluate the potential efficacy of the simultaneous administration of high-dose methylprednisolone (mPSL) and favipiravir, an antiviral agent, for COVID-19 with respiratory failure.

Methods : Fourteen COVID-19 patients with respiratory failure were enrolled in this study. All patients were treated with high-dose mPSL (≥125 mg/day) and favipiravir. Clinical courses and laboratory measurements were retrospectively reviewed using medical records.

Results : The median (interquartile range) time between symptom onset and administration of favipiravir was 6 (3.8-7) days. The median (IQR) time from initiation of medication with favipiravir to high-dose mPSL was 1 (1-3) day. The median (IQR) 4C score on the day of favipiravir initiation was 11.5 (5.5-13.3), indicating that the predicted mortality was 31.4-34.9%. Thirteen patients (93%) recovered, and one patient (7%) who refused intubation died.

Conclusion : Treatment with high-dose mPSL and favipiravir appears to be superior to the predicted outcome. Therefore, treatment with high-dose mPSL and favipiravir may be safe and effective for COVID-19 patients with respiratory failure.

Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) started to spread rapidly since the end of 2019 and continues to spread worldwide as of January 2021. The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is one of the most severe health challenges worldwide. Although the majority of COVID-19 patients show a mild clinical course, a substantial number of patients develop life-threatening pneumonia. Effective and appropriate treatments are urgently required to combat COVID-19.

The efficacies of several agents have been explored, and some antiviral agents have demonstrated beneficial effects. Remdesivir has been reported to shorten the time to recovery in hospitalized COVID-19 patients[1]. Favipiravir has been reported to show better treatment effects on COVID-19, in terms of disease progression and viral clearance, compared with lopinavir/ritonavir[2]. Dexamethasone has demonstrated a favorable reduction in mortality in COVID-19 patients with respiratory failure[3]. An exaggerated inflammatory response is

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known to contribute to the mortality of COVID-19 patients. Patients with severe COVID-19 have been reported to show higher levels of pro-inflammatory cytokines compared to patients with moderate disease[4]. Furthermore, high levels of cytokines are associated with a poor prognosis[5]. Thus, the use of immunosuppressive agents, such as corticosteroids, is a promising strategy for the treatment of COVID-19.

Corticosteroids have broad-spectrum immunosuppressive potency and can reduce exaggerated inflammatory responses, which cause tissue damage, by inhibiting the production of inflammatory cytokines. However, corticosteroid therapy is a double-egged sword that may impair antiviral activity, leading to the worsening of COVID-19. In fact, several reports have failed to show favorable outcomes of corticosteroid therapy[6-8]. The simultaneous preservation of antiviral activity and reduction of the exaggerated inflammatory response by corticosteroids is considered important.

A potential option to minimize the corticosteroid-induced reduction of antiviral activity is the simultaneous administration of an antiviral agent. However, the efficacy of corticosteroids in combination with antiviral agents has not been well elucidated. Here, we investigated the clinical outcomes of COVID-19 patients treated simultaneously with high-dose methylprednisolone (mPSL) and favipiravir, an antiviral agent.

Methods

Patient enrollment and study design

COVID-19 patients treated with high-dose mPSL and favipiravir simultaneously at Tokyo Medical University Hospital between April 2020 and December 2020 were enrolled in this study. The diagnosis of COVID-19 was based on positive polymerase chain reaction (PCR) results for SARS-CoV-2. Clinical courses and laboratory measurements were retrospectively reviewed using medical records. This study was approved by the Ethics Committee of Tokyo Medical University (approval number, T2020-0161).

Treatment

The dosage of favipiravir was 1,800 mg twice daily on the first day, followed by 800 mg twice daily for up to 14 days. High-dose mPSL was defined as greater than 125 mg/day. After administration of high-dose mPSL, corticosteroids were tapered gradually or ceased based on the attending physician's decision. High-dose mPSL was administered only to patients with blood oxygen saturation < 93% at rest. Favipiravir was administered orally and mPSL, intravenously.

Statistical analysis

Statistical significance was set at $p < 0.05$. Variables are presented as medians and interquartile ranges. Correlations were analyzed using Spearman's correlation test. Statistical analyses were performed using GraphPad Prism software (GraphPad, San Diego, CA).

Results

Patient characteristics

Fourteen patients diagnosed with COVID-19 using PCR were studied. All patients showed bilateral lung infiltrates on chest computed tomography on admission. The median age of patients was 64.5 (56-76.5) years. The patients included 12 men (86%) and 2 women (14%). Two patients (14%) were current smokers, eight patients (57%) were ex-smokers, and four patients (29%) were never smokers. The median body mass index was 27.2 (23.4-28.2) kg/m^2.

Data on the day of administration of favipiravir are as follows : the median white cell count was 6,050 (4,300-8,000) /mm^3 ; median lymphocyte count was 931 (617-1,171) /mm^3 ; median levels of lactate dehydrogenase (LDH), C-reactive protein, and d-dimer were 321 (246-472) IU/L, 5.9 (3.2-11.5) mg/dL, and 1.25 (0.9-2.49) μg/dL, respectively. The median 4C score, which is a risk stratification score that predicts mortality for hospitalized COVID-19 patients[9], was 11.5 (5.5-13.3), indicating that the mortality was predicted to be 31.4-34.9%. The characteristics of the study patients are summarized in Table 1.

The time between symptom onset and administration of favipiravir was 6 (3.8-7) days. The median time from the initiation of medication with favipiravir to high-dose mPSL was 1 (1-3) days. In 12 patients (86%), favipiravir was administered first, and high-dose mPSL was administered later. Favipiravir and high-dose mPSL were administered simultaneously in one patient (7%). In one patient (7%), high-dose mPSL was administered first, and favipiravir was started 2 days later. Favipiravir was administered for 14 days in 12 patients, 12 days in 1 patient, and 9 days in 1 patient.

High-dose mPSL was administered if the patient's blood oxygen saturation fell to 93% at rest. The median duration of high-dose mPSL was 3.5 (3-9) days. The initial dose of mPSL was 1,000 mg/day in seven patients, 500 mg/day in five patients, and 125 mg/day in two patients. The mPSL was tapered off or ceased based on the attending physician's decision. The median duration of treatment with corticosteroids after the administration of high-dose of mPSL was 7 (0.75-14.75) days. The details of the treatments are shown in Table 2.

Clinical outcome

Thirteen patients (93%) recovered, and one patient (7%) who refused intubation died. The median duration of hospitalization was 26.5 (18-39.8) days. Six patients (43%) required intubation. The median duration of mechanical ventilation was 9 (6-46.8) days. One patient (7%) required extracorporeal membrane oxygena-

Table 1 Characteristics of patients

Age, years	64.5 (56-76.5)
Gender, *n* (%)	
Male	12 (86%)
Female	2 (14%)
Body mass index, kg/m^2 (*n*=13)	27.2 (23.4-28.2)
Smoking status, *n* (%)	
Current smoker	2 (14%)
Ex-smoker	8 (57%)
Never-smoker	4 (29%)
Time between symptom onset and administration of Favipiravir, days	6 (3.8-7)
4C mortality score	11.5 (5.5-13.3)
Comorbidities, *n* (%)	
Hypertension	11 (79%)
Diabetes	10 (71%)
Dyslipidemia	4 (29%)
Chronic obstructive pulmonary disease	1 (7%)
Chronic kidney failure	3 (21%)
Blood test variables	
White blood cell count /mm^3	6,050 (4,300-8,000)
Lymphocyte count /mm^3	931 (617-1,171)
D-dimer, μg/dl	1.25 (0.9-2.49)
LDH, IU/l	321 (246-472)
BUN, mg/dl	20.7 (11.1-38.5)
Creatinine, mg/dl	0.94 (0.63-1.38)
CRP, mg/dl	5.9 (3.2-11.5)
KL-6, U/ml	378 (284-512)

BUN, blood Urea nitrogen ; CRP, c-reactive protein ; LDH, lactate dehydrogenase ; mPSL, methylprednisolone.
Data are presented as median (interquartile range).

Table 2 Details of treatments

Time from initiation of Favipiravir to high-dose mPSL, days	1 (1-3)
Duration of high-dose mPSL therapy (mPSL ≥125 mg), days	3.5 (3-9)
Duration of corticosteroid treatment following high-dose mPSL therapy, days	7 (0.75-14.75)
Duration of administration of Favipiravir, days	14 (13.5-14)
Additional medication, *n* (%)	
Heparin	13 (93%)
Sivelestat Sodium Hydrate	8 (57%)
Nafamostat Mesilate	5 (36%)
Azithromycin	6 (43%)
Other antibiotics	10 (71%)

mPSL, methylprednisolone.
Data are presented as median (interquartile range).

tion (ECMO). The duration of ECMO was 6 days. Six patients (43%) required stay in the intensive care unit (ICU). The median duration of stay in the ICU was 14 (8-55.3) days. All patients required oxygen supplementation during the treatment for COVID19. One patient was unable to withdraw supplemental oxygen. In the patients who were able to withdraw supplemental oxygen, the median duration of need for oxygen supplementation was 15 (9.5-16.5) days. There were no correlations between the duration of treatment with high-dose mPSL and the duration of hospitalization and ICU stay (p=0.8882 and p=0.411, respectively). There were no correlations between the duration of corticosteroid treatment and the duration of hospitalization and ICU stay (p=0.3639 and p=0.2035, respectively). There were no differences in the proportion of patients who required

mechanical ventilation and the duration of hospitalization between the patients whose initial dose of mPSL was 1,000 mg/day (n=7) and ≤ 500 mg/day (n=7) (p=0.5921 and p=0.0647, respectively). A summary of the clinical course and outcomes is shown in Table 3.

Adverse events

Eleven patients (79%) developed hyperglycemia that required insulin supplementation. Six patients (43%) developed bacterial pneumonia with a positive sputum culture. The detected bacteria were as follows: *Klebsiella sp.* in three patients, methicillin-susceptible *Staphylococcus aureus* (MSSA) in five patients, methicillin-resistant *Staphylococcus aureus* (MRSA) in one patient and *Citrobacter sp.* in one patient. Four cases of bacterial pneumonia were diagnosed as ventilator-associated pneumonia (VAP). Despite negative sputum culture results, four patients were clinically suspected to have bacterial pneumonia. In total, 10 patients (71%) were treated with antibacterial agents. Five patients (36%) developed hyperuricemia (uremic acid > 7 mg/dL) and five (36%) developed liver dysfunction (aspartate aminotransferase > 150 IU/L or alanine aminotransferase > 150 IU/L). A summary of the adverse events is shown in Table 4.

Discussion

The clinical courses and outcomes of COVID-19 patients treated with high-dose mPSL in combination with favipiravir were investigated in this study. According to the 4C score, which predicts mortality for hospitalized COVID-19 patients, the mortality was predicted to be 31.4-34.9%. However, in this study, 93% of the patients survived, and only one patient who refused intubation died. Thus, treatment with high-dose mPSL and favipiravir is thought to potentially improve the clinical outcomes of COVID-19 patients.

Table 3 Clinical outcomes

Patients who required intubation, *n* (%)	6 (43%)
Duration of mechanical ventilation, days (*n*=6)	9 (6-46.8)
Patients who required ECMO, *n* (%)	1 (7%)
Duration of ECMO support, days	6
Patients who required admission in ICU, *n* (%)	6 (43%)
Duration of stay in ICU, days (*n*=6)	14 (8-55.3)
Length of hospital stay, days	26.5 (18-39.8)
Need for supplemental oxygen, days (*n*=13)	15 (9.5-16.5)
Death, %	1 (7%)

ECMO, extracorporeal membrane oxygenation ; ICU, intensive care unit.
Data are presented as median (interquartile range).

Table 4 Adverse events

Hyperglycemia, *n* (%)	11 (79%)
Hyperuricemia, *n* (%)	5 (36%)
Bacterial pneumonia, *n* (%)	6 (43%)
Ventilator-associated pneumonia, *n* (%)	4 (29%)
Liver dysfunction, *n* (%)	5 (36%)

The efficacy of corticosteroids against COVID-19 has been extensively investigated. The RECOVERY trial demonstrated that dexamethasone reduced the mortality in COVID-19 patients who required oxygen supplementation and invasive mechanical ventilation, while dexamethasone tended to increase the mortality in COVID-19 patients who did not require oxygen supplement[3]. A meta-analysis that evaluated the efficacy of systemic corticosteroids on mortality among critically ill COVID-19 patients also demonstrated that systemic corticosteroid administration was associated with lower 28-day all-cause mortality[10]. Moreover, in a trial that evaluated the efficacy of dexamethasone for moderate and severe acute respiratory distress syndrome caused by COVID-19, dexamethasone was reported to increase the number of ventilator-free days[11]. Systemic corticosteroid therapy is currently the most promising treatment for COVID-19 patients with respiratory failure.

Systemic corticosteroid therapy has a variety of adverse effects, including suppression of the immune system. Systemic corticosteroid therapy has been reported to delay the clearance of SARS-CoV-2 RNA[6], and the persistence of the virus is associated with poor prognosis[8]. As mentioned above, several reports have failed to demonstrate that systemic corticosteroid therapy has a beneficial effect on the treatment of COVID-19[6-8]. In particular, administration of high-dose corticosteroids has been reported to increase mortality, suggesting that excessive suppression of the immune system may deteriorate COVID-19[6][12]. However, given that the exaggerated inflammatory response plays a pivotal role in the pathogenesis of severe COVID-19, high-dose corticosteroid therapy may improve the clinical outcome of COVID-19 if the adverse effects of corticosteroids can be adequately controlled. Among the adverse effects of corticosteroids, the reduction of antiviral activity is a serious adverse effect in the treatment of COVID-19, but the impact of antiviral agents during systemic corticosteroid therapy has not been elucidated.

Favipiravir is a potent and broad-spectrum viral RNA polymerase inhibitor that was initially developed against influenza. Favipiravir demonstrated antiviral activities against other RNA viruses[13], and its antiviral effect against SARS-CoV-2 has been confirmed in vitro[14]. In SARS-CoV-2-infected hamsters, high doses of favipiravir have been reported to reduce infectious virus titers in the lungs and markedly improve lung histopathology, whereas hydroxychloroquine lacks antiviral activity[15]. Clinically, favipiravir has been shown to have a superior effect to lopinavir/ritonavir in the treatment of COVID-

19[2]. Regarding the combination with corticosteroids, a case of COVID-19 successfully treated with systemic corticosteroids and favipirvir was reported[16]. Moreover, the mortality rate of patients treated with dexamethasone was reported to be 23.3% even in the RECOVERY trial which demonstrated the beneficial effect of systemic corticosteroids therapy[3], while the mortality rate was 7% in our study, suggesting that favipirvir has an additional effect to systemic corticosteroids therapy. Therefore, favipirvir is thought to be a promising antiviral agent for administration with corticosteroids.

The adverse events frequently observed were hyperglycemia and bacterial pneumonia. Hyperglycemia was controlled by insulin supplementation and did not become a significant problem. All bacterial pneumonia was successfully treated with antibacterial agents. However, during high-dose corticosteroid therapy, attention should be paid to bacterial pneumonia, especially VAP, because bacterial pneumonia can be life-threatening in an immunosuppressive situation.

This study had several limitations. First, this was a retrospective, single-center study with a small number of patients. Second, there was no control group to compare the efficacy of the treatment. Thus, we were unable to conclude that simultaneous administration of high-dose mPSL and favipiravir has better effect on outcome of COVID-19 patients than usual care. Third, the impact of additional treatments, such as heparin, was not evaluated.

This is the first report to demonstrate the clinical outcomes of patients treated with high-dose mPSL in combination with favipiravir. The outcome of the treatment was superior to the predicted outcome. Simultaneous administration of high-dose mPSL and favipiravir may be safe and effective for COVID-19 patients with respiratory failure. Further investigations are required to confirm the efficacy and safety of this treatment.

Conflict of interest

The authors have no conflicts of interest relevant to the content of this article.

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呼吸不全を伴う新型コロナウイルス感染症に対する高用量ステロイドとファビピラビル併用療法の検討

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【要旨】 呼吸不全を伴う新型コロナウイルス感染症（COVID-19）において全身ステロイド投与は致死率を低下させると報告されている。しかし、全身ステロイド投与はウイルス排泄の遷延につながることや、持続ウイルス排泄を認める患者は予後が悪いことが報告されている。ステロイドと抗ウイルス薬の同時投与は、ステロイドによるウイルス排泄遷延を予防しながら炎症を制御する意味で、魅力的な治療法であるが、ステロイドと抗ウイルス薬の同時投与の効果は十分に検証されていない。以上より、我々は高用量メチルプレドニゾロンとファビピラビルの同時投与を行ったCOVID-19患者の経過を後方視的に検証した。対象は東京医科科大学病院に2020年4月から12月までに入院した呼吸不全を伴うCOVID-19患者で高用量メチルプレドニゾロン（≥125 mg/日）とファビピラビルの同時投与を行った14例。13例（93%）は回復し、死亡したのは人工呼吸管理を拒否した1例（7%）のみであった。COVID-19患者の死亡率予測スコアである4Cスコアの中央値（四分位範囲）は11.5（5.5-13.3）であり、予測される死亡率は31.4-34.9%であった。本研究における死亡率は4Cスコアから予測される死亡率より低く、高用量メチルプレドニゾロンとファビピラビルの同時投与は呼吸不全を伴うCOVID-19患者に効果がある可能性が示唆された。

〈キーワード〉 新型コロナウイルス感染症、高用量ステロイド、ファビピラビル、メチルプレドニゾロン