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Rapid Communication

Outcome of early-stage combination treatment with favipiravir and methylprednisolone for severe COVID-19 pneumonia: A report of 11 cases

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ABSTRACT

Although the use of corticosteroids is not recommended in the World Health Organization statement for the treatment of coronavirus disease 2019 (COVID-19), steroid therapy may be indicated for critical cases in specific situations. Here, we report the successful treatment of 11 cases of severe COVID-19 pneumonia with favipiravir and methylprednisolone. All cases were severe and patients required oxygen administration or had a blood oxygen saturation ≤93% on room air. All were treated with favipiravir and methylprednisolone, and 10 of 11 patients responded well and required no further oxygen supplementation or ventilator management. This study shows the importance of the early-stage use of a combination of favipiravir and methylprednisolone in severe cases to achieve a favorable clinical outcome.

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; GGO, ground-glass opacities; LDH, lactate dehydrogenase; MERS, Middle East respiratory syndrome; NIH, national institute of health; RdRp, novel RNA-dependent RNA polymerase; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TLC, total lung capacity; U-HRCT, ultra-high-resolution chest computed tomography; WHO, World Health Organization.

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1. Introduction

In December 2019, coronavirus disease 2019 (COVID-19) emerged from Wuhan, China, and the World Health Organization (WHO) declared COVID-19 a pandemic in March 2020. No specific treatments have yet been established, although several clinical trials, including those investigating favipiravir, chloroquine, and remdesivir as antiviral therapies, are currently underway to evaluate their efficacy on the outcome of COVID-19. Favipiravir is a novel RNA-dependent RNA polymerase (RdRp) inhibitor that is effective in the treatment of influenza and is therefore also expected to be a promising drug for COVID-19. However, the use of antiviral treatment only may not be sufficient to control disease progression and avoid the need for ventilator management. A previous report showed that half of the patients requiring ventilator management for critical COVID-19 died [1]. Anti-inflammatory treatment is therefore important to avoid the progression of COVID-19 to a critical stage.

The use of corticosteroids for COVID-19 is not recommended in the WHO statement [2], as previous steroid treatment in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) was associated with complications. Severe COVID-19 is associated with elevated cytokine levels [3], and immunosuppression may therefore play a protective role during COVID-19 infection by preventing or reducing excessive immune responses that may drive clinical deterioration [4]. In our institution, ultra-high-resolution chest computed tomography (U-HRCT) of patients with COVID-19 indicated an association between lung volume loss, calculated as the ratio of mean lung volume to the predicted total lung capacity (predTLC), and COVID-19 severity [5]. This suggests that early-stage anti-inflammatory treatment may be necessary to avoid progression to critical disease or acute respiratory distress syndrome (ARDS). Accordingly, severe cases may require early therapeutic intervention with a combination of antiviral and anti-inflammatory drugs. Although anti-inflammatory drugs such as tocilizumab reportedly show promising results, they are expensive and may not be appropriate for all cases.

At our institution, we classified COVID-19 according to the National Institutes of Health (NIH) criteria [6] and used combination treatment with favipiravir and methylprednisolone (80, 250, or 500 mg/day) for a short period (3–6 days) in patients with severe illness before the development of critical disease or ARDS. The initial dose of methylprednisolone was 80 mg/day for 3 days, and in some cases, this was increased to 250 or 500 mg/day for 3 days at the clinician's discretion.

The present report retrospectively investigated the outcome of the combination treatment of favipiravir and methylprednisolone in 11 patients with severe COVID-19, who had a blood oxygen saturation $\leq$93% on room air or required oxygen inhalation in the early stages.

2. Results

The clinical characteristics of patients with severe illness before steroid administration are listed in Table 1. Mean age was 63.2 years and the mean time from onset to hospitalization was 6.4 days. There was one diabetic patient, but this subject experienced no significant side effects other than hyperuricemia during treatment. The mean fever duration was 5.7 days from post-steroid use to fever recovery. In cases 4 and 5, there was no fever relapse after the completion of steroid administration. The mean time to first-time negative conversion of viral RNA was 18 days in six negative confirmed cases. Ten cases diagnosed as severe disease before steroid administration avoided ventilation management, although the respiratory condition in case 7 worsened on the day of admission, and the patient was transferred to another hospital for ventilator management the following day. Some patients received azithromycin, ciclesonide aerosol, or intravenous human immunoglobulin in addition to favipiravir and methylprednisolone at the discretion of each doctor.

The laboratory findings for cases of severe COVID-19 are listed in Table 2. Four patients showed reduced lymphocyte count; eight, high serum lactate dehydrogenase (LDH) levels; seven, high serum ferritin; and all showed high C-reactive protein (CRP) levels. These results were consistent with previous reports of COVID-19 aggravation factors, including reduced lymphocyte count and elevated serum LDH, CRP, and ferritin. U-HRCT showed lung volume loss due to alveolar collapse in seven cases, with mean lung volume/predTLC as low as 78.6%.

3. Case report: case 10

A 37-year-old female patient was admitted to another hospital before being transferred to our hospital in April for fever, cough, dyspnea, and fatigue. A nucleic acid test performed in April was positive for COVID-19. She had never smoked and had bronchial asthma and depression. Examination at admission showed an SpO_2 of 92% on room air, and laboratory analyses showed elevated serum CRP, LDH, and ferritin (Table 2). A U-HRCT scan performed at admission revealed bilateral multifocal ground-glass opacity (GGO), mixed GGO, crazy paving with peripheral predominance (Fig. 1A), and low lung volume/predTLC% on CT (Table 2).

The patient received methylprednisolone (80 mg/day for 3 days, followed by 250 mg/day for 3 days) for a total of 6 days, favipiravir (1.8 g twice per day on day 1, followed by 0.8 g twice per day) for a total of 14 days, and intravenous immunoglobulin for 3 days. The patient A was able to finish oxygen administration and her chest CT on day 11 after admission showed improvement (Fig. 1B). Negative conversion of viral RNA was confirmed twice, and the patient was discharged on day 29.

4. Discussion

Here, we reported 11 cases of severe COVID-19 patients treated with favipiravir and methylprednisolone at early-stage disease. In total, 10 of 11 patients avoided the need for ventilation management and no longer required oxygen administration. According to a previous report, seven of 14 patients diagnosed with severe illness progressed to critical

Table 1 – Patient characteristics.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
Age (years)	82	45	36	84	59	49	70	73	77	37	83
Sex	female	male	male	male	male	male	male	female	male	female	male
Current smoker	no	yes	yes	yes	no	yes	yes	no	no	no	yes
Comorbidities	breast cancer	HT	–	HT, Cushing's disease	–	–	HT, type 2 DM	CTEPH	–	BA, depression	HT, stroke, dementia
Clinical manifestations											
Diarrhea	no	yes	yes	yes	no	No	yes	no	no	no	no
Fever	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Cough	no	no	yes	yes	yes	yes	yes	no	yes	yes	yes
Dyspnea	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
Fatigue	yes	yes	yes	no	yes	yes	no	no	yes	yes	yes
Disease severity before methylprednisolone use	severe	severe	severe	severe	severe	severe	severe	severe	severe	severe	severe
Time from onset to admission (days)	1	6	9	1	10	4	9	11	5	5	9
Time from onset to methylprednisolone use (days)	1	6	9	2	11	4	9	11	5	6	9
Daily methylprednisolone dose (mg)	80	80	80	500	80	80	80	80	500	80 → 250	80
Methylprednisolone use (days)	3	3	3	3	3	3	3	3	3	6	3
Time of fever recovery (<37.0 °C) (days)	5	3	21	4	12	14	–	–	7	12	20
Time from methylprednisolone use to fever recovery (<37.0 °C), (days)	2	2	15	3	2	7	–	–	3	5	12
Time from diagnosis to first negative PCR (days)	14	15	14	–	–	–	–	24	18	–	23
Time from O_2 start to O_2 finish (days)	4	6	–	9	–	12	–	10	11	10	14
Treatment											
Favipiravir	yes	yes	yes	yes	Yes	yes	Yes	yes	yes	Yes	yes
Methylprednisolone	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Azithromycin	yes	no	yes	yes	yes	yes	yes	no	yes	yes	yes
Ciclesonide aerosol	no	yes	yes	yes	yes	yes	yes	no	no	no	no
Human immunoglobulin	no	no	no	yes	no	yes	yes	no	yes	yes	no
Outcome	discharge	no oxygen at rest	discharge	no oxygen at rest	discharge	discharge	mechanical ventilation	no oxygen at rest	no oxygen at rest	no oxygen at rest	no oxygen at rest

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; HT, hypertension; DM, diabetes mellitus; BA, bronchial asthma; PCR, polymerase chain reaction.

Table 2 – Laboratory findings of patients with severe coronavirus disease 2019 (COVID-19).

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
WBC count ($\times 10^9$/L)	7.32	5.74	4.45	8.56	5.38	7.11	4.3	7.39	8.47	6.61	4.36
Lymphocyte count ($\times 10^9$/L)	0.64	1.48	1.09	1.32	0.46	0.94	0.82	0.9	0.45	1.12	0.59
Neutrophil count ($\times 10^9$/L)	6.2	3.9	3.12	6.63	4.67	5.78	3.25	6.68	7.77	4.73	3.21
Hemoglobin (g/L)	9.0	16.0	16.3	13.1	13.8	14.6	12.3	14.6	16	13.7	10.5
Platelets ($\times 10^9$/L)	13.2	14.2	14.5	22.3	13.3	20.1	18.9	26.7	14.3	26.3	11
Albumin	2.1	3.6	3.6	3.0	3.5	3.4	3.2	2.9	–	3.5	3.0
AST (U/L)	30	76	55	55	53	45	43	23	73	32	22
ALT (U/L)	17	107	43	31	45	65	20	12	35	25	13
LDH (U/L)	167	310	439	476	316	254	383	324	682	501	247
Total bilirubin (mmol/L)	0.3	1.4	0.5	0.7	0.7	0.4	0.6	0.6	1.4	0.2	0.3
BUN (mmol/L)	15.3	12	11.9	23.8	14.9	10.9	17.1	42.9	46.1	9.2	10.3
Creatinine (μmol/L)	0.45	0.55	0.94	1.27	1.13	0.8	1.19	1.26	1.05	0.75	0.79
D-dimer (μg/L)	–	–	1.95	6.95	1.59	–	1.75	–	–	–	1.78
CRP (g/L)	14.02	4.52	7.3	4.88	11.79	4.44	11.61	8.12	5.93	8.77	6.39
Ferritin (ng/mL)	611.1	1855.6	876.5	69.3	1293.8	870.8	919.9	–	–	330	101.3
CTLV (mL)	2762	4223[a]	6379	3440	4718	5771	3901	4240	4934	2292	2987
CTLV/predTLC (%)	79.3	74.1[a]	100.8	66.9	78.9	94.6	72.6	111.5	91.1	59.1	63.2

Abbreviations: WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; CRP, C-reactive protein; CT, computed tomography; CTLV, computed tomography lung volume; predTLC, predicted total lung capacity.

[a] Reference value for other hospital CT.

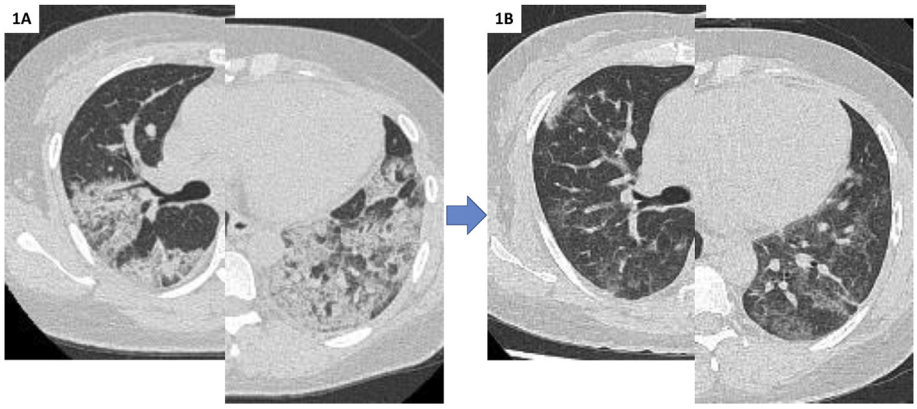

Fig. 1 – Chest ultra-high-resolution chest computed tomography (U-HRCT) of case 10. A, U-HRCT shows bilateral multifocal ground-glass opacity (GGO), mixed GGO, and crazy paving with peripheral predominance before methylprednisolone administration. B, bilateral GGO disappeared in both lungs 11 days after administration of favipiravir and methylprednisolone.

illness and required either ventilator management or extracorporeal membrane oxygenation [7]. Here, in contrast, 10 patients with disease classified as severe before steroid administration avoided the need for ventilation management and successfully discontinued oxygen administration at rest.

A previous report showed the efficacy of favipiravir in a comparative study of the clinical effects of lopinavir/ritonavir and favipiravir for the treatment of mild COVID-19 [8]. As of April 25, 2020, the effectiveness of favipiravir against COVID-19 has not been proven, but its usefulness for the treatment of COVID-19 has been shown in several case reports, including the present report.

Corticosteroid treatment for COVID-19 is thought to inhibit viral clearance and delay antibody production [9] but may play a role in reducing lung injury due to excessive inflammatory responses. The efficacy of steroid therapy in patients with critical COVID-19 was reported in China, as methylprednisolone treatment may reduce disease progression in patients with ARDS [1].

Early-stage combination use of favipiravir and methylprednisolone may reduce the need for tracheal intubation by suppressing SARS-CoV-2 replication and decreasing the cytokine storm. The patient in case 7 who progressed to critical illness and was intubated at the transfer hospital had many aggravating factors highlighted in previous reports, such as being a smoker diabetes and having high CRP, high ferritin, and lung volume loss on CT [1,4,5,10]. Lung volume measured by CT is correlated with pulmonary function test results such as TLC [11], and CT lung volume loss may be an important indicator of disease severity. To avoid overwhelming hospitals, it is important to halt progression from severe to critical illness and reduce the need for ventilator

management. The early-stage use of combination treatment of favipiravir and methylprednisolone shows promising results.

The present report has some limitations. First, our study was retrospective and was limited to a small number of patients with no comparison group. In order to confirm the applicability of our findings, further large-scale, multi-institutional, prospective collaborative studies are required. Furthermore, the use of azithromycin, ciclesonide, and intravenous human immunoglobulin may have also contributed to clinical outcomes in some patients.

5. Conclusion

We report 11 cases of patients with severe COVID-19 treated with favipiravir and methylprednisolone at our institution. Early-stage combination treatment of favipiravir and methylprednisolone in severe COVID-19 may prevent worsening of symptoms and disease progression.

Conflict of Interest

None of the authors have any real or perceived conflicts of interest to declare regarding the subject of this manuscript.

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