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Nafamostat mesylate treatment in combination with favipiravir for patients critically ill with Covid-19: a case series

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Development of specific therapy against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is urgently required. Several drugs such as antimalarial and anti-Ebola virus drugs are under investigation for coronavirus disease 2019 (Covid-19). Transmembrane protease serine 2 (TMPRSS2) plays a crucial role for SARS-CoV-2 entry into the cytoplasm [1]. Inhibition of TMPRSS2 protease activity is assumed to prohibit viral entry of SARS-CoV-2. Through high-throughput screening of 1017 existing drugs, a clinically available serine protease inhibitor nafamostat mesylate was identified as a potent inhibitor of Middle East respiratory syndrome coronavirus entry into human epithelial cells [2]. More recently, nafamostat mesylate was shown to inhibit the entry of SARS-CoV-2 into the human epithelial cells at EC_{50} of ~ 10 nM [3, 4]. Nafamostat mesylate has been clinically used for the treatment of acute pancreatitis and disseminated intravascular coagulation in Japan. By intravenous administration, its blood concentrations are maintained at 30–240 nM, which are sufficient to block the virus entry [3]. An anti-influenza A H1N1 virus drug favipiravir exhibits antiviral activity against other RNA viruses and therefore is expected to have antiviral action against SARS-CoV-2. This drug has been approved in Japan for novel influenza virus disease.

Eleven adults with reverse transcriptase polymerase chain reaction-confirmed SARS-CoV-2 infection were admitted to the intensive care unit (ICU) at The University of Tokyo Hospital between April 6 and April 21, 2020, and treated with nafamostat mesylate in combination with favipiravir. The demographic and clinical characteristics and the laboratory and radiologic findings at ICU admission are listed in Table 1. All the patients needed oxygen therapy. Eight patients (73%) needed invasive mechanical ventilation (MV), and 3 patients (27%) needed venovenous extracorporeal membrane oxygenation (VV-ECMO).

Patients received combination treatment with nafamostat mesylate [0.2 mg per kg per hour by continuous intravenous infusion, median treatment 14 days (IQR, 10 to 14 days)] and favipiravir [3600 mg on day 1 and at 1600 mg per day on day 2 and subsequently median treatment 14 days (IQR, 12 to 14 days)]. No interruption of antiviral treatment occurred due to adverse drug reactions except for one patient who developed hyperkalemia on day 9 (by nafamostat mesylate). All 11 patients had at least 33 days of hospital follow-up. As of May 22, 1 patient, who had a do-not-resuscitate order, died on ICU day 7. Seven patients were successfully weaned from MV [median duration of MV 16 days (IQR, 10 to 19 days)] and 9 and 7 patients were discharged from the ICU and the hospital, respectively (Fig. 1).

This is the first report on nafamostat mesylate treatment in combination with favipiravir against

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Table 1 Clinical characteristics, laboratory data, and imaging results at ICU admission

Characteristic	Measurement
Age, median (IQR), years	68 (60–69)
Male, no. (%)	10 (91%)
Body weight, median (IQR), kg	71 (69–82)
Number of patients with coexisting disorders, no. (%)	
Asthma	0 (0%)
Cancer	1 (9%)
Chronic kidney disease	0 (0%)
Chronic obstructive pulmonary disease	1 (9%)
Diabetes mellitus	3 (27%)
Hypertension	4 (36%)
Duration of symptoms before admission, median (IQR), days	8 (7–11)
Number of patients with symptoms, no. (%)	
Fever	9 (82%)
Cough	5 (45%)
Shortness of breath	8 (73%)
Laboratory data	
White blood cell count, median (IQR), per mm^3	6900 (5800–10,850)
Lymphocyte count, median (IQR), per mm^3	851 (759–1164)
Hemoglobin, median (IQR), g/dl	15.0 (13.5–16.3)
Platelet count, median (IQR), per mm^3	19.6 (18.6–26.4)
Lactate dehydrogenase level, median (IQR), U/l	518 (417–752)
Aspartate aminotransferase level, median (IQR), U/l	54 (49–90)
Alanine aminotransferase level, median (IQR), U/l	47 (35–58)
Serum creatinine level, median (IQR), mg/dl	0.85 (0.70–1.03)
Creatinine kinase level, median (IQR), U/l	213 (129–579)
Prothrombin time, median (IQR), international normalized ratio	1.08 (1.03–1.13)
Activated partial thromboplastin time, median (IQR), s	28.8 (28.4–32.1)
D-dimer level, median (IQR), μg/dl	1.4 (1.1–11.8)
PaO_2/FiO_2 ratio, median (IQR)	131 (114–198)
SOFA score, median (IQR)	3.0 (2.5–4.5)
APACHE II score, median (IQR)	14.0 (12.0–15.5)
Computed tomography findings	
Patients with consolidation, no. (%)	6 (55%)
Patients with ground-glass opacities, no. (%)	10 (91%)
Patients with pulmonary infiltration, no. (%)	2 (18%)

APACHE Acute Physiology and Chronic Health Evaluation, *FiO_2* fraction of inspired oxygen, *ICU* intensive care unit, *IQR* interquartile range, *PaO_2* partial pressure of arterial oxygen, *SOFA* sequential organ failure assessment

Covid-19. In comparison with previous reports about critically ill patients with Covid-19, our case series also demonstrated a high number of patients (8 [73%]) who required MV requirement; however, the mortality rate was low (1 patient [9%]). Patients with severe Covid-19 often suffer from microvascular thrombosis and hemorrhage with extensive alveolar and interstitial inflammation in the lung [5]. Nafamostat mesylate might thus be effective, because it inhibits intravascular coagulopathy, in addition to directly targeting the virus entry in host epithelial cells.

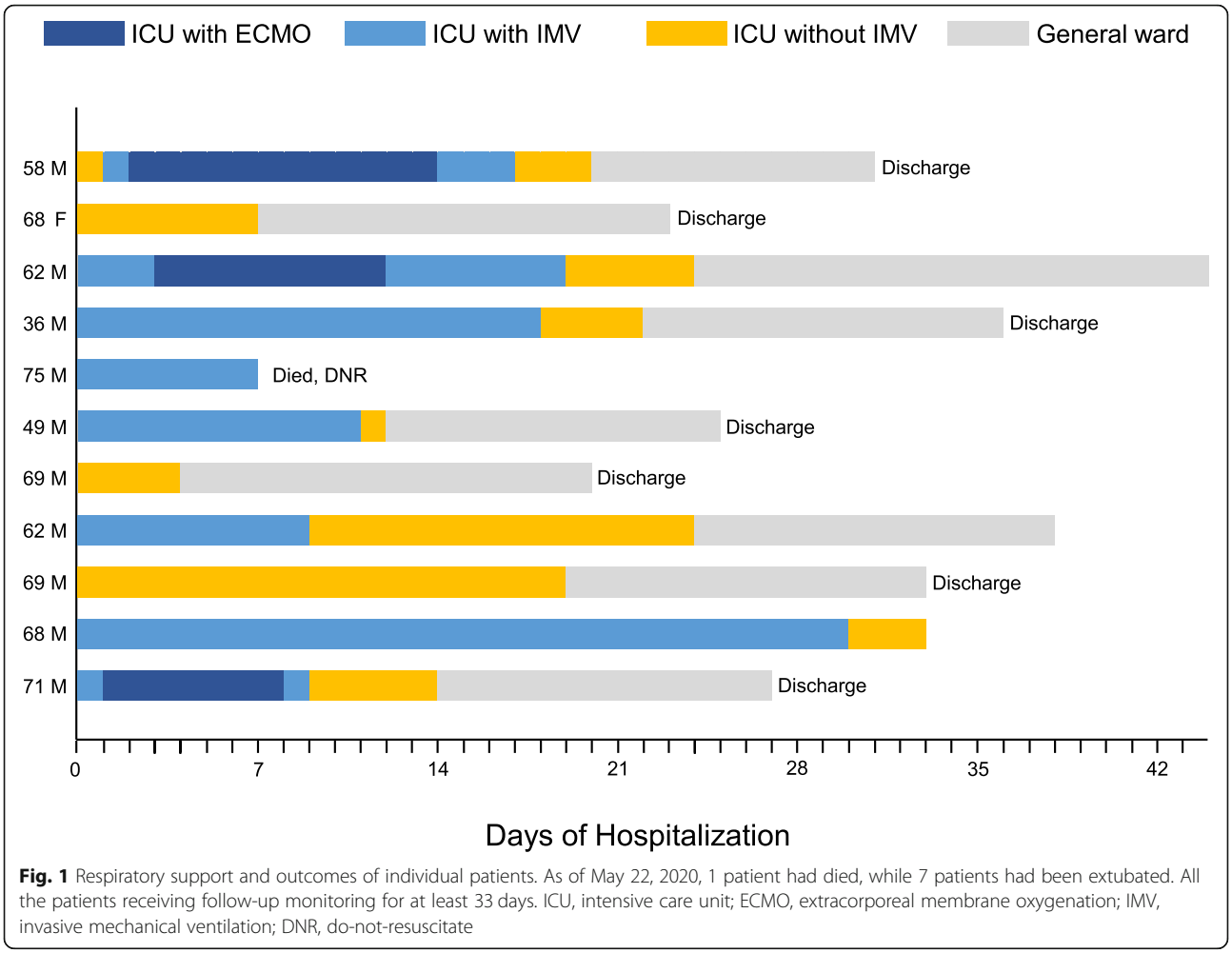

Fig. 1 Respiratory support and outcomes of individual patients. As of May 22, 2020, 1 patient had died, while 7 patients had been extubated. All the patients receiving follow-up monitoring for at least 33 days. ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; DNR, do-not-resuscitate

In conclusion, nafamostat mesylate therapy in combination with favipiravir may allow blockade of virus entry and replication, as well as inhibition of pathogenic host response, i.e., hyper-coagulopathy. Although the number of patients in this case series was very small, this low mortality rate suggests that combination treatment of favipiravir and nafamostat mesylate may be effective for critically ill Covid-19 patients. A clinical trial for the combination treatment of nafamostat mesylate and favipiravir against Covid-19 will be initiated in Japan (jRCTs031200026).

Abbreviations

Covid-19: Coronavirus disease 2019; ICU: Intensive care unit; IQR: Interquartile range; MV: Mechanical ventilation; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TMPRSS2: Transmembrane protease serine 2; VV-ECMO: Venovenous extracorporeal membrane oxygenation

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Authors' contributions

KD, MI, and KM designed the study and had full access to all data in the study and take responsibility for the integrity of data and the accuracy of the data analysis. NH contributed to the data collection, data interpretation, literature searches, and clinical management. MI and KM had roles in the management of treatment of favipiravir and nafamostat mesylate. KM and NM supervised this study and contributed to the writing of the manuscript. All authors contributed to the data acquisition, data analysis, or data interpretation, and reviewed and approved the final version of the manuscript.

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Availability of data and materials
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Ethics approval and consent to participate
This case series was approved by the institutional review board at the University of Tokyo (#3820). The institutional treatment board at The University of Tokyo Hospital approved the treatment protocol of antiviral agents of favipiravir and nafamostat mesylate (#2020001CL). Informed consent for treatment was obtained from each patient or legal representative.

Consent for publication
Not applicable

Competing interests
One author (JI) has submitted a provisional application for a patent related to this work to USPTO under the application no. 62988962. The other authors declare that they have no conflicts of interest with the contents of this article.

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