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Case report

Potential mechanisms of nafamostat therapy for severe COVID-19 pneumonia with disseminated intravascular coagulation

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ABSTRACT

Nafamostat, a serine proteinase inhibitor with various actions including antithrombin, antiplasmin, and antitrypsin effects, has been used in clinical practice to treat disseminated intravascular coagulation (DIC) and pancreatitis. This case report describes the clinical course of a patient with COVID-19 pneumonia whose severe hypoxemia, probably caused by DIC and pulmonary embolism, showed remarkable improvement with combination heparin and nafamostat therapy. In addition, beneficial mechanisms of nafamostat against COVID-19 and the necessity of attention to hyperkalemia as an adverse effect are discussed.

Introduction

Nafamostat, a serine proteinase inhibitor, has been used to treat disseminated intravascular coagulation (DIC) and pancreatitis in Japan for over 30 years. Although nafamostat is an antithrombin drug, it has a characteristically strong antiplasmin action. Therefore, it is considered suitable for enhanced-fibrinolytic-type DIC (Asakura, 2014). Further, it would be beneficial especially for DIC because nafamostat does not result in hemorrhagic side effects. As nafamostat has recently been shown to block viral entry by inhibiting membrane fusion between SARS-CoV-2 and human cells (Hoffmann et al., 2020a,b; Yamamoto et al., 2020), the drug is also expected to be effective for COVID-19.

Indeed, Jang et al. reported three cases of elderly patients with COVID-19 pneumonia who showed sufficient recovery with nafamostat therapy in this journal (Jang and Rhee, 2020). Their successful experience encourages its future use in COVID-19.

By reviewing four reported cases that include the present case, the mechanisms of action of nafamostat, the pros and cons of suppressing plasmin, and the disadvantage of the drug and how to overcome it are discussed.

Case

A 65-year-old man complained of pharyngeal pain for nine days before hospitalization, developed a fever for eight days before hospitalization, and showed ground-glass opacity with a mottled appearance in the right lung on chest CT taken at a local physician's office five days before hospitalization. Based on the CT imaging characteristics and blood test findings that suggested viral infection, COVID-19 pneumonia was suspected, and the patient was admitted to our hospital. The RT-PCR test of the pharyngeal swab was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Vital signs on admission were temperature, 38.1 °C; pulse, 100/min; and SpO_2, 94% on a 10-L oxygen mask.

Lopinavir/ritonavir and meropenem were started after hospitalization. Favipiravir was added on Day 2. From Day 3, hydroxychloroquine sulfate, ciclesonide, and methylprednisolone were also added. However, the fever continued, and from Day 6, D-dimer increased to 40.3 μg/mL (reference level, <1.0 μg/mL), the respiratory condition worsened, and the presence of bloody sputum was observed. Based on these observations, concurrent pulmonary embolism was suspected. On Day 7, the patient started unfractionated heparin (Unfractionated heparin (UFH): target APTT two times the normal range). Nonetheless, on Day 9, D-

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dimer increased markedly to 159.2 μg/mL, and the platelet count decreased. With a diagnosis of DIC, nafamostat (200 mg/24 h) was added to UFH from Day 11. Rapid improvement in fibrin/fibrinogen degradation products (FDP), D-dimer, C-reactive protein (CRP), and lactate dehydrogenase (LDH) levels was then observed. Moreover, with combination heparin and nafamostat therapy, the respiratory condition improved, and the oxygen administered could be decreased from 15 L/min to 2 L/min. Nafamostat was discontinued on Day 16 due to hyperkalemia which is a known side effect (Figure 1). PCR tests for SARS-CoV-2 were confirmed to be negative on Days 61 and 63 of admission.

Discussion

Abnormal coagulation, DIC, and venous thromboembolism are known to occur frequently in severe cases of COVID-19, and they are also likely to become the causes of death (Tang et al., 2020, Zhou et al., 2020). Although pulmonary embolism, which is diagnosed by antemortem imaging, is also frequently observed, multiple fibrin thrombi are often found in the microcirculation of the lung at autopsy even without an antemortem diagnosis of thrombosis (Dolhnikoff et al., 2020, Fox et al., 2020). This indicates that, to save the lives of severely ill patients with COVID-19, antithrombotic measures along with anti-coronavirus treatment are essential.

In the present case, nafamostat was added to UFH in a patient presenting with COVID-19 pneumonia and concurrent DIC, with marked improvements in DIC and the respiratory condition. Nafamostat is a serine proteinase inhibitor (SPI) with various actions, including antithrombin, antiplasmin, and antitrypsin effects. It has been used in clinical practice in Japan for over 30 years to treat DIC and pancreatitis. It has antithrombin actions without hemorrhagic side effects. However, careful attention is necessary when it is used because hyperkalemia is an occasional side effect, as observed in the present case. When hyperkalemia appears, daily interruption about 4 h might allow the continuation of nafamostat administration.

Potential mechanisms of nafamostat therapy for severe COVID-19

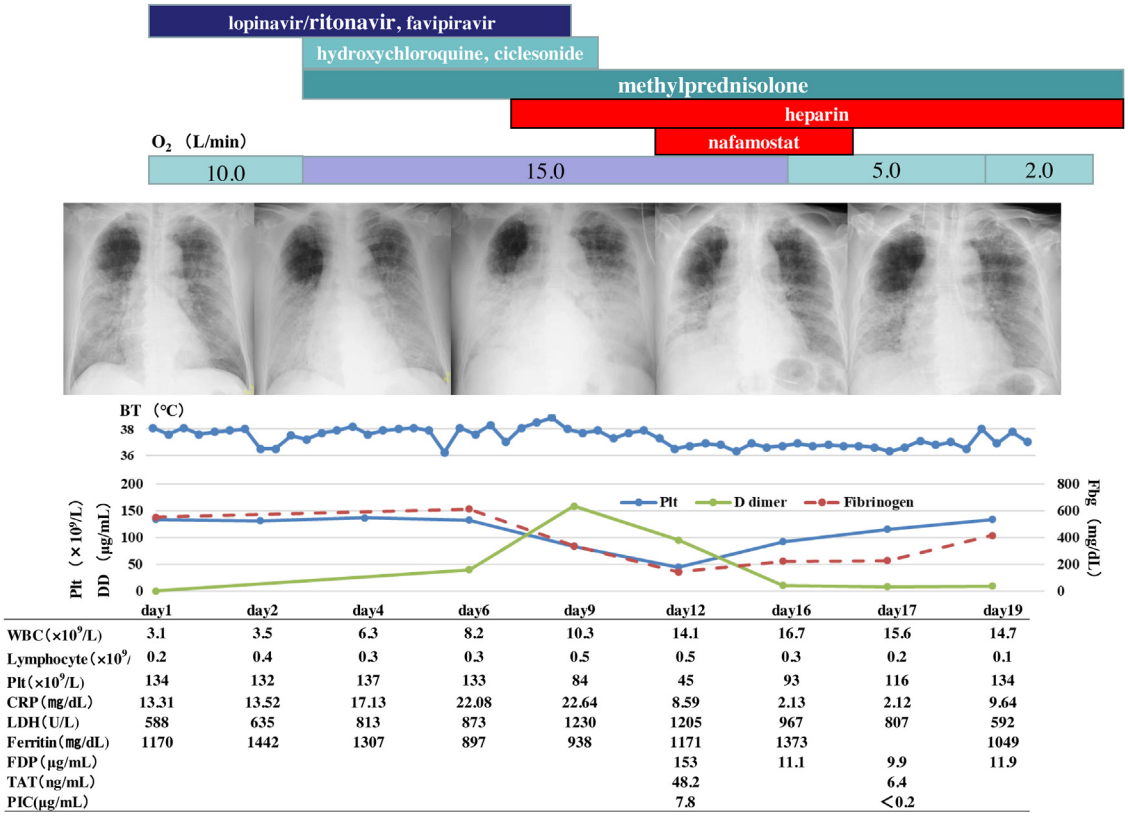
Nafamostat is thought to be effective against COVID-19 based on the three mechanisms described below.

Anti-coronavirus action

It has been reported that angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) present on the host lung epithelial cells are required for a coronavirus such as SARS-CoV-2 to infect these cells (Hoffmann et al., 2020a Apr 16). Yamamoto et al. reported that, in MERS-CoV, another type of coronavirus, nafamostat blocks TMPRSS2 activity, thereby suppressing membrane fusion between the virus and human cells, consequently inhibiting MERS-CoV infection (Yamamoto et al., 2016). Similarly, in SARS-CoV-2, nafamostat blocks viral entry by inhibiting membrane fusion between the outer membrane of the virus and human cells (Hoffmann et al., 2020a,b, Yamamoto et al., 2020).

Anti-DIC action

Although COVID-19 is an infectious disease, it differs on many points from DIC with suppressed fibrinolysis caused by a severe



	day1	day2	day4	day6	day9	day12	day16	day17	day19
WBC(×10⁹/L)	3.1	3.5	6.3	8.2	10.3	14.1	16.7	15.6	14.7
Lymphocyte(×10⁹/	0.2	0.4	0.3	0.3	0.5	0.5	0.3	0.2	0.1
Plt(×10⁹/L)	134	132	137	133	84	45	93	116	134
CRP(mg/dL)	13.31	13.52	17.13	22.08	22.64	8.59	2.13	2.12	9.64
LDH(U/L)	588	635	813	873	1230	1205	967	807	592
Ferritin(mg/dL)	1170	1442	1307	897	938	1171	1373		1049
FDP(μg/mL)						153	11.1	9.9	11.9
TAT(ng/mL)						48.2		6.4	
PIC(μg/mL)						7.8		<0.2	

Figure 1. Clinical course and laboratory results of the patient.
BT, body temperature; Plt, platelet; DD, D-dimer; WBC, white blood cell; LDH, lactate dehydrogenase; FDP, fibrin/fibrinogen degradation products; TAT, thrombin-antithrombin complex; PIC, plasmin-α_2-plasmin inhibitor complex; Fbg, fibrinogen.

infectious disease; for example, it presents with significant cytokine storm-induced activation of fibrinolysis (Asakura, 2014, Tang et al., 2020, Zhou et al., 2020). The current case also showed markedly increased FDP and decreased fibrinogen, reflecting the extensive activation of fibrinolysis. Another distinctive point is that marked elevations are observed not only in thrombin-antithrombin complex (TAT), a coagulation activation marker, but also in plasmin-α_2-plasmin inhibitor complex (PIC), a fibrinolysis activation marker. The elevations of TAT and PIC improved dramatically with heparin and nafamostat combination therapy. Nafamostat is compatible for DIC with marked activation of fibrinolysis, as seen in COVID-19 (Asakura and Ogawa, 2020).

Antiplasmin action

Plasmin has been reported to enhance the pathogenicity and infectivity of the virus by cleaving the S protein of the novel coronavirus (SARS-CoV-2) (Ji et al., 2020). Nafamostat has antiplasmin actions (Aoyama et al., 1984) and is thought to decrease the pathogenicity and infectivity of SARS-CoV-2.

Further, tranexamic acid is known as a strong antifibrinolytic agent that suppresses plasmin production and is thus also expected to prevent mild cases of COVID-19 (Barker and Wagener, 2020). However, nafamostat, an antiplasmin agonist that also has antithrombin activity, is much safer in ordinary clinical practice than tranexamic acid, which has the adverse effect of fatal thrombosis (Ogawa and Asakura, 2020).

The three points above are the advantages of nafamostat. However, nafamostat has a disadvantage: its antithrombin action (anticoagulant effect) is milder than its antiplasmin action (antifibrinolytic effect) (Aoyama et al., 1984). Thus, its combination with heparin to compensate for this weakness is considered beneficial (Asakura and Ogawa, 2020).

Early identification of thrombotic conditions such as DIC and pulmonary embolism and appropriate treatment should reduce the number of patients requiring ventilation and decrease mortality. Treatment with nafamostat is thought to be beneficial due to its anticipated anti-coronavirus action (and mild antithrombin action) combined with heparin to reinforce the anticoagulant effect (Asakura and Ogawa, 2020).

In a patient with severe COVID-19 pneumonia, the combination of heparin and nafamostat, in addition to anti-SARS-CoV-2 treatment, dramatically improved severe hypoxemia likely caused by DIC and pulmonary embolism. Nafamostat is thought to be efficacious not only for its positive effects on DIC, but also for its antiviral effects, indicating its potential as a powerful treatment option for COVID-19.

A clinical trial for the combination treatment of nafamostat and favipiravir against COVID-19 is currently underway in Japan (jRCTs031200026). We hope that the sub-analysis of the trial would also reveal the sufficient efficacy of heparin and nafamostat combination therapy.

Author contributions

WT, HO, and HA wrote the manuscript. TY, HK, TU, and NT were involved in treating the patient.

Ethical approval

The patient gave permission and informed consent for the publication of this case report.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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