COVID-19 Nafamostat Observational Study in Japan: Preliminary Report

Fujita Health University Antiviral Observational Study Group

Introduction

Nafamostat mesylate, which will be referred to as nafamostat in this report, is a protease inhibitor that was approved for the treatment of acute pancreatitis in 1986 then disseminated intravascular coagulation (DIC) in 1989 and has been used widely in hospitals in Japan.

The spike proteins of severe acute respiratory syndrome virus (SARS-CoV), Middle East respiratory syndrome virus (MERS-CoV) and severe acute respiratory syndrome 2 (SARS-CoV-2) are activated by transmembrane protease serine 2 (TMPRSS2) located on the cell surface before the viruses infect the cells[1-3]. Nafamostat has been shown to inhibit SARS-CoV-2 infection of the alveolar epithelial cells by inhibiting TMPRSS2[4,5]. In a case series of 11 severe to critical COVID-19 patients treated with a combination of nafamostat and favipiravir, an oral RNA polymerase inhibitor, 7 patients were successfully weaned from ventilator and 7 patients were discharged alive from hospital[6].

The Antiviral Observational Study Group has primarily collected information on COVID-19 patients who have received favipiravir or ciclesonide. Here, we report the characteristics and outcome of patients who also received nafamostat in this cohort.

Methods

Patients with confirmed diagnosis of COVID-19, registered to the Antiviral Observational Study and given nafamostat during hospitalization were included. The majority of the patients also received favipiravir, ciclesonide, or both. The information collected included patient demographics, comorbidities, severity of disease, clinical outcome approximately one month after admission to the hospital, dose and duration of nafamostat, use of other medications to treat COVID-19. As for severity of disease, the disease severity recorded for the first day of favipiravir or ciclesonide, whichever was closer to the first day of nafamostat, was used. The study was approved by the institutional review board of Fujita Health University and Toho University.

Results

As of October 29, 2020, 699 COVID-19 patients who received nafamostat were registered to the study from 171 hospitals across Japan. Patient background was available in 690 cases, and clinical outcome at one month from admission was recorded in 515 cases.

In this cohort, 66.7% of the patients were male, 64.4% were age 60 or older, and 57.4% had at least one underlying diseases such as diabetes (Table 1). The majority (50.6%) had respiratory failure defined by oxygen saturation of 90% or lower. The A-DROP score, a prognostic scoring system developed for community-acquired pneumonia and recorded on the first day of favipiravir or ciclesonide in this study, classified 31.5%, 53.2%, 12% and 3.3% of the patients as having mild, moderate, severe and critical disease. In terms of other medications targeting COVID-19, 85.1% of the patients also received favipiravir, 51.6% ciclesonide, 18.9% dexamethasone, 10.9% methylprednisolone and 9.3% remdesivir. These medications were started prior to nafamostat in most instances (Table 2).

Administration of nafamostat was continuous infusion in 76% of the patients and intermittent infusion in 24% of the patients (Table 3). The median duration of treatment was 6 days. The median time from report of a positive SARS-CoV-2 test result to the start of the drug was 2 days, and the median time from admission to the start of the drug was 1 day. By defining mild, moderate and severe COVID-19 as disease not requiring supplemental oxygen, requiring supplemental oxygen, and requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), respectively, 43% had mild disease, 42.5% had moderate disease, and 14.5% had severe disease.

Table 1. Demographics of patients with COVID-19 who received nafamostat

Variables	N	N = 699	
Age group	699		
<10		1	(0.1%)
10-19		0	(0%)
20-29		19	(2.7%)
30-39		25	(3.6%)
40-49		89	(12.7%)
50-59		115	(16.5%)
60-69		158	(22.6%)
70-79		157	(22.5%)
80-89		101	(14.4%)
≥90		34	(4.9%)
Age	699		
≥60		450	(64.4%)
<60		249	(35.6%)
Sex	699		
Female		233	(33.3%)
Male		466	(66.7%)
Diabetes	694		
Present		207	(29.8%)
Absent		487	(70.2%)
Cardiovascular diseases	696		
Present		211	(30.3%)
Absent		485	(69.7%)
Diabetes or cardiovascular diseases	695		
Present		333	(47.9%)
Absent		362	(52.1%)
Chronic lung diseases	694		
Present		77	(11.1%)
Absent		617	(88.9%)
Immunosuppression	691		
Present		57	(8.2%)
Absent		634	(91.8%)
Any of the above comorbidities	692		
Present		397	(57.4%)
Absent		295	(42.6%)

Variables	N	N = 699	
Favipiravir	698		
Given		594	(85.1%)
Not given		104	(14.9%)
Ciclesonide	684		
Given		353	(51.6%)
Not given		331	(48.4%)
Lopinavir-ritonavir	699		
Given		22	(3.1%)
Not given		677	(96.9%)
Methylprednisolone	699		
Given		76	(10.9%)
Not given		623	(89.1%)
Dexamethasone	699		
Given		132	(18.9%)
Not given		567	(81.1%)
Camostat	699		
Given		24	(3.4%)
Not given		675	(96.6%)
Hydroxychloroquine	699		
Given		40	(5.7%)
Not given		659	(94.3%)
Remdesivir	699		
Given		65	(9.3%)
Not given		634	(90.7%)
Age ≥70 (male) or age ≥75 (female)	699	255	(36.5%)
BUN ≥21 mg/dL or dehydrated	594	141	(23.7%)
Oxygen saturation ≤90%	589	298	(50.6%)
Disturbance of consciousness	591	62	(10.5%)
Systolic blood pressure ≤90 mmHg	586	16	(2.7%)
A-DROP score	575		
Mild (0)		181	(31.5%)
Moderate (1)		185	(32.2%)
Moderate (2)		121	(21.0%)
Severe (3)		69	(12.0%)
Critical (4)		15	(2.6%)
Critical (5)		4	(0.7%)

Table 2. Timing of start of other therapies targeting COVID-19

(a) Prior to or simultaneous with start of nafamostat

	N=699	
Favipiravir	489	(70.0%)
Ciclesonide	311	(44.5%)
Lopinavir–ritonavir	16	(2.3%)
Camostat	10	(1.4%)
Hydroxychloroquine	30	(4.3%)
Remdesivir	26	(3.7%)
Dexamethasone	101	(14.4%)
Methylprednisolone	52	(7.4%)
Tocilizumab	31	(4.4%)

(b) After start of nafamostat

	N=699	
Favipiravir	90	(12.9%)
Ciclesonide	34	(4.9%)
Lopinavir–ritonavir	3	(0.4%)
Camostat	10	(1.4%)
Hydroxychloroquine	7	(1.0%)
Remdesivir	36	(5.2%)
Dexamethasone	28	(4.0%)
Methylprednisolone	23	(3.3%)
Tocilizumab	39	(5.6%)

The numbers do not match Table 1 as dates were missing in some cases.

Table 3. Administration of nafamostat

(a) Dosing of nafamostat

N	Dosign	n	(%)
513	10 mg once a day	16	(3.1%)
	10 mg twice a day	14	(2.7%)
	Other intermittent doses	93	(18.1%)
	Continuous infusion	390	(76.0%)

(b) Duration of nafamostat

N	Mean	SD	Median	Q1	Q3
643	8	9.3	6	4	9

(c) Days from positive PCR to first dose of nafamostat

N	Mean	SD	Median	Q1	Q3
678	3.5	4.3	2	1	5

(d) Days from hospital admission to first dose of nafamostat

N	Mean	SD	Median	Q1	Q3
682	3.8	8.8	1	0	4

Clinical outcome was assessed approximately one month into hospitalization as discharged alive, died in hospital, transferred for de-escalation of care, transferred for escalation of care, and still in hospital (Table 4). The mortality rates at the time of survey were 6.3%, 19.9% and 42.1% for mild, moderate and severe disease, respectively, for an overall one-month mortality rate of 17.3% (Table 4a). The mortality rates were higher in the higher age groups, at 15%, 18.8%, 44.9% and 50% for those in their sixties, seventies, eighties and nineties, respectively (Table 4b).

The approved mode of administration of nafamostat is intermittent infusion for acute pancreatitis and continuous infusion for DIC. Patients who received continuous infusion were more likely to be 60 years or older, have diabetes and have received additional COVID-19 therapy (favipiraivir, ciclesonide, dexamethasone, remdesivir) than those who received intermittent infusion (Table 5), but the one-month clinical outcome appeared to be comparable between the two groups (Table 6).

Table 4. Clinical outcome stratified by severity of disease and age groups in patients who received nafamostat

(a) Severity of illness

Outcome		Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
(n=515)	Mild	14 (6.3%)	14 (6.3%)	10 (4.5%)	18 (8.1%)	167 (74.9%)
	Moderate	43 (19.9%)	19 (8.8%)	19 (8.8%)	22 (10.2%)	113 (52.3%)
	Severe	32 (42.1%)	2 (2.6%)	9 (11.8%)	14 (18.4%)	19 (25.0%)
	Total	89 (17.3%)	35 (6.8%)	38 (7.4%)	54 (10.5%)	299 (58.1%)

(b) Age groups

Outcome		Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
(n=515)	<10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	10-19	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	20-29	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (100%)
	30-39	0 (0%)	1 (7.1%)	1 (7.1%)	0 (0%)	12 (85.7%)
	40-49	1 (1.5%)	6 (9.1%)	4 (6.1%)	7 (10.6%)	48 (72.7%)
	50-59	2 (2.2%)	9 (9.9%)	4 (4.4%)	7 (7.7%)	69 (75.8%)
	60-69	18 (15.0%)	7 (5.8%)	11 (9.2%)	16 (13.3%)	68 (56.7%)
	70-79	22 (18.8%)	9 (7.7%)	8 (6.8%)	12 (10.3%)	66 (56.4%)
	80-89	35 (44.9%)	3 (3.8%)	8 (10.3%)	6 (7.7%)	26 (33.3%)
	≥90	11 (50.0%)	0 (0%)	2 (9.1%)	6 (27.3%)	3 (13.6%)
	Total	89 (17.3%)	35 (6.8%)	38 (7.4%)	54 (10.5%)	299 (58.1%)

Table 5. Demographics of patients with COVID-19 who received nafamostat stratified by infusion method

Variables	N	Intermittent, N = 93	Continuous, N = 420
Age group	513		
<10		0 (0%)	0 (0%)
10-19		0 (0%)	0 (0%)
20-29		9 (9.7%)	6 (1.4%)
30-39		8 (8.6%)	9 (2.1%)
40-49		14 (15.1%)	48 (11.4%)
50-59		19 (20.4%)	65 (15.5%)
60-69		14 (15.1%)	98 (23.3%)
70-79		14 (15.1%)	107 (25.5%)
80-89		10 (10.8%)	65 (15.5%)
≥90		5 (5.4%)	22 (5.2%)
Age	513		
≥60		43 (46.2%)	292 (69.5%)
<60		50 (53.8%)	128 (30.5%)
Sex	513		
Female		35 (37.6%)	143 (34.0%)
Male		58 (62.4%)	277 (66.0%)
Diabetes	509		
Present		20 (21.7%)	134 (32.1%)
Absent		72 (78.3%)	283 (67.9%)
Cardiovascular diseases	511		
Present		27 (29.0%)	115 (27.5%)
Absent		66 (71.0%)	303 (72.5%)
Diabetes or cardiovascular diseases	510		
Present		40 (43.0%)	196 (47.0%)
Absent		53 (57.0%)	221 (53.0%)
Chronic lung diseases	509		
Present		7 (7.6%)	46 (11.0%)
Absent		85 (92.4%)	371 (89.0%)
Immunosuppression	506		
Present		6 (6.5%)	37 (8.9%)
Absent		86 (93.5%)	377 (91.1%)
Any of the above comorbidities	507		
Present		49 (52.7%)	236 (57.0%)
Absent		44 (47.3%)	178 (43.0%)

Variables	N	Intermittent, N = 93	Continuous, N = 420
Favipiravir	512		
Given		43 (46.2%)	373 (89.0%)
Not given		50 (53.8%)	46 (11.0%)
Ciclesonide	508		
Given		23 (24.7%)	236 (56.9%)
Not given		70 (75.3%)	179 (43.1%)
Lopinavir–ritonavir	513		
Given		4 (4.3%)	8 (1.9%)
Not given		89 (95.7%)	412 (98.1%)
Methylprednisolone	513		
Given		7 (7.5%)	51 (12.1%)
Not given		86 (92.5%)	369 (87.9%)
Dexamethasone	513		
Given		4 (4.3%)	127 (30.2%)
Not given		89 (95.7%)	293 (69.8%)
Camostat	513		
Given		0 (0%)	13 (3.1%)
Not given		93 (100%)	407 (96.9%)
Hydroxychloroquine	513		
Given		2 (2.2%)	10 (2.4%)
Not given		91 (97.8%)	410 (97.6%)
Remdesivir	513		
Given		2 (2.2%)	60 (14.3%)
Not given		91 (97.8%)	360 (85.7%)
Age ≥70 (male) or age ≥75 (female)	513	27 (29.0%)	165 (39.3%)
BUN ≥21 mg/dL or dehydrated	432	13 (32.5%)	89 (22.7%)
Oxygen saturation ≤90%	425	22 (56.4%)	166 (43.0%)
Disturbance of consciousness	428	5 (12.5%)	36 (9.3%)
Systolic blood pressure ≤90 mmHg	424	0 (0%)	9 (2.3%)
A-DROP score	417		
Mild (0)		11 (28.9%)	131 (34.6%)
Moderate (1)		12 (31.6%)	119 (31.4%)
Moderate (2)		7 (18.4%)	75 (19.8%)
Severe (3)		6 (15.8%)	45 (11.9%)
Critical (4)		2 (5.3%)	9 (2.4%)

Table 6. Clinical outcome stratified by infusion method in patients who received nafamostat

Outcome		Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
(n=374)	Intermittent	7 (17.5%)	0 (0%)	4 (10.0%)	12 (30.0%)	17 (42.5%)
	Continuous	51 (15.3%)	27 (8.1%)	25 (7.5%)	22 (6.6%)	209 (62.6%)

Discussion

This study reports characteristics and clinical outcome of nearly 700 patients who received nafamostat for COVID-19 in hospitals across Japan. The patients were typically older with underlying diseases and developing respiratory failure from COVID-19, which is not surprising given the need for continuous infusion of nafamostat and its use for approved indications concentrated in intensive care units. The high rates of therapy with favipiravir and ciclesonide reflect the nature of the cohort that primarily captures COVID-19 patients received these two medications. However, it is plausible that COVID-19 patients for whom

nafamostat is considered are also likely to receive other directed therapies such as favipiravir and remdesivir in clinical practice.

The one-month mortality rate of this cohort was 17.3% and exceeded 40% among those with severe disease. The mortality rates increased with age, which is in line with the findings from the favipiravir observational study[7].

Nafamostat has been used in the clinic for over 30 years in Japan, for various indications including acute pancreatitis, DIC, and anticoagulation during extracorporeal circulation. As a serine protease inhibitor, it has no direct antiviral activity, but instead inhibits TMPRSS2 which is abundant in human alveolar epithelial cells. TMPRSS2 activates the spike protein of coronaviruses allowing it to bind ACE2, thus nafamostat protects infection of human alveolar epithelial cells by SARS-CoV, MERS-CoV and SARS-CoV-2 *in vitro*[2,4,5]. Additionally, it has been postulated that nafamostat may prevent clot formation and excessive inflammation that accompany severe COVID-19[5].

The 50% effective concentration (EC_{50}) of nafamostat in preventing infection of alveolar epithelial cells by SARS-CoV-2 is in the range of 5-10 nM[4,5]. The steady-state plasma concentrations of nafamostat when infused to patients with DIC at 0.1 mg/kg/h or 0.2 mg/kg/h are 14-130 ng/mL, which easily exceeds the EC_{50}[8]. Since nafamostat is cleared from blood promptly after infusion, continuous infusion is likely preferred over intermittent infusion when it is used for the treatment of COVID-19 for its potential indirect antiviral efficacy.

Known side effects of nafamostat include hyperkalemia, hyponatremia, thrombocytopenia and liver function test abnormalities. This study did not collect information on possible/probable side effects of nafamostat. Nonetheless, periodic monitoring of complete blood count, electrolytes and liver function is recommended when nafamostat is used.

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