Ensitrelvir as a Treatment Option for Persistent SARS-CoV-2 Infection After Remdesivir in Hospitalized Patients With Comorbidities: A Single-Center Case Series From Japan

Masaya Yamato[1], Masahiro Kinoshita[2], Shogo Miyazawa[3], Masayuki Seki[1], Tomoki Mizuno[1], Takuhiro Sonoyama[4]

[1] Department of General Internal Medicine and Infectious Diseases, Rinku General Medical Center, Izumisano, Japan, [2] Medical Affairs Department, Shionogi & Co., Ltd., Osaka, Japan, [3] Data Science Department, Shionogi & Co., Ltd., Osaka, Japan, [4] Drug Development and Regulatory Science Division, Shionogi & Co., Ltd., Osaka, Japan

Rinku General Medical Center
+81-72-469-3111
m-yamato@rgmc.izumisano.osaka.jp

BACKGROUND

- Ensitrelvir is an oral inhibitor of 3CL protease of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) approved under the emergency regulatory approval system in Japan for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) [1]
  - Ensitrelvir has shown early alleviation of symptom and cessation of viral shedding in patients with mild-to-moderate COVID-19 [2]
  - In this case series we explore whether patients suffering from persistent SARS-CoV-2 infection could benefit from ensitrelvir
- We herein report a case series describing treatment outcomes of hospitalized patients with comorbidities who showed persistent SARS-CoV-2 infection after remdesivir and switched to ensitrelvir treatment (UMIN Clinical Trials identifier: UMIN000051300)

METHODS

- A retrospective chart review was conducted at Rinku General Medical Center (Osaka, Japan)
- All patients with COVID-19 who were hospitalized between November 2022 and April 2023, and were treated with ensitrelvir after ≥3-day remdesivir treatment were eligible for the analysis
  - Ensitrelvir was administered orally once daily (375 mg on Day 0, 125 mg on Days 1 to 4) according to the product label
- Data on patient characteristics, COVID-19 severity, post-treatment virologic outcomes, clinical outcomes, and drug-related adverse events were retrospectively captured until Day 13
  - COVID-19 severity (mild, moderate I [without respiratory failure], moderate II [with respiratory failure], or severe) was assessed per the treatment guidelines published by the Ministry of Health, Labour and Welfare of Japan [3] (**Table 1**)
  - Clinical outcomes (e.g., improvement, admission to the intensive care unit [ICU], disease progression, and death) and adverse events were assessed based on the investigator's judgment
- Quantitative antigen levels in patients' nasal swabs were assessed using Lumipulse® (Fujirebio, Japan)
  - The maximum and cutoff viral antigen levels were set at 5000 pg/mL and 1.34 pg/mL, respectively, according to the manufacturer's instructions
  - Viral clearance was defined as an antigen level of <89.73 pg/mL based on the published literature [4]

RESULTS

Patient disposition

- Among the 52 patients with COVID-19 who were treated with ensitrelvir at Rinku General Medical Center, 21 patients were considered eligible for this study as they were hospitalized and received ensitrelvir after ≥3-day remdesivir treatment (**Fig. 1**)

Fig. 1 Patient disposition

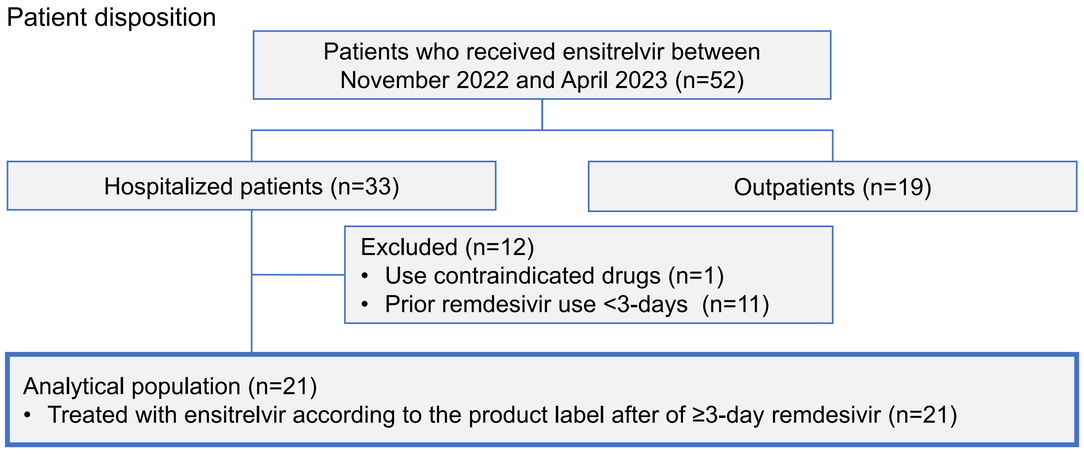


Table 1 COVID-19 disease severity criteria (according to Japanese guideline)

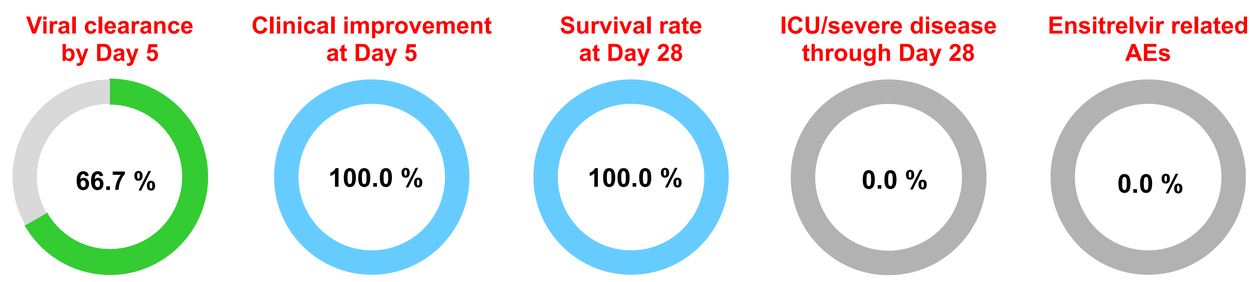
Severity	SpO2	Clinical condition
Mild	≥ 96%	No respiratory symptoms or cough only (no dyspnea, no evidence of pneumonia)
Moderate I	93% < SpO2 < 96%	Dyspnea, pneumonia
Moderate II	SpO2 ≤ 93%	Requires oxygen
Severe		ICU admission or requires mechanical ventilator

Table 2 Patient demographics and clinical characteristics on Day 0 (before the initiation of ensitrelvir treatment)

	Overall (n=21)	Mild (n=17)	Moderate I (n=2)	Moderate II (n=2)
Male sex, n (%)	10 (47.6)	6 (35.3)	2 (100.0)	2 (100.0)
Age (years), mean±SD	78.0±8.9	77.4±8.4	73.5±12.0	87.5±9.2
Prior treatment for SARS-CoV-2 infection, n (%)				
Remdesivir	20 (95.2)	16 (94.1)	2 (100.0)	2 (100.0)
Remdesivir + casirivimab/imdevimab	1 (4.8)	1 (5.9)	0 (0.0)	0 (0.0)
Duration of remdesivir treatment (days), mean±SD	6.6±3.9	6.5±4.2	7.5±3.5	6.0±2.8
No SARS-CoV-2 vaccination, n (%)	5 (23.8)	4 (23.5)	0 (0.0)	1 (50.0)
Concomitant use of systemic corticosteroids, n (%)	5 (23.8)	5 (29.4)	0 (0.0)	0 (0.0)
Comorbidity, n (%)				
Malignant tumors	7 (33.3)	6 (35.3)	0 (0.0)	1 (50.0)
Diabetes mellitus	6 (28.6)	2 (11.8)	2 (100.0)	2 (100.0)
Renal failure	4 (19.0)	3 (17.6)	0 (0.0)	1 (50.0)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation

Outcomes



- Two patients experienced viral rebound (viral antigen level ≥89.73 pg/mL) after viral clearance by Day 13, but neither of the two reported rebound of symptoms nor received additional antiviral.
- Patient #14 did not achieve viral clearance and received remdesivir between Day 7 and Day 11
- Five patients developed a transient increase of body temperature (≧37.5 degree Celsius) after completion of ensitrelvir treatment.
- Twenty of 21 patient were discharged (by Day 77)
  - Patient #17 died on Day 59 due to an underlying comorbidity of ANCA-associated vasculitis.

CONCLUSIONS

This retrospective chart review shows efficacy of ensitrelvir in hospitalized Japanese patients with persistent COVID-19 after remdesivir treatment

The current results indicate that ensitrelvir is a treatment option for patients with persistent SARS-CoV-2 infection with risk factors for severe disease

Table 3 Individual patient characteristics and viral antigen levels (pg/mL)

#	Last remdesivir dose	Remdesivir treatment period (days)	COVID-19 severity	Sex	Age Range (years)	Number of vaccinations	Prior SARS-CoV-2 agents	Comorbidities				Day -1 Day -2	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
								DM	Renal Failure	Cancer	Others															
1	Day 0	8	Moderate II	M	90-94	0	Remdesivir	X	X		CHF	5000	5000		5000	5000	5000				1233	495		255	8.67	44.6
2	Day 0	4	Moderate II	M	80-84	2	Remdesivir	X		Pulmonary metastasis from colon	Suspected BSI	5000	5000			87.07	25.39	8.5	6.81	7.94	94.59	0.14	2.29	0.05	1.73	0.57
3	Day -2	5	Moderate I	M	65-69	4	Remdesivir	X			Chronic Atrial Fibrillation, Chronic Subdural Hematoma	206	3430	235	10.35	1.06	0.95									
4	Day 0	10	Moderate I	M	80-84	4	Remdesivir	X			CHF, CI	5000	5000			538		84.4	7.89	43.06	3.56	2.08	0.01	0.06		
5	Day -1	5	Mild	M	80-84	5	Remdesivir			Esophagus	Hypertension	5000	5000		571			21.75	18.67	9.43	2.81	0.06	4.79	0.01	0.1	
6	Day -1	5	Mild	F	80-84	2	Remdesivir			Lung	CI	255	5000			36.55		25.72	1.61	0.3	0.01					
7	Day -1	5	Mild	F	75-79	0	Remdesivir				Traumatic Subarachnoid Hemorrhage, Heart Failure	5000	5000		1394		39.12	43.49	46.3		28.65	0.83	0.89			
8	Day 0	4	Mild	F	50-54	2	Remdesivir			Liver metastasis (from sigmoid colon), breast			5000		1676					27.73						
9	Day -1	8	Mild	F	70-74	0	Remdesivir				Osteoarthritis	5000	2729	3736	142		13.5	0.3								
10	Day 1	22	Mild	F	75-79	0	Remdesivir	X	X		ANCA Associated Vasculitis	5000	5000		2588		4.77	1211		5000	5000	5000				
11	Day 0	8	Mild	F	80-84	5	Remdesivir				Asthma, CI	5000	5000	5000		1087	4091			16.27	11.83	3.76	1.73	0.01		
12	Day -1	7	Mild	M	75-79	4	Remdesivir			Melanoma	Atrial Fibrillation	5000			1.04	0.11										
13	Day -1	6	Mild	F	65-69	0	Remdesivir				Valve Disorders, Gastric Ulceration	5000	5000		53.22			2.1	0.62							
14	Day 0	5	Mild	F	75-79	3	Remdesivir				Upper Gastrointestinal Bleeding, Hypertension	4329	5000		5000			2468		5000		3637			114.93	12.95
15	Day 0	5	Mild	F	80-84	4	Remdesivir			Colon	Candidemia	1728	2393		1354			2.51	1.61	1.05	2.59	1.03	0.01			
16	Day -6	5	Mild	M	80-84	3	Remdesivir		X		Liver Failure	5000		5000			7.42	8.09	1.97	4.39	0.71	2.78	0.67	1.72	0.08	0.24
17	Day 0	3	Mild	F	80-84	4	Remdesivir + casirivimab/ imdevimab				ANCA Associated Vasculitis, UTI	5000	5000			224		2.37	8.01	5.99	41.02		1.23	0.01		
18	Day -1	7	Mild	M	70-74	5	Remdesivir			Stomach	Rheumatoid Arthritis	1305	5000			1021				19.95	1.89	0.57	0.24			
19	Day -1	6	Mild	F	90-94	5	Remdesivir		X		CHF	5000			1767	275	246	148	111			3.44	6.81	1.92	1.15	0.56
20	Day -2	5	Mild	M	75-79	3	Remdesivir	X			COPD, Organizing Pneumonia	5000	5000		5000		1330									
21	Day -1	5	Mild	F	70-74	4	Remdesivir				CI, Hypertension	5000	5000		1292			63.29		9.86	11.31	1.56	0.01			

Day 0 is the date of the first ensitrelvir dose. Shading (green) represents days the patient was hospitalized
COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, Renal Failure includes Chronic Kidney Disease, Chronic Renal Failure
DM: Diabetes Mellitus, BSI: Bloodstream Infection, CI: Cerebral Infarction, CHF: Chronic Heart Failure, UTI: Urinary Tract Infection

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CONFLICTS OF INTEREST

M. Yamato has received lecture fees from, and serves as an advisor for, Shionogi & Co., Ltd. M. Kinoshita, S. Miyazawa, and T. Sonoyama are full-time employees of Shionogi & Co., Ltd. M. Seki and T. Mizuno have no conflict of interest.