Ensitrelvir in Hospitalised Patients with SARS-CoV-2 During the Omicron Epidemic: A Single-Center Observational Study

P5015

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Background and Objective

- The Omicron variant of SARS-CoV-2 exhibits significantly higher transmissibility relative to previous variants, resulting in a global increase in case numbers[1,2]
- There is an urgent need for antiviral agents that can effectively counteract the Omicron variant
- Ensitrelvir, an oral 3C-like protease inhibitor targeting SARS-CoV-2,[3] received emergency authorisation in November 2022 and regular approval in March 2023 in Japan for the treatment of SARS-CoV-2 infection
- Several case reports have documented the use of ensitrelvir in real-world settings, including its application in hospitalised patients[4,5,6]
- The present chart review aimed to investigate the treatment patterns, patient characteristics and treatment outcomes of hospitalised patients receiving ensitrelvir versus remdesivir

Methods

Study Design and Study Period

- A single-center chart review was conducted at the Rinku General Medical Center, one of four designated medical institutions for specific infectious diseases in Japan
- This observational study (UMIN000056047) examined hositalised patients with COVID-19 who received ensitrelvir or remdesivir between November 2022 and August 2024

Eligibility Criteria

Inclusion criteria	Exclusion criteria
• Patients with data on start and end dates of ensitrelvir or remdesivir administration	• Non-adherence to treatment dosage guidelines for ensitrelvir and remdesivir
• A positive SARS-CoV-2 test result	• Refusal to participate
• Availability of data on clinical outcomes of COVID-19 infection	

Data Collection, Study Endpoints and Study Analyses

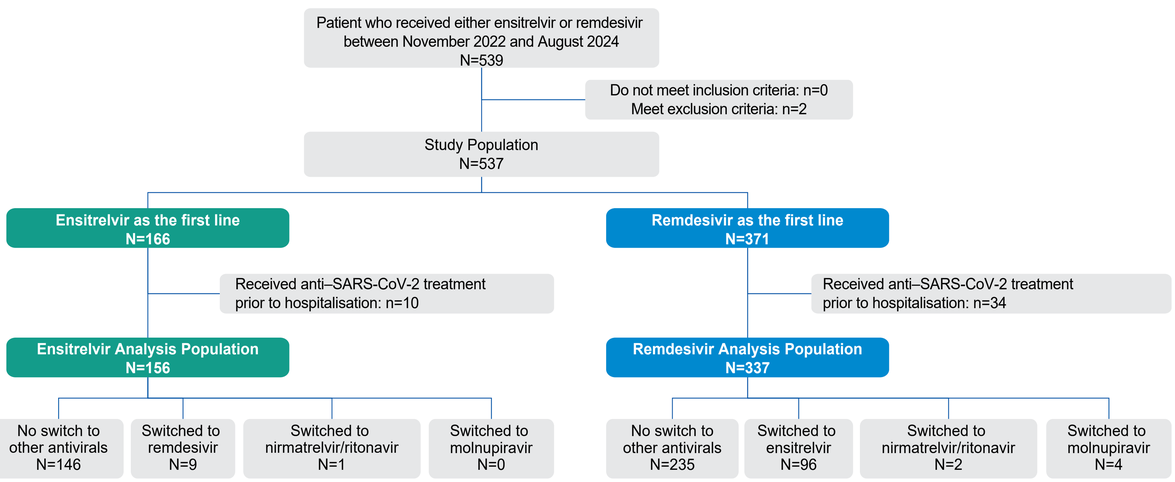
- Data were collected using electronic medical records
  - Data on patient demographics, disease severity, post-treatment mortality status, virologic and clinical outcomes were extracted
- The primary analysis population was the patients who took ensitrelvir or remdesivir as a first-line therapy
- Endpoints of the study were all-cause mortality on Day 28, time to discharge and time to viral clearance up to Day 14
- Inverse Probability of Treatment Weighting (IPTW) was used to standardise the baseline characteristics across the ensitrelvir and remdesivir groups to mitigate differences in patient characteristics affecting life prognosis
  - For each endpoint, estimators were calculated before and after adjusting for IPTW
- Subgroup analyses were carried out based on baseline COVID-19 severity (moderate I, moderate II or severe patients), immunosuppressive conditions and vaccination history
- Quantitative antigen level in nasopharyngeal swabs was assessed using Lumipulse® (Fujirebio, Tokyo, Japan), viral clearance was defined as an antigen level of <89.73 pg/mL

Results

Patient Disposition and Baseline Characteristics

- A total of 156 and 337 patients received ensitrelvir and remdesivir, respectively, as their first-line anti–SARS-CoV-2 treatment **(Figure 1)**

Figure 1. Patient Disposition



- The severity and other factors were balanced between the two groups in the adjusted-analysis cohorts

Table 1. Baseline Characteristics

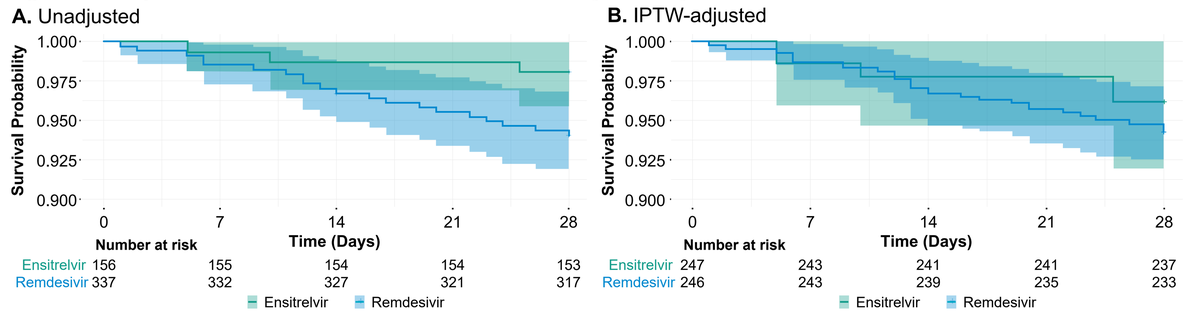
Baseline characteristics	Ensitrelvir (N=156)	Remdesivir (N=337)
Male	100 (64.1)	201 (59.6)
Age, Mean (SD)	76.8 (11.5)	75.7 (14.6)
COVID-19 disease severity*		
Mild	118 (75.6)	166 (49.3)
Moderate I	14 (9.0)	14 (4.2)
Moderate II	19 (12.2)	97 (28.8)
Severe	5 (3.2)	60 (17.8)
Oxygen supplementation	29 (18.6)	178 (52.8)
Immunosuppressive conditions	31 (19.9)	54 (16.0)
Presence of pneumonia	35 (22.4)	147 (43.6)
Vaccination history		
Yes	141 (90.4)	277 (82.2)
No	14 (9.0)	59 (17.5)
Unknown	1 (0.6)	1 (0.3)
Underlying risk factor		
Cardiovascular	104 (66.7)	222 (65.9)
Hypertension	78 (50.0)	161 (47.8)
Malignancy	67 (42.9)	87 (25.8)
Diabetes mellitus	46 (29.5)	99 (29.4)

Data are presented as n (%) unless otherwise specified, or mean (SD). *Mild: SpO_2 ≥96% with no respiratory symptoms or, with cough only (no dyspnoea, no evidence of pneumonia); Moderate I: SpO_2 <93% or 96% with dyspnoea, pneumonia; Moderate II: SpO_2 ≤93% with oxygen requirement; severe: requiring ICU admission or mechanical ventilator

All-Cause Mortality on Day 28

- All-cause mortality on Day 28 was 1.9% (n=3/156) and 5.9% (n=20/337) in patients who received ensitrelvir and remdesivir, respectively, as their first-line anti–SARS-CoV-2 treatment (HR: 0.32 [95% CI: 0.09-1.07]; **Figure 2A**)
- All-cause mortality after IPTW adjustment on Day 28 was 3.8% with ensitrelvir and 5.7% with remdesivir (HR: 0.66 [95% CI: 0.19-2.29]; **Figure 2B**)

Figure 2. Kaplan-Meier Curve for All-Cause Mortality on Day 28



95% confidence bands are shown in the figure

Table 2. Day 28 All-cause Mortality in Sensitivity Analysis and Subgroup Analysis

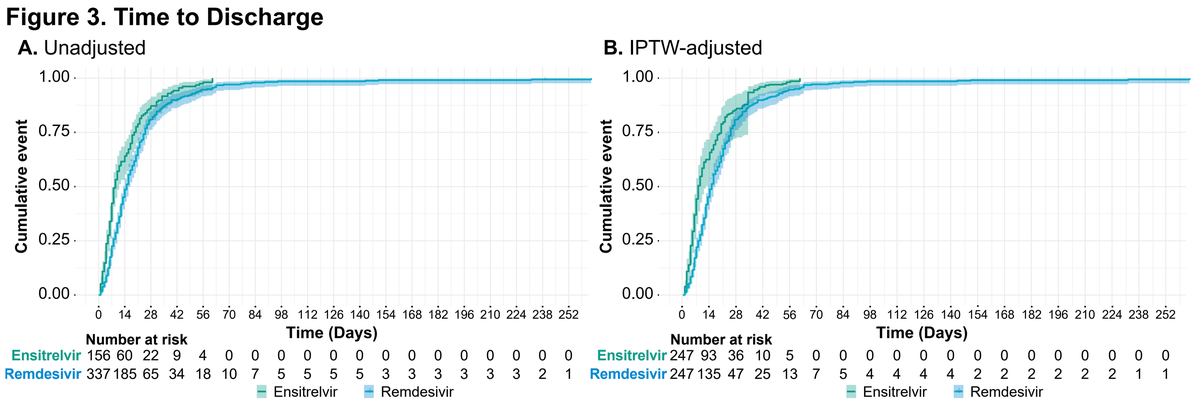
	Ensitrelvir	Remdesivir	HR (95% CI)
Sensitivity analysis			
Unadjusted	1.8 (3/166)	6.2 (23/371)	0.29 (0.09-0.95)
IPTW-adjusted	3.2 (9/268)	5.6 (15/268)	0.56 (0.16-1.94)
Subgroup analysis			
Moderate and severe severity			
Unadjusted	5.3 (2/38)	5.8 (10/171)	0.89 (0.19-4.06)
IPTW-adjusted	5.6 (5.9/107)	5.3 (5.5/105)	1.04 (0.22-4.94)
Immunosuppressive conditions			
Unadjusted	3.2 (1/31)	9.3 (3/54)	0.34 (0.04-2.91)
IPTW-adjusted	5.3 (2.1/40)	10.1 (4.5/44)	0.52 (0.06-4.51)

Data are shown as "% (n/N)", where n = number of deaths in each subgroup and N = number in each subgroup

Time to Discharge

- The time to discharge was significantly shorter with ensitrelvir compared with remdesivir, with an IPTW-adjusted HR of 1.52 (95% CI: 1.19-1.96; **Figure 3A and 3B**)

Figure 3. Time to Discharge



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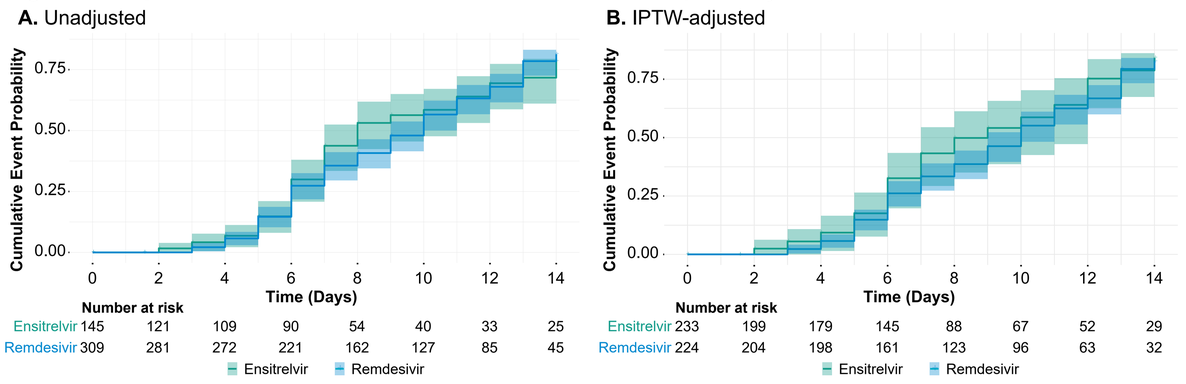
Time to Viral Clearance up to Day 14

- The Kaplan-Meier curves for time to viral clearance up to Day 14 overlapped in both the ensitrelvir and remdesivir treatment groups **(Figure 4A and 4B)**
- The IPTW-adjusted HR for viral clearance was 1.15 (95% CI: 0.87 - 1.50)

Figure 4. Kaplan- Meier Curve for Time to Viral Clearance up to Day 14



95% confidence bands are shown in the figure

Limitations

- Firstly, this study is a single-center observational study, limiting the generalizability of the results to other settings. Further multi-center studies are required to establish broader applicability
- Secondly, the decision regarding treatment was determined by the investigator's clinical judgment. Although IPTW was used to adjust for baseline characteristics between the two groups, as demonstrated in this presentation, there remains a possibility of confounding by indication, which has not been fully addressed
- While remdesivir is given intravenously and ensitrelvir orally, confounding factors linked to these methods may remain. IPTW adjustment balanced patient characteristics, but route-related confounders might still exist

Conclusions

- Ensitrelvir was associated with a low all-cause mortality on Day 28 in hospitalised patients with COVID-19, despite the inclusion of patients with complicating factors such as advanced age, various pre-existing comorbidities, immunosuppressive conditions and moderate to severe COVID-19 upon admission
- These findings suggest the potential of ensitrelvir as a valuable treatment option for hospitalised patients with COVID-19

References

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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, Y. Yoshida and T. Sonoyama are employees of Shionogi & Co., Ltd. Y. Yamamoto and R. Izuhara have no conflicts of interest to disclose

Abbreviations

CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SpO_2, oxygen saturation

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