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Case Series

Ensitrelvir improved SARS-CoV-2 viral titers of COVID-19 patients refractory to remdesivir

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Abstract: Background: The titers of SARS-COV-2 antigens are frequently used as markers of viral activity and threshold for release from quarantine and treatment. COVID-19 patients were treated with several antiviral agents, including remdesivir (RDV) and ensitrelvir (ESV), which is a novel anti-SARS-CoV-2 agent recently suggested to have strong antiviral activity. **Cases**: We present the cases of two patients whose SARS-CoV-2 antigens were successfully decreased by oral administration of ESV after they could not be decreased by RDV drip infusion. Case 1 was a 74-year-old man who was admitted with SARS-CoV-2 infection and had been infected by the virus a month earlier and relapsed twice. He had been treated with rituximab for diffuse B cell lymphoma and not received vaccination for SARS-CoV-2. RDV was administered intravenously two weeks earlier and again 4 days earlier, but it failed to control the infection, and he was transferred to our hospital (day 1). Intravenous RDV was restarted on day 1, but viral antigens remained high until day 5. The RDV was then switched to oral ESV, and viral antigen titers were successfully decreased on days 8, 10, and 12. Case 2 was an 81-year-old man who was admitted with SARS-CoV-2 infection on day 0. He had heart failure and diabetes mellitus, and had not received vaccination for SARS-CoV-2. Intravenous RDV was started on day 1, but viral antigens were still high until day 8. He was then switched from RDV to oral ESV, and viral antigen titers were successfully decreased on day 11. **Conclusions:** These cases suggest that ESV might be more effective than RDV for reducing viral activity, and it is easy to administer orally.

Keywords: COVID-19, SARS-CoV-2, Ensitrelvir, Remdesivir, Viral titer

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1. Background

SARS-CoV-2 is currently well treated using antiviral agents, such as remdesivir (RDV: Gilead, Foster City, CA, USA), and this agent has been recommended as the first-choice treatment for moderate and hospitalized COVID-19 patients [1, 2]. RDV can improve the patient's condition along with reduction of viral antigen titers, and the patient is usually released from quarantine after the standard RDV treatment regimen lasting 5 days. However, in some patients, the virus is not eliminated, and high viral titers persist in the nasal swabs, especially in patients with hematological malignancies, because they are immunocompromised by the impairment of lymphocytes, and viral clearance is inhibited by steroid and rituximab treatment [3]. Therefore, the RDV treatment period had to frequently be extended to up to 10 days, and the 3 to 5-day regimen of RDV was repeated in such immunocompromised patients with underlying diseases.

Recently, ensitrelvir (ESV; Shionogi CO. LTD., Osaka, Japan) was developed, and its use was started from autumn 2022 in Japan, and strong activity for eliminating SARS-CoV-2 was reported [4, 5]. ESV inhibits 3C-like protease (3CL protease) and effectively reduces viral replication. In fact, ESV treatment was reported to result in clinical improvement of symptoms along with the strong elimination of SARS-CoV-2 in COVID-19 patients [6].

In this report, two cases of COVID-19 patients who showed persistently high viral antigen titers though they received repeated or extended RDV treatment and were then successfully treated and released from quarantine after being switched to ESV are described.

These cases study was approved by the Institutional Review Board of Saitama Medical University International Medical Center (#2022-032) on July 6, 2022 and registered as UMIN000047691. The patients whose specimens were used provided written, informed consent to have their case details and any accompanying images published.

2. Case Reports

2.1. Case 1

A 74-year-old man with diffuse B cell lymphoma was admitted to our hospital because he had COVID-19 a month earlier, but relapsed twice. He had been treated with rituximab and steroid for diffuse B cell lymphoma and had not been vaccinated for SARS-CoV-2. RDV was administered intravenously two weeks earlier and again 4 days earlier for 5 days each time, but his infection remained uncontrolled, and he was then transferred to our hospital (day 1). SARS-CoV-2 antigen (Ag) showed a high titer of 2711 IU (Cobas SARS-CoV-2 Ag, Roche, Basel, Switzerland) in the nasal swab (Figure 1A). Laboratory data on admission at our university hospital were mild, as follows: white blood cell (WBC) count, 3.44 x 10^3/μL, with 94.0% neutrophils, 1.3% lymphocytes, 3.0% monocytes, 1.5% eosinophils, and 0.2% basophils; platelet count, 14.2 × 10^4/μL; hemoglobin, 10.1 g/dL; blood urea nitrogen, 26.2 g/L; serum creatinine, 0.65 mg/dL; aspartate aminotransferase (AST), 13 U/L; alanine aminotransferase (ALT), 15 U/L; and C-reactive protein (CRP), 0.177 mg/dL.

Antiviral therapy with RDV drip infusion 200 mg, followed by 100 mg per day for 5 days intravenously, was started, but the viral antigen titer remained high, reaching 631 IU on day 5, although the viral titer decreased to 195 IU on day 2 (Figure 1A). Therefore, the patient was switched from RDV to oral administration of ESV for 5 days.

On day 8, viral antigen titer was statistically significantly reduced to 2.31 IU, and they became almost negative, at 1.27 IU on day 10 and 1.19 IU on day 12 (Figure 1A, p=0.0045). He successfully completed the treatment for COVID-19 and was released from quarantine.

2.2. Case 2

An 81-year-old man with diabetes mellitus was admitted to our hospital because he showed high fever (38.6 °C) and was found to be COVID-19-positive; SARS-CoV-2 Ag in the nasal swab showed a high titer, 7340 IU, on day 1 (Figure 1B). Laboratory data on admission to our university hospital were mild, as follows: white blood cell (WBC) count, 8.23 x 10^3/μL, with 66.4% neutrophils, 21.0% lymphocytes, 9.8% monocytes, 2.4% eosinophils, and 0.4% basophils; platelet count, 31.7 × 10^4/μL; hemoglobin, 12.9 g/dL; blood urea nitrogen, 58.6 g/L; serum creatinine, 1.16 mg/dL; aspartate aminotransferase (AST), 18 U/L; alanine aminotransferase (ALT), 15 U/L; and C-reactive protein (CRP), 0.359 mg/dL.

Antiviral therapy with RDV drip infusion 200 mg, followed by 100 mg per day for 5 days was started, but the viral antigen titer was still high, 945 IU, on day 5 (Figure 1B). RDV administration was extended until day 8, but the viral antigen titer was still 607 IU. Therefore, he was switched from RDV to oral administration of ESV for 5 days.

On day 11, the viral antigen titer was decreased to 81.1 IU: this viral reduction was not statistically significant (Figure 1B, p=0.0719), but less than the regular threshold (excluding hematological patients) of our hospital (100 IU). He successfully completed the treatment for COVID-19 and was released from quarantine.

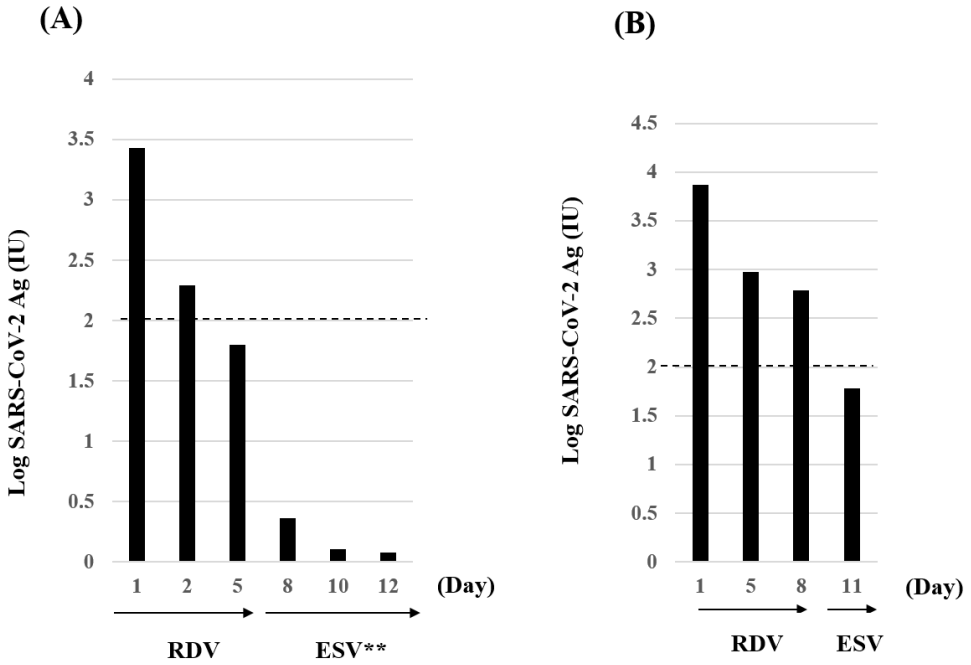

Figure 1. Decreases of SARS-CoV-2 antigen titers in the nasopharyngeal swabs after switching from remdesivir (RDV) to ensitrelvir (ESV) in Case 1 (A) and Case 2 (B). Viral antigen titers are presented using log scales, and statistical analysis were performed by geometric and Kraskal-Wallis analysis judged by *p<0.05 as the significant. Statistical significant viral reduction was found in Case 1 (**p<0.01), and tendency in the Case 2. Dotted lines mean the regular threshold (excluding hematological patients) of the viral antigen titer in our hospital (100=10^2 IU).

3. Discussion

Recently, COVID-19 treatments have advanced with the development of novel antiviral agents, including RDV and oral drugs, and most immunocompetent adults survived the Omicron era [1, 2, 7, 8]. However, some immunocompromised patients showed persistent viral excretion despite adequate treatment using RDV drip infusion [3, 9], and extended use of RDV and/or switching to other antiviral agents, including ESV, was needed.

In this report, two cases of patients whose viral titers were sufficiently decreased by switching from RDV to ESV were described. Viral antigen titers have been reported to improve to almost negative in patients with hematological malignancies and to less than 100 IU, equal to a 35 Ct value of RT-PCR, in the nasopharyngeal swabs of immunocompetent to mildly immunocompromised patients [10, 11]

ESV is a novel, oral SARS-CoV-2 3CL protease inhibitor for the treatment of COVID-19; it inhibits a cysteine protease that is essential for viral replication, and since spike proteins and 3CL proteases are encoded by distinct regions; thus, it may be assumed that the antiviral efficacy of ESV will not be impacted by mutations in viral spike proteins [5, 12]. In addition, antiviral treatment options such as remdesivir and molnupiravir have been shown to be efficacious against Omicron [13], but recent clinical studies have highlighted the therapeutic potential of nirmatrelvir, which is a peptide-like, covalent, oral 3CL protease inhibitor, similar to ESV [14]. These findings suggest the 3CL protease

molecule may be a potentially stable target for antiviral agents. However, the elimination of nirmatrelvir in humans is rapid due to its low metabolic stability, and nirmatrelvir requires the coadministration of ritonavir as a pharmacokinetic booster to maintain the target exposure. Consequently, this leads to a limitation in the use of nirmatrelvir due to potential drug-drug interactions (DDIs) with ritonavir [14].

Protocols for the use of ESV have it boosted by a loading dose of 375 mg/day orally on the first day, followed by maintenance with 125 mg/day from the second to fifth days, and there is almost no concern about potential DDIs, although nilmatrelvir/ritonavir needs DDI checks before prescription to COVID-19 patients who concomitantly take other drugs for their underlying diseases. Furthermore, 3-CL, the target of ESV, is involved in the early stage of viral replication; therefore, inhibition of 3-CL may be more effective than inhibition of parts of the viral replication process including that of RNA-dependent RNA polymerase, which is the target of RDV [2]. In fact, ESV showed rapid viral clearance by approximately 50 h in clinical trials [6]. These data suggested that ESV may be an alternative candidate agent for COVID-19 patients refractory to intravenous RDV administration and other oral-intake drugs. This case series is in the limited sample size, and we should investigate this viral reduction efficacy of ensitrelvir in the more substantial number of the cases. Further investigation and comparisons with ESV and other anti-COVID-19 agents will be needed.

4. Conclusions

Two cases of COVID-19 patients refractory to RDV treatment were described. Both patients had not been vaccinated for the infecting virus, and they had underlying diseases, including hematological malignancies. Switching from RDV to a novel antiviral agent, namely ESV, effectively decreased viral antigen titers to below the threshold of non-activated virus levels. The patients' conditions improved, and they were released from quarantine. ESV inhibits 3-CL protease before the viral replication process, and it appears to show more effective clinical inhibition of viral titers than does RDV.

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None

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References

[1] Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis, 2020:doi: 10.1093/cid/ciaa478.

[2] Beigel JH, Tomashek M., Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med, 2020. 383: 1813-1826.

[3] Seki M, Hashimoto K, Kondo N, Ohya Y, Kotajima F, Mitsutake K., Sequential Treatment by Antiviral Drugs Followed by Immunosuppressive Agents for COVID-19 Patients with Hematological Malignancy. Infect Drug Resist. 2022. 15: 7117-7124.

[4] Shimizu R, Sonoyama T, Fukuhara T, Kuwata A, Matsuo Y, Kubota R. Safety, Tolerability, and Pharmacokinetics of the Novel Antiviral Agent Ensitrelvir Fumaric Acid, a SARS-CoV-2 3CL Protease Inhibitor, in Healthy Adults. Antimicrob Agents Chemother, 2022. 66: e0063222.

[5] Mukae H, Yotsuyanagi H,, Ohmagari N, et al. A Randomized Phase 2/3 Study of Ensitrelvir, a Novel Oral SARS-CoV-2 3C-Like Protease Inhibitor, in Japanese Patients with Mild-to-Moderate COVID-19 or Asymptomatic SARS-CoV-2 Infection: Results of the Phase 2a Part. Antimicrob Agents Chemother. 2022. 66: e0069722.

[6] Mukae H, Yotsuyanagi H,, Ohmagari N, et al. Efficacy and Safety of Ensitrelvir in Patients With Mild-to-Moderate Coronavirus Disease 2019: The Phase 2b Part of a Randomized, Placebo-Controlled, Phase 2/3 Study. Clin Infect Dis. 2023. 76:1403-1411.

[7] Ebina S, Seki M, Karaushi H, Shimizu A, Mitsutake K. Antibiotic prescriptions for COVID 19 patients increased during the BA.5 period. World J Med Microbiol. 2023. 2: 11-13.
[8] Seki M, Karaushi H, Enami K, et al. Use of Molnupiravir for COVID-19 Patients in Japan Use of Molnupiravir for COVID-19 Patients in Japan. 2022. 4: 121.
[9] Seki M. Trends in the management of infectious disease under SARS-CoV-2 era: From pathophysiological comparison of COVID-19 and influenza. World J Virol. 2021. 10: 62-68.
[10] La Scola B, Le Bideau M, Andreani J, Hoang VT, Grimaldier C, Colson P, Gautret P, Raoult D. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. Eur J Clin Microbiol Infect Dis. 2020. 39: 1059-1061.
[11] Kase F, Ota T, Ota H, Aoyama S, Ouchi K, Hoshi H, Iida Y. Negative confirmation and infectivity estimation by quantitative antigen test of COVID-19. Igaku-Kensa. 2022. 71: 250-256.
[12] Huang Y, Yang C, Xu X, Xu W, Liu S. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-1. Acta Pharmacologica Sinica. 2020. 41: 1141-1149.
[13] Takashita E, Kinoshita N, Yamayoshi S, et al., Efficacy of Antibodies and Antiviral Drugs against Covid-19 Omicron Variant. N Engl J Med. 2022. 386: 995-998.
[14] Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med. 2022. 386: 1397-1408.