Infection and Drug Resistance Dovepress

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Clinical Features of Patients with COVID-19 Recurrence During Hospitalization in the Omicron Variant Surge

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Background: Repeat positive results for SARS-CoV-2 by antigen detection test/RT-PCR in recovered COVID-19 patients were not very rare even when omicron variants became dominant, but the clinical features of patients with recurrent COVID-19 during hospitalization are still unclear.

Methods: The clinical characteristics of patients with recurrent COVID-19 during hospitalization were retrospectively investigated from January 2023 to December 2023.

Results: Recurrence of COVID-19 was found in 7 of 275 (2.5%) patients during hospitalization. Their mean age was 80.3 (74–89) years, and 4 of 7 (57.1%) patients were hospitalized on the hematology ward with B cell/non-Hodgkin lymphoma. These 4 lymphoma patients had been vaccinated, but the other 3 patients hospitalized on the emergency ward and the neurology ward had not been vaccinated. Of the 7 patients, 6 (85.7%) were initially treated with remdesivir (RDV), but only 3 patients were re-treated with RDV, and the other 4 patients were successfully re-treated with oral 3C-like protease inhibitors, such as ensitrelvir (ESV) and nirmatrelvir/ritonavir (N/R).

Conclusion: These data suggest that COVID-19 recurrence was found in patients with hematological disorders, such as lymphoma, and/or patients with no vaccination history. However, these patients were treated successfully by re-administration of anti-SARS-CoV-2 agents, including ESV and N/R.

Keywords: SARS-CoV-2, remdesivir, nirmatrelvir/ritonavir, ensitrelvir, rituximab, Anti-CD20+ B cell depletion

Commentary

COVID-19 has had an enormous impact on societies worldwide, and SARS-CoV-2 is currently well treated using antiviral agents, such as remdesivir (RDV: Gilead, Foster City, CA, USA), which 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, but in some patients, the virus is not eliminated completely, and there is recurrence of COVID-19 even though the patients remain hospitalized and quarantined.[3,4]

In this study, we investigated the recurrent patients and found that there were 7 recurrent cases of COVID-19 during hospitalization of a total of 275 (7/275= 2.5%) COVID-19 patients admitted to our hospital from January 2023 to December 2023 (Table 1). This case 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. All patients participating in this study provided written, informed consent as part of the comprehensive consent obtained at admission to have any accompanying images and their case details published. The patients were provided the means to opt out of these clinical studies in particular. This study adhered to the Declaration of Helsinki.

Received: 7 July 2024
Accepted: 7 November 2024
Published: 11 November 2024

Table 1 Characteristics of Patients with COVID-19 Recurrence During Hospitalization

	Age (years old)	Male/ Female	Ward	Underlying diseases	Vaccine (times)	Ag before 1st treatment (IU)	Ag after 1st treatment (IU)	1st Treatment drug	Interval (days)	Ag before 2nd treatment (IU)	Ag after 2nd treatment (IU)	2nd Treatment drug	Survive/ Death
1	74	M	Hematology	B lymphoma	3	Positive	None	RDV	9	2771	63	RDV	S
2	84	F	Hematology	Non Hodgkin Lymphoma	1	37.9	0.81	RDV	9	867	0.71	ESV	S
3	89	M	ER	Nursing home residents	0	2024	21	RDV	5	217	9.46	ESV	S
4	77	M	ER	Lung cancer	0	Positive	None	None	6	192	13.3	RDV	S
5	76	F	Neurology	Brain infarction	0	3190	63	RDV	3	1265	6.9	RDV	S
6	74	M	Hematology	B lymphoma	5	849	48.4	RDV	4	285	1.91	N/R	S
7	88	F	Hematology	Non Hodgkin Lymphoma	4	2773	11.5	RDV	9	661	8.76	ESV	S

Abbreviations: Ag, Antigen (IU); EST, Ensitrelvir; M, Male; F, Female; N/R, Nirmatrelvir/Ritonavir; RDV, Remdesivir; S, Survive.

https://doi.org/10.2147/IDR.S485976 DovePress

In addition, the definition of the recurrence of COVID-19 was matched with the following both 1) and 2) although the patients continued the isolated hospitalization and had been already asymptomatic and negative of SARS-Cov-2 antigens/Ct value of PCR upper than 35 after the first the anti-COVID-19 therapy: 1) the patients who had the fever and/or respiratory symptoms, including 8 investigated symptoms (cough, chills, dyspnea, fatigue, fever, nasal discharge, sore throat, and sputum) again, and 2) SARS-Cov-2 antigens became positive andor/Ct value of PCR became 35 and the less again.

The mean age of the 7 patients was 80.3 (74–89) years, and the male-to-female ratio was 4:3, with 57.1% males. In detail, 4 of the 7 (57.1%) patients were hospitalized on the hematology ward due to B cell/non-Hodgkin lymphoma. The 4 lymphoma patients had been vaccinated at least once by pfizer-BioNTech COVID-19 vaccines (Comirnaty, Pfizer Inc. New York, NY, USA) or Moderna COVID-19 vaccines (Spikevax, Moderna Inc. Cambridge, MA, USA), but the 3 other patients who had been hospitalized on the emergency ward and the neurology wards had not been vaccinated. Of the 7 patients, 6 (85.7%) were initially treated with RDV 200 mg drip infusion, followed by 100 mg per day for 5 days, and the other one patient did not receive antiviral treatment. In 5 of the 7 patients, the SARS-CoV-2 antigen (Ag) level was measured quantitatively by Cobas SARS-CoV-2 Ag (Roche, Basel, Switzerland) and was 1774.8 (37.9–3190) IU before initial treatment. In the other 2 patients, the SARS-CoV-2 Ag was detected qualitatively by Espline SARS-CoV-2 (Fujirebio, Tokyo, Japan). After initial treatment, SARS-CoV-2 Ag levels were decreased to less than the usual threshold of our hospital (100 IU) (mean 28.9 IU, range 0.81–63 IU).

However, after 6.4 (3–9) days, the patients had fever and increased SARS-CoV-2 Ag levels, although all patients remained hospitalized, and they were diagnosed as having recurrent COVID-19. Before the second treatment, SARS-CoV-2 Ag levels were increased to 894 (192–2771) IU, but they decreased to 14.9 (0.71–63) IU after the second treatment. As the second treatment, 3 of 7 (42.9%) patients received RDV again, but the 4 other patients were successfully re-treated using oral 3C-like protease (3CL-protease) inhibitors, such as ensitrelvir (ESV, Shionogi CO. LTD., Osaka, Japan: 3 patients) and nirmatrelvir/ritonavir (N/R; Paxlovid, Pfizer Inc., New York, NY, USA: 1 patient). All 7 patients survived and did not relapse after the second treatment.

Interestingly, the patients were vaccinated only 1.9 times, although 6–7 courses of vaccinations had been completed in Japan at that time. In addition, 3 of 7 (42.9%) patients had not been vaccinated, and the 4 other patients who had been vaccinated but developed recurrent COVID-19 were admitted to the hematological ward due to lymphoma. We previously reported 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 had not been vaccinated for SARS-CoV-2.[5] Furthermore, in patients with hematological malignancies, it might be better to use antiviral agents first to reduce the viral titers, and then add steroids and related immunosuppressive agents appropriately later to inhibit the excessive inflammatory state.[6] These data suggested that non-vaccinated persons and/or patients with hematological disorders were critical for persistence of SARS-CoV-2 and recurrence of COVID-19.

In the present study, all 7 recurrent COVID-19 cases during hospitalizations were patients with either no history of vaccination or hematological disorders. It has been reported that COVID-19 has worse outcomes in hematologic patients than in non-haematologic, independently of age, and that the development of ARDS and thrombotic complications drive the higher in-hospital mortality.[7] Among them, the patients who received Anti-CD20+ B cell depletion therapy, including rituximab use, were known to be the issue of relapse and/or persistent COVID-19.[8–10] In our cases, all 4 patients with hematologic diseases, such as lymphomas received anti-CD20+ B cell depletion therapy. They were also received the vaccination for COVID-19 and neutralizing antibody therapy, such as intramuscular administration of tixagevimab-cilgavimab (data not shown),[11] but COVID-19 were relapsed. Vaccines and neutralizing antibody therapy might not be useful for these kinds of the patients.

In addition, more than half of these patients received protease inhibitors, including ESV or N/R, as the second treatment agents, despite initial RDV therapy. ESV, a recently developed 3C-like protease inhibitor that was approved for use in Japan in autumn 2022, exhibits strong activity for eliminating SARS-CoV-2.[12,13] ESV effectively reduces viral replication, and in fact, treatment was reported to result in clinical improvement of symptoms along with the strong elimination of SARS-CoV-2 in COVID-19 patients during the omicron surge.[14] Nirmatrelvir is also an oral protease inhibitor that is active against the main proteases of SARS-CoV-2, including 3CL protease, and it is packaged with ritonavir, a strong cytochrome P450 (CYP) 3A4 inhibitor; co-administration of ritonavir is required to increase

nirmatrelvir concentrations to the target therapeutic range.[15] Therefore, nirmatrelvir combined with ritonavir (N/R) is approved by the Food and Drug Administration (FDA) for the treatment of mild-to-moderate COVID-19 in adults who are at high risk of progressing to severe COVID-19 in the USA, and it also became available worldwide as the most commonly used standard anti-SARS-CoV-2 agent. These two 3CL-protease inhibitors were expected to have stronger anti-viral effects than RDV, which inhibits RNA-dependent RNA polymerase, and they completely inhibited further recurrence of COVID-19 in the patients presented. These data suggest that ESV and N/R might be better to use for recurrent COVID-19 patients to inhibit further recurrence in non-vaccinated patients or patients with hematological disorders. 2 or 3 combined antiviral therapy, including these 3 CL-protease inhibitors, RDV/molnupiravir, plus, if available, anti-spike monoclonal antibodies might also be expected to use for the immunocompromised patients with prolonged/relapsed COVID-19.[16] We may try these kinds of combination therapy in the near future.

Furthermore, Ormazabal Vélez I et al reported that convalescent plasma therapy had been useful for two lymphoma patients with relapsed COVID-19 in the setting of low gamma globulin levels because of previous rituximab chemo-immunotherapy, and found the disappearance of viral load.[9] However, convalescent plasma therapy was recently off-label indication and not recommended for the patients with moderate to severe patients with COVID-19 in the guideline;[1] therefore, we did not use convalescent plasma in our relapsed patients and did not measure the neutralizing antibodies, which were suggested to be escaped from SARS-CoV-2 Omicron variants,[17] to identify the patients with a risk for recurrence.

As the limitation, this commentary was retrospective and observation study data, therefore, no control group and statistical analysis was performed. In addition, this is the data from one tertiary hospital. Further, and lager-scale study will be needed.

In conclusion, 7 (2.5%) recurrent COVID-19 patients during hospitalization in the omicron pandemic period were reported. Recurrences during hospitalization were found at approximately 1-week intervals even though adequate initial therapy, such as RDV drip infusion. We should consider second treatment with not only RDV but also stronger anti-viral inhibitors, such as 3CL-protease inhibitors including ESV and N/R, in non-vaccinated patients and patients with hematological disorders with anti-CD 20+ B cell depletion therapy because neutralizing antibodies also might not be able to prevent the COVID-19 recurrences.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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