



Safety of casirivimab/imdevimab administration in a SARS-CoV-2 positive maintenance dialysis patient in Japan

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Abstract

Controlling excessive cytokine secretion is a crucial therapeutic strategy for managing coronavirus disease 2019 (COVID-19). Patients on dialysis are at a high risk of severe disease, given abnormal immune responses that can lead to prolonged inflammation. Moreover, patients undergoing dialysis have limited treatment options, as neither remdesivir nor baricitinib is available. The novel neutralizing monoclonal antibody cocktail REGEN-COV (formerly known as REGN-COV2; casirivimab/imdevimab), recently approved in Japan, is a promising drug for preventing severe diseases. However, there are few reports regarding its use in patients undergoing dialysis in Japan. Herein, we report the safe use of antibody cocktail therapy in patients with COVID-19 on hemodialysis receiving maintenance dialysis in Japan. Infusion reactions were not observed during administration. Due to the increasing number of patients with COVID-19 and the limited capacity of the healthcare system, antibody cocktail therapy needs to be enhanced. Antibody cocktail therapy for severe diseases can be safely administered to patients undergoing dialysis who do not require supplemental oxygen.

Keywords Hemodialysis · COVID-19 · Casirivimab/imdevimab

Introduction

Coronavirus disease 2019 (COVID-19) is currently recognized as one of the most threatening infectious diseases worldwide, and patients on dialysis are at a high risk of developing a severe clinical course. COVID-19 causes excessive cytokine secretion, especially in severe cases. Cytokine storm, also known as cytokine release syndrome, is an excessive immune response triggered by external stimuli such as viruses and bacteria. During the early stages of COVID-19, the primary challenge is to control the proliferation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical course of COVID-19 shows that in the early stages (approximately 1 week after the onset), the main problem is the proliferation of SARS-CoV-2. Notably, 80% of the patients recover spontaneously, whereas 20% develop

moderate to severe disease at approximately 1 week to 10 days due to immune/inflammatory system abnormalities. Overall, 5–10% of patients tend to develop severe and life-threatening diseases. Moreover, patients undergoing dialysis are at a higher risk of severe disease as inflammation can be prolonged owing to an abnormal immune response [1].

Recently, it has been suggested that complications and death from SARS-CoV-2 may be related to high viral loads, and the novel neutralizing monoclonal antibody cocktail REGEN-COV (formerly known as REGN-COV2; casirivimab/imdevimab) was shown to effectively reduce the viral load [2] REGEN-COV, recently approved in Japan, is a combined cocktail of neutralizing monoclonal antibodies against the SARS-CoV-2 spike protein. However, although the novel cocktail can be employed in patients undergoing dialysis (as well as in patients with other risk factors for severe disease), in Japan, there have been few reports of the administration of cocktail therapy during hemodialysis. Herein, we report a case of a patient undergoing hemodialysis who was safely administered antibody cocktail therapy.

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Case report

An African man in his 50 s undergoing maintenance dialysis was admitted to our department with a diagnosis of SARS-CoV-2 infection. He was a living-kidney transplant recipient with medical histories of hypertension and acute myocardial infarction. One day before admission, the patient also tested positive. He reported developing a dry cough a few days prior to admission. At admission, the physical symptoms included dry cough. The body temperature was 36.8 °C; pulse rate, 75 beats per minute; blood pressure, 122/79 mmHg; respiratory rate, 15 breaths per minute; and, oxygen saturation, 97% while breathing ambient air. His body weight was 75.4 kg; height, 180 cm; and, body mass index (weight in kilograms divided by the square of the height in meters), 23.3. A chest radiograph obtained on admission showed no findings suggestive of pneumonia (Fig. 1A). The laboratory data are presented in Table 1.

The antibody cocktail REGEN-COV 1200 mg was administered on day 2. REGEN-COV 1200 mg/10 mL dissolved in 100 mL saline was administered for 30 min after dialysis. No infusion reactions were observed during administration. Blood tests and chest radiographs obtained after REGEN-COV administration showed no obvious changes as compared to those before administration. The patient was discharged on day 9, with a temperature of 35.9 °C; pulse rate, 72 beats per minute; blood pressure, 136/102 mmHg; respiratory rate, 16 breaths per minute; and, oxygen saturation, 96% while breathing ambient air (Fig. 1B).

Discussion

Patients with end-stage kidney disease requiring maintenance dialysis present a high risk for severe SARS-CoV-2 infection, not only in other countries but also in Japan. To date, there are four therapies available for patients with COVID-19 in Japan: remdesivir, dexamethasone, baricitinib, and REGEN-COV (casirivimab/imdevimab). Currently, remdesivir is not recommended for use in patients with advanced chronic kidney disease (CKD) with estimated glomerular filtration rates (eGFR) < 30 mL/min. It should be considered only when the therapeutic benefit is judged to outweigh the potential risks. Recent reports have indicated that it can be safely used in patients on dialysis [3].

Steroid use was initially controversial, given reports of delayed viral elimination and increased mortality in Middle East respiratory syndrome coronavirus (MERS-CoV) and influenza. The RECOVERY trial [4] was a large, multicenter, randomized, open-label study that assessed hospitalized patients with COVID-19. It included 6425 patients randomized to receive dexamethasone (6 mg/day, once daily) orally or intravenously for up to 10 days (2104 patients) or usual care alone (4321 patients). The primary outcome was 28-day mortality, and the use of dexamethasone in patients admitted with COVID-19 reportedly reduced 28-day mortality in patients receiving ventilatory management or oxygen on randomization, but not in patients who did not receive respiratory support. Based on the results of the RECOVERY trial, the National Institutes of Health revised its treatment guidelines to recommend the use of dexamethasone for patients with COVID-19 requiring ventilatory support or oxygen, and the Ministry of Health, Labor, and Welfare

Fig. 1 Chest radiographs on admission show no findings suggestive of pneumonia (A). In addition, there is no particular pneumonia image after antibody cocktail therapy, and the patient on maintenance hemodialysis was successfully discharged (B)

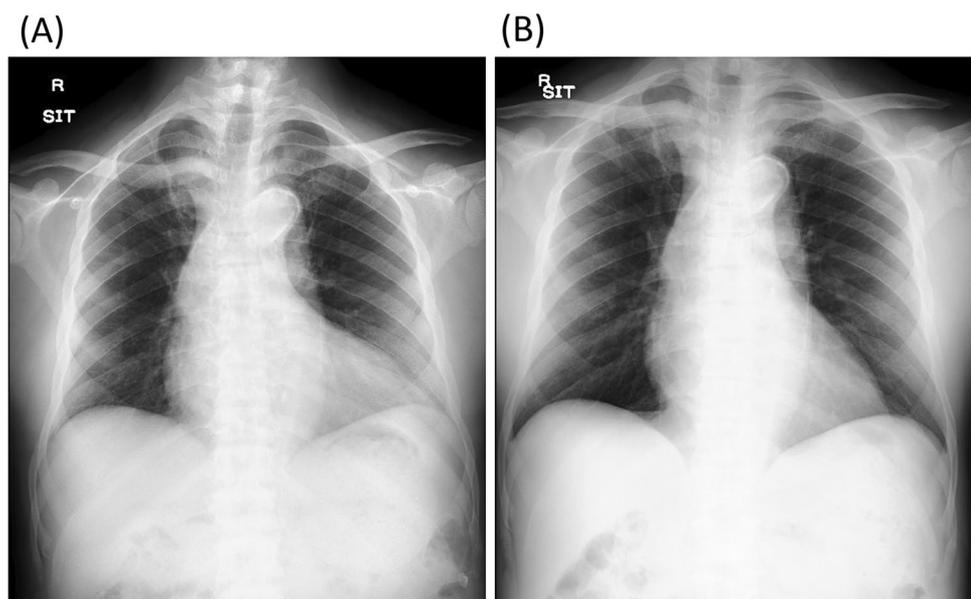


Table 1 Blood data at admission, during antibody cocktail therapy, and before discharge

	Day 0	Day 2 (antibody cocktail was administered)	Day 7	Reference range
White blood cell (μl)	3710	2750	3180	3200–7900
Hemoglobin (g/dl)	11.7	10.9	10.9	11.3–15.0
Platelet ($\times 10^3/\mu\text{L}$)	160	131	148	155–350
Albumin (g/dL)	4.0	3.5	3.6	4.1–5.1
Total bilirubin	0.3	0.3	0.4	0.3–1.1
Blood urea nitrogen (mg/dL)	32.6	22.5	40.5	8–21
Creatinine (mg/dL)	13.33	10.84	14.59	0.6–1.0
C-reactive protein (CRP)	2.24	1.77	0.62	<0.3
Sodium (mEq/L)	144	143	141	138–145
Chloride (mEq/L)	107	106	103	101–108
Potassium (mEq/L)	3.8	3.7	4.3	3.6–4.8
Aspartate aminotransferase (IU/l)	16	15	14	11–38
Alanine transaminase (IU/l)	9	8	10	6–50
Lactate dehydrogenase (IU/l)	156	138	173	103–190
Glucose (mg/dL)	87	81	81	73–109
Hemoglobin A1c (%)	4.1			4.9–6.0
PT-INR	1.02	1.00	1.04	0.90–1.10
APTT (sec)	28	29	31	25–35
Fib (mg/dL)	354	334	317	200–400
D-Dimer ($\mu\text{g/mL}$)	1.4	1.7	2.9	0.0–1.0

Hemodialysis was performed on day 1, 2, 5, 7. Blood samples were taken before dialysis

added dexamethasone to the "Guide to the Treatment of Novel Coronavirus Infections" on July 21, 2020. Therefore, for patients with COVID-19 undergoing dialysis showing only mild symptoms and no need for supplemental oxygen, as in this case, dexamethasone use may not be beneficial owing to its side effects and prolonged virus clearance [5].

Janus kinase (JAK), a non-receptor tyrosine kinase, known as JAK1, JAK2, JAK3, and TYK3, is considered a therapeutic target in rheumatoid arthritis and several autoimmune diseases, given its involvement in multiple cytokine signaling. Baricitinib is highly selective for JAK1 and JAK2. The ACTT-2 study [6] was performed as a randomized, double-blind, placebo-controlled trial in which patients received baricitinib or placebo in addition to remdesivir. Of the 1033 patients, 515 were assigned to the baricitinib group and 518 to the control group. The results revealed a median reduction in the recovery time of 1 day, from 8 days in the control group to 7 days in the baricitinib group. The mortality rate at 28 days was 5.1% in the baricitinib group and 7.8% in the control group. In the United States, an emergency use authorization (EUA) was issued in November 2020, and on April 21, 2021, the Japanese Ministry of Health, Labour, and Welfare approved the drug, making it the third drug approved in Japan, following remdesivir and dexamethasone. Given renal excretion, the dose should be reduced in patients with CKD presenting eGFRs from 30 to 60 mL/min/1.73

m^2 , and its administration is contraindicated in patients with eGFRs < 30 mL/min/1.73 m^2 . Thus, while patients undergoing maintenance hemodialysis are at a high risk of COVID-19 progression, they have limited treatment options.

As for the antibody cocktail REGEN-COV (casirivimab/imdevimab), a recently published study [2] assessing 275 patients reported that it could reduce the viral load, and the effect was greater in patients who had not yet shown an immune response or had a high viral load at baseline. In addition, a pre-printed study examined 4057 outpatients with SARS-CoV-2 infections who had at least 1 risk factor for severe disease and compared REGEN-COV 2400 mg and 1200 mg doses with the placebo. REGEN-COV 2400 mg and 1200 mg significantly reduced SARS-CoV-2-related hospitalizations and all-cause mortality as compared to the placebo, with a 70.4% reduction. Furthermore, the time to resolution of COVID-19 symptoms was significantly shorter in both the treatment groups as compared to the placebo group [7]. Antibody cocktails have been reported effective in vivo in rhesus monkeys, a model of mild disease, and golden hamsters, a model of more severe disease [8]. According to this report, REGEN-COV significantly reduced the viral loads in the lower and upper airways, and the prophylactic or therapeutic administration of REGEN-COV suppressed weight loss and improved lung capacity and pneumonia.

Casirivimab/imdevimab was approved in Japan on July 19, 2021. However, unlike in Europe and the United States, casirivimab/imdevimab is not employed in outpatients in Japan but rather in patients with underlying diseases or hospitalized patients over 50 years old with disease onset within 7 days. The drug is reportedly effective against mutant strains *in vitro* and is expected to be efficacious in suppressing the development of mutant strains. The most important side effects to watch out for are the possibility of anaphylaxis and infusion reactions. In this case, no such side effects were observed, and no special side effects were noted in the blood sampling data. Drug interactions have not been investigated, but no drugs of note have been reported. Casirivimab and imdevimab are monoclonal antibodies that are not excreted in the urine or metabolized by cytochrome P450 enzymes. At present, there is no need to adjust the dosage according to the renal function. Renal failure is one of the aggravating factors of COVID-19, and the phase III randomized placebo-controlled trial of REGEN-COV [9] included patients with CKD, including those undergoing maintenance dialysis. Fluid balance is crucial in patients undergoing dialysis. As the drug dissolves in as little as 100 mL of saline, there was no need for excessive water removal during dialysis. On the package insert of REGEN-COV, "immunosuppressed status" is listed as one category of patients at risk of severe disease requiring treatment. REGEN-COV was also reported to be effective in immunosuppressed patients with COVID-19 who were receiving rituximab twice a year for myasthenia gravis [10]. REGEN-COV may be a good indication for immunosuppressed patients. Regarding the relationship between the antibody cocktail therapy and the vaccine, according to the Centers for Disease Control and Prevention, the vaccine may be less effective when the antibodies are still in the body. As for vaccination, it is advisable to wait for approximately 3 months after the administration of REGEN-COV [11].

For REGEN-COV, the data on dialyzability and pharmacokinetics in patients with renal dysfunction are the same as before, and the information is insufficient. REGEN-COV is a high-molecular weight drug (casirivimab, 148,000 Da and imdevimab, 147,000 Da); therefore, it is not expected to be dialyzable. It can be administered before, during, or after dialysis, and the dosage may not need adjustment. However, as this was the first time that the drug was administered at our institution, we administered it after the dialysis. If the drug was administered before or during hemodialysis, events such as hypotension may occur, and it may not be clear whether it is an effect of hemodialysis or a side effect of the drug. In conclusion, among the four drugs approved for patients with COVID-19 in Japan, only dexamethasone and REGEN-COV are available for patients on dialysis. Notably, dexamethasone

is beneficial if the disease is severe and the patient needs supplemental oxygen, while REGEN-COV is a good option for patients with mild disease and no oxygen needs.

In this study, we reported that antibody cocktail therapy can be safely administered to patients undergoing hemodialysis in Japan. When the number of patients infected with SARS-CoV-2 increases, it is difficult to ensure that medical institutions admit SARS-CoV-2-positive patients on dialysis; and, this has become a major social problem. Initially, antibody cocktail therapy could not be administered to outpatients in Japan. However, recently, antibody cocktail therapy could be administered in an outpatient setting with the following requirements for outpatient clinics without beds: a system should be in place to check for deterioration of the patient's condition within 24 h and the clinic should collaborate with the medical institution where the patient will be hospitalized if the condition worsens. In this case report, we were able to safely administer the drug to a patient undergoing dialysis. When such a patient is infected with SARS-CoV-2, the general policy is to admit the patient to the hospital. Administration of REGEN-COV in the outpatient setting may be a treatment option to prevent severe disease in patients who do not require oxygen administration when hospitalization becomes difficult due to a rapid increase in the number of infected patients.

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Declarations

Conflict of interest The authors declare no competing financial interests or conflicts of interest.

Ethical statement This case study was conducted in accordance with the principles of the Declaration of Helsinki. Additional informed consent was obtained from the patients for whom identifying information was included in this study.

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