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Case Report

Intravenous Immunoglobulin (IVIG) Therapy for COVID-19 Omicron (B.1.1.529) Variant with Acute Respiratory Distress Syndrome

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ABSTRACT

Background: COVID-19 become the pandemic and infect more than million people. The World health organization and other clinical institutions have not yet established a definitive therapy to treat this disease due to a rapid virus mutation and anomaly.

Case: A 78-year-old man who had previously confirmed COVID-19 was referred from another hospital to the Saiful Anwar Hospital with a positive polymerase chain reaction (PCR) swab. The patient came with chief complaints of decreased consciousness accompanied by shortness of breath with an oxygen saturation of 86% with Non-rebreathing mask. We decided to intubate in the emergency room because we had signs of respiratory problems. We referred from emergency room to the COVID-19 intensive care room. After that, another PCR swab examination was carried out using the S-gene Target Failure (SGTF) method and it was stated that it was positive for the Omicron type COVID-19. The patient had geriatric comorbidities, cerebrovascular accident (CVA) infarction (shown on computed tomography (CT) scan, and hypertension. Patients receive standard therapy for COVID-19. On the second day, patient receive intravenous immunoglobulin (IVIG) 20 g. IVIG therapy perform for five days. On the fifth day of treatment in the ICU, the patient's complaints had decreased and the patient breathed spontaneously with high flow nasal cannula (HFNC).

Conclusion: Intravenous immunoglobulin (IVIG) therapy on the COVID-19 Omicron variant patient with ARDS produce a positive outcome. Patients treat with IVIG for 5 days show an improvement in breathing, laboratory result and chest x-ray.

Keywords: acute respiratory distress syndrome, COVID-19, IVIG

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INTRODUCTION

In December 2019, Wuhan Province, China, reported the first coronavirus disease 2019 (COVID-19) cases. The illness swiftly hit every continent, and by early 2020, it had become a pandemic. As of April 20, 2020, the pandemic had affected more than 2.4 million people worldwide.[1] COVID-19 virus is continually evolving and creating new variations. The Omicron variety, also known as the B.1.1.529 variant, was discovered most recently. On November 24, 2021, South Africa first reported these varieties, which have since spread worldwide.[2, 3]

Currently, the World health organization (WHO) has classified the Omicron variant as a variant of concern (VOC).[2] This classification is based on discovering many mutations of this variant, and some of them are alarming. A previous study suggested Omicron variant has a higher risk of re-infection than other VOC variants. In addition, this variant also shows rapid growth that will have a detrimental impact epidemiologically. [4]

The management of COVID-19 includes prevention, immunomodulator administration, antiviral therapy, and plasma transfusions. One of the management of coronavirus disease 2019 is intravenous immunoglobulin (IVIG), a treatment involving a blood product that has been refined from healthy individuals' mixed plasma, which is enriched in both bacterial antibodies and viral IgG.[5]

This case report aims to show the use of Intravenous immunoglobulin in 78 years old-male patients who have a respiratory failure because of acute respiratory distress syndrome (ARDS) due to confirm cases of COVID-19 probable omicron who experienced an improvement in clinical symptoms and support after intravenous immunoglobulin administration.

CASE

A 78-year-old man who had previously confirmed COVID-19 was referred from another hospital to the Saiful Anwar Hospital with a positive polymerase chain reaction (PCR) swab. The patient came with chief complaints of decreased consciousness accompanied by shortness of breath with an oxygen saturation of 86% with a Non-rebreathing mask. We decided to intubate in the emergency room because we had signs of respiratory problems. We were referred from the emergency room to the COVID-19 intensive care room. After that, another PCR swab examination was carried out using the S-gene Target Failure (SGTF) method and it was stated that it was positive for Omicron-type COVID-19. The patient had geriatric comorbidities, cerebrovascular accident (CVA) infarction (shown on computed tomography (CT) scan (Figure 1), and hypertension.

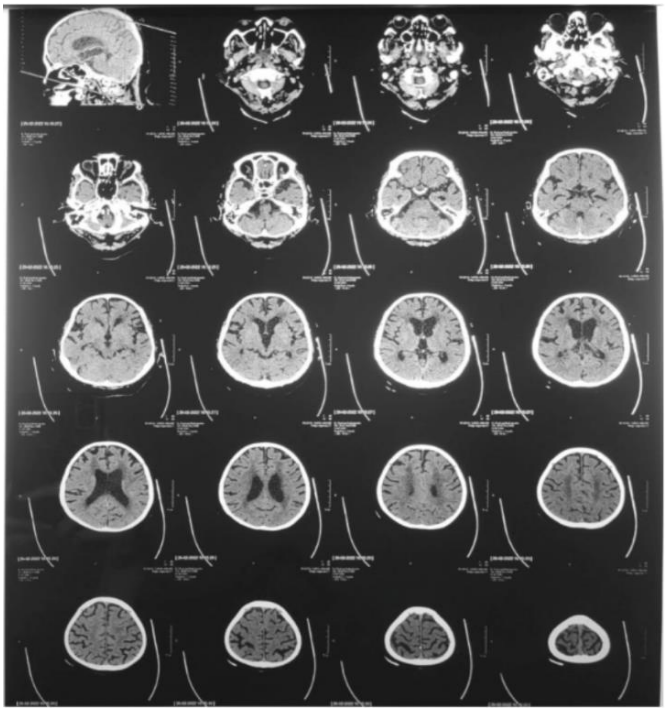

Figure 1. CT-scan result show a cerebrovascular accident (CVA) infarction

On the first day, the ventilator setting of pressure synchronized intermittent mandatory ventilation (PSIMV) with respiration rate (RR) 20 times/minute, Pisnp 14 Psupp 14 Peep 10 FiO_2 100 was installed. Patients were given 200 mg of remdesivir antivirals once daily, dexamethasone 6 mg once daily, citicoline 500 mg, a syringe of midazolam 5 mg/h, a syringe of fentanyl 50 µg/h, subcutaneous (s.c) lovenox 0.4 cm^3 twice a day, atorvastatin 40 mg once daily at night, candesartan 8 mg once daily, Vit E 300 mg once daily, and Vit D 5000 IU once daily.

On the second day in the ICU, the patient's general state was seriously ill. The patient has no desaturation, hypotension, or sedation awareness. The ventilator was installed PSIMV with RR of 20 times/minutes Pisnp 14 Psupp 14 positive end-expiratory pressure (PEEP) 9 FiO_2 70% to RR of 22 times/minutes, TV 426, SpO_2 96%. The patient received remdesivir 100 mg once daily, levofloxacin 750 mg once daily, syringe n-acetyl cysteine (NAC) 5g/72 h, s.c. lovenox 0.4 cm^3 twice a day, intravenous immunoglobulin 20g, increases the patient's food intake, and bleeding monitoring.

On the fourth day of ICU, the general state was remaining the same. The ventilator was installed spontaneous Ps with Psupp 7 Peep 7 FiO_2 50% to RR 18, TV 343, SpO_2 97%, with intravenous (i.v) remdesivir of 100mg once daily, levofloxacin 500 mg/48 h starting the odd date, omeprazole 40 mg once daily, dexamethasone 6 mg once daily, syringe NAC 5 g/72 h, s.c. lovenox 0.4 cm^3 twice daily, intravenous immunoglobulin 20 g (day-3 of IVIG administration), fasting for the preparation of extubating.

On the fifth day in the ICU, the patient breathed spontaneously with HFNC, flow 50 FiO_2 60% to RR 24 SpO_2 98% rox index 6.4, the patient had no desaturation and hypotension, and consciousness was between 345–356. The patient receives dexmedetomidine 0.4 µg/kg/h, IV remdesivir 100 mg once daily, levofloxacin 750 mg once daily, omeprazole 40 mg once daily, dexamethasone 6mg once daily, s.c. lovenox 0.4 cm^3 twice a day, intravenous immunoglobulin 20g (day-4 of IVIG administration), and increase patient's food intake.

On the sixth day in the ICU, the patient breath spontaneously with HFNC, flow 40 FiO_2 40% to RR 24-25 SpO2 98% rox index 6.2, the patient had no desaturation or hypotension, consciousness was between 345 – 356 on dexmedetomidine 0.4mcg/kg/h, IV remdesivir 100mg once daily, levofloxacin 750 mg once daily, Dexamethasone 6mg once daily, Intravenous immunoglobulin 20 g (day-5), and increase patient's food intake.

The patient was diagnosed with COVID-19, a severe type. IVIG was administered immediately at a dose of 20 g/day for 5 days. The patient's breathing gradually improved and extubation was done on the third day of IVIG treatment. X-ray thorax was repeated on day 4, showing improvement compared with the x-ray from day 1 (Figure 2). Laboratorium finding (Table 1) became gradually improved compared to day 3.

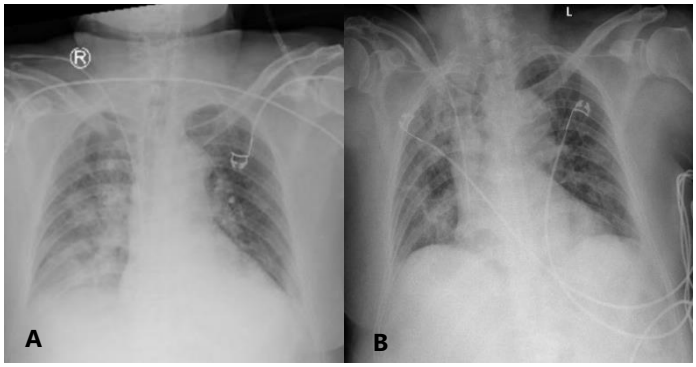

Figure 2. Thorax X-ray before IVIG. A) day 1 of IVIG, B) day 4 of IVIG

Table 1. Laboratorium results show an improvement

Laboratorium result	IVIG treatment			
	Day 1	Day2	Day 3	Day 4
Haemoglobin	12.2	11.5	10.9	12.2
Leukocyte	7680	9270	11.720	17.700
Absolute lymphocyte	11.10	880	2750	4550
Neutrophil absolut	6170	7550	7410	12.08
Neutrophil lymphocyte ratio	7.26	8.58	2.69	2.65
C- reactive protein	11.75	14.85	3.26	8.93
Procalcitonin	0.42	0.89	0.17	-
Lactate dehydrogenase	-	-	274	-
Ferritin	-	-	1700	-
Interleukin 6	1126	143.1	-	-

DISCUSSION

The omicron variant was immediately announced as a variant of concern because it was found that there were more than 30 spike protein mutations accompanied by a rapid increase in the confirmed case, as well as mutations in other non-structural proteins. The omicron variant was more infectious than the Delta variant. However, it had a lower disease severity and fatality rate.[17] The omicron variant showed up to 13 times more transmission than SARS-CoV-2 early in the pandemic. The rate of reinfection in individuals who have suffered from COVID-19 previously reached 2.39 times. This is due to the omicron variant's ability to avoid neutralization by antibodies in convalescent serum or vaccine. Omicron is reported to be able to infect individuals who have already received the complete vaccine and booster doses.[5] The management of COVID-19 includes prevention, immunomodulator administration, antiviral therapy, and plasma transfusions. One of the options for managing coronavirus disease in 2019 is intravenous immunoglobulin.[5]

A previous study suggested that intravenous immunoglobulin administration in COVID-19 patients with moderate to severe ARDS does not affect the patient's clinical outcome.[6] However, a study conducted on three patients diagnosed with severe COVID-19 showed improvement after being given high doses of IVIG. [7] Similar results were also reported, showing that the provision of IVIG in COVID-19 patients provided rapid improvement in clinical symptoms, laboratory examinations, and imaging.[8] Patients with the persistence of respiratory failure experienced improvements in clinical symptoms, decreased inflammatory markers, normalization of liver function, and restoration of lung function after being given an infusion of IVIG. In addition, the correlation test obtained a significant relationship between the time of starting IVIG treatment and the duration of therapy in the ICU.[5]

Preventing hyperinflammation is the goal of intravenous immunoglobulin administration for infectious disorders, and treating initial infections with IVIG's anti-infective characteristics. Additionally, IVIG may defend against comorbid conditions, lowering morbidity and mortality. According to the IVIG preparation's ingredients, the patient's immune system, and the extent of the illness, IVIG may have beneficial effects.[9]

A blood product from a healthy donor called intravenous immunoglobulin contains polyclonal IgG antibodies. Intravenous immunoglobulin has been used for several immune system disorders such as Kawasaki disease and multiple sclerosis due to its anti-inflammatory effects. Based on the experience of treating earlier coronavirus viruses such as swine-origin influenza virus (SOIV), Middle East respiratory syndrome, and severe acute respiratory syndrome (SARS), H1N1. Although there is not enough clinical data, IVIG is believed to be usable in COVID-19 patients and become one of the valuable therapeutic options. The controversy over the efficacy of IVIG for COVID-19 is increasingly discussed as the number of COVID-19 patient increases.[10]

A pure concentrate of polyclonal immunoglobulin G (IgG) generated from donated human plasma serves as the main ingredient of IVIG. In replacement therapy, the pathogen is neutralized, toxins are rendered inactive, toxins are opsonized, B and T cell activities are increased, and complement is activated. The neutralization of autoantibodies and pro-inflammatory cytokines, inhibition of activated complement and/or adhesion molecules, disruption of the idiotypic/anti-idiotypic network, and improved autoantibody clearance are only a few examples of anti-inflammatory actions. It has been hypothesized that IVIGs can treat COVID-19 through several different methods.[18]

Antibody-dependent enhancement has been suggested as a potential mechanism to account for regional variations in severity. Unmodified human intravenous immunoglobulin formulations have shown a cross-reactivity to SARS-CoV-2 and other coronaviruses. A promising study showed a sharp rise in the concentration of specific neutralizing antibodies among preparations created during the pandemic year, even though the study that came after it found no cross-neutralization antibodies against SARS-CoV-2 detected in intravenous immunoglobulin during the pre-pandemic period. [11]

IVIG therapy also reduces inflammatory pathways in COVID-19, including interleukin (IL-6), tumor necrosis factor (TNF), matrix metalloproteinase-9 activity, T-cell activation, and IL-12/23p40 in macrophage formation. On the other side, anti-inflammatory systems are activated, leading to a rise in macrophages, PPAR-gamma, and IL-10 production in the gut, among other things. The expression of the toll-like receptor 4 (TLR-4) is decreased concurrently. It is found that these IVIG-induced effects on the inflammatory storm do not lead to a greater tendency for immunosuppression in patients. Additionally, dendritic cell maturation is prevented, IL-12 expression is decreased, and IL-33, IL-4, and IL-13 production are enhanced by IVIG, all of which may impact COVID-19 development.[12] In China, a clinical trial was established in positive COVID-19 patients aged >18 to asses the IVIG efficacy.[13]

IVIG is given in two different circumstances at two different doses. First, individuals who are immunodeficient can receive replacement therapy with a peak serum level of 12–14 mg/ml. Second, in patients with inflammatory or autoimmune diseases, a high dosage of intravenous immunoglobulin can be given to achieve a blood level of 25–35 mg/ml. In most cases, IVIG therapy fills in for the lost antibodies in the initial method of administration (replacement therapy). In COVID patients, it also promotes B cell proliferation, normalizes monocyte differentiation, and increases antibody production. [12]

When a patient is deteriorating, such as when the A-gradient starts to approach 200 mmHg but the patient has not yet reached respiratory failure, IVIG administration seems to be most beneficial if administered right away. This is also true within the first two days of mechanical ventilation. A gradient of 200 mmHg is typically considered to be a state where the patient needs FiO_2 levels above 45%, practically at humidity and altitude comparable to coastal towns in Indonesia. These trials used a wide range of intravenous immunoglobulin doses, although the majority of them used high doses for 3 or 5 days straight, averaging around 0.3-0.5 grams/kg/day. There is still not enough evidence to recommend giving IVIG to Covid-19 patients. [14]

The World Health Organization was notified by South Africa on November 24, 2021, of the discovery of a novel SARS-CoV-2 strain, B.1.1.529 (Omicron) (WHO). Three deletions, one insertion, and 30 amino acid polymorphisms are common in the gene that codes for the Omicron Spike (S) protein. Three primary operational consequences are present. First, Omicron undergoes a number of alterations in the receptor-binding domain (RBD) linked to ACE-2 binding affinity and antibody avoidance. It also shows polymorphisms, such as those at positions 484 and 477, which are recognized for their propensity to evade antibodies. Second, a large number of modifications to the receptor-binding domain (RBD) have the potential to raise the enzyme's affinity (ACE2) significantly. The Omicron variant also shows furin cleavage (P681H) and in the area (H655Y and N679K).

Lastly, Omicron shared changes at (P681H) and around

(H655Yand N679K) furin cleavage sites S1/S2. This polymorphism is associated with increased S1/S2 furin cleavage and more efficient fusogenic entry mediated by TMPRSS2 3 protease serine. Currently, no virus-specific data is available to assess whether monoclonal antibody administration is effective against the Omicron variant. Based on data from other variants with far fewer RBD changes, it is expected that the Omicron variant will remain susceptible to some monoclonal antibody administration, while others may have less potential. Based on these characteristics, IVIG is expected to be an effective procedure for omicron variants to increase the clinical outcome and reduce patient mortality.[15]

CONCLUSION

Intravenous immunoglobulin (IVIG) therapy on the COVID-19 Omicron variant patient with ARDS produces a positive outcome. Patients treated with IVIG for 5 days show an improvement in breathing, laboratory result, and chest condition. IVIG could become a consideration in COVID-19 Omicron variant management. However, more clinical trials still need to provide more empirical data of IVIG efficacy.

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CONFLICT OF INTEREST

None

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