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Intravenous Immunoglobulin Treatment on a Patient Presenting with Severe COVID-19 and Impending Respiratory Failure: A Case Report

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Abstract: ***Background: As of February 2022, COVID-19 virus pandemic still plagues the earth with cases mostly related to the emergence of new variant, Omicron. Even after 2 years since its discovery, no mainstay of therapy has been established for severe-critical COVID-19. Amongst the proposed options of therapy, IVIG remain a controversy with studies stating for and against being equally vocal. In this article, we report a case of severe COVID-19 patient presenting with bilateral pneumonia, impending respiratory failure, acute kidney injury, and high risk for arteriovenous thromboembolism administered with IVIG therapy for 3 days. Patient saw improvement in his clinical condition several days following the final dose. Based on the outcome and pre-existing literatures, IVIG is recommended to be taken as an early consideration for those presenting with severe-critical COVID-19, particularly with suspected cytokine storm marked by high inflammatory value.***

Keywords: IVIg, COVID-19, Immunoglobulin

1.Introduction

Since its emergence in December 2019, COVID-19 virus has inflicted millions of death tolls across the globe, with the whooping total worldwide case of above 400 million and death case of 6 million as of February 27th, 2022.[1] The virus was first publicly documented on December 29th, 2019 in Wuhan, China as a novel virus in patients presenting with unusual severe acute respiratory disease syndrome. In March 20th 2021, the World Health Organization (WHO) officially declared the virus as an ongoing Pandemic, which was the same month the first case of COVID-19 was documented in Indonesia.[2,3] As of February 2022, the virus was still a great medical burden in Indonesia, with cases primarily related to the emergence of OMICRON variant which was first documented in mid-December 2021 in our country. Cases of this variant started to rose in late January 2022, and peaked around mid-February 2022, with the incidence was cited as the "third wave" in our country.[4] Based on animal study and recent reports, Omicron variant is signified by a higher virulence rate, yet less severe signs and symptoms and better survivability.[5] Vaccines of COVID-19 were introduced early 2021 in Indonesia which served to not giving full-immunity, but rather alleviate the supposedly fast deterioration of cases. Nevertheless, populations with serious comorbidities and traits remain at risk of developing a potentially fatal clinical progression, and the greater virulence rate might increase the rate of hospitalization thus further weighing the resource burden of health facilities.

The virus is a single stranded RNA virus which traverses mainly through the respiratory system and binds to Angiotensin Converting Enzyme 2 (ACE-2) receptors expressed abundantly on pneumocyte type 2 within the lung's alveolar, which the virus uses as a mode of cell entry. The virus is described as having a strong affinity with the receptors.[6] Incubation period ranges from 2-11 days with median of 5.1.

Signs and symptoms greatly ranged from mild such as common cold, lost sense of smell and taste, malaise, general weakness, flu-like symptoms, to severe and fatal like Acute Respiratory Distress Syndrome (ARDS) which seemed to be determined by some various factors such as age, pre-existing chronic comorbidities, and less predictable ones such as aberrant immune response which leads to what is termed as "cytokine storm".[2,6,7] Based on our national guideline, the symptoms primarily classified into 5 criteria: 1) **Asymptomatic**, 2) **Mild**, with predominantly flu like symptoms without hypoxia or pneumonia, 3) **Moderate**, with clinical sign of pneumonia without severe pneumonia and hypoxia, SaO2 > 93%, 4) **Severe**, those presenting with moderate symptoms + either SpO2 < 93%, Respiratory Rate > 30x/minute, OR severe respiratory distress, 5) **Critical**, those presenting with ARDS, septic, septic shock, or other conditions requiring life support such as mechanical ventilation or vasopressors.[7] Patients who present with severe and critical condition commonly see a significant increase in their laboratory inflammatory value, which suggests aberrant immune response stemming from cytokine dysregulation.

Since nearly two years after being cited as a pandemic, therapeutic agents regarding patients with critical conditions remain controversial, particularly the use Intravenous Immunoglobulin (IVIG).[8] IVIG therapy refers to the use of plasma-derived byproduct from donor which contains predominantly IgG and traces of IgA and IgM which, outside this case, is commonly used to treat immunodeficiencies and autoimmune-related disorders and served to either fulfill the immunity requirements or modulate/replace the pre-existing defective immune response, the later of which is aimed in the case of critical

COVID-19, which as a method to modulate the highly aggressive immune response in order to prevent irreversible tissue damages and respiratory distress syndrome.[9] Several studies and case reports have documented that the IVIG therapy has shown some benefits in severe or critical cases presenting with high inflammatory lab results (high C-Reactive Protein, D-Dimer value) provided the therapy was given in the early course of clinical deterioration. Yet several systematic reviews and studies have shown there was no difference in a rate of mortality, severity of illness, and length of hospitality for patients given with the IVIG.[8,9]

In this article, we present a case of severe COVID-19 patient with high inflammatory value administered with IVIG doses for 3 days, which showed a slow, yet steady clinical improvement mainly in his chief complaint and clinical condition.

2.Case Illustration

A 69-year-old male patient was referred from a tertiary hospital to Emergency Room on February 13th 2022 with chief complaint shortness of breath since 5 days prior admission. Patient also complained productive cough with expellable phlegm, runny nose, and general weakness. Difficulty of breathing was felt worse a day prior admission. Patient had also significantly decreased appetite. Past history revealed two occurrences of non-hemorrhagic stroke in 2020 and 2021 with residual right sided weakness, but daily activities can be exercised independently. Patient had not received any dose of Covid Vaccine. Routine medications include simvastatin 20 mg PO s.i.d and aspirin 20 mg PO s.i.d due to the past cerebrovascular history.

Patient was referred from a tertiary hospital due to needing intensive care treatment with the diagnosis of Confirmed COVID-19, Pneumonia, impending respiratory failure, and acute kidney injury. He was treated there as an inpatient since February 11th before the date of the referral. The patient had received levofloxacin 750 mg IV s.i.d (third day), remdesivir 1x100 mg IV s.i.d (third day), heparin 500 PO IU s.i.d, dexamethasone 5 mg IV s.id, clopidogrel 75 mg PO s.i.d, N-Acetylcysteine 400 mg t.i.d, Vitamin D 1000 IU PO s.i.d, combivent nebulization t.i.d, and the rests are simvastatin and aspilet which the patient had been consuming on regular basis.

Physical examination revealed a compos mentis consciousness (E4V5M6), Blood pressure of 142/91, pulse 121x/minute , respiratory rate 32x/minute, temperature 36,1 C, and SaO2 of 90% supported by oxygen flow of 15 liters per minute via non rebreathing mask. Lung examination revealed vesicular breathing, with audible crackles best seen on the basal of both lungs which suggest rhonchi, no wheezing sound was heard. Other physical examinations were unremarkable.

Complete Blood Count revealed leukocyte count of 9.94, hemoglobin count 14.5, hematocrit 42.2 and platelet count 200. Blood chemistry revealed random blood glucose 100, AST 25, ALT 21, urea 28, serum creatinine 0.66, natrium 135, kalium 3.7, and C-Reactive Protein 34.02. Blood gas analysis yielded critical value with pH 7.534, PO2 140, PCO2 24.9, HCO3 21.0, SO2 99, BE-ecf-2. Chest X-Ray revealed bilateral pneumonia. Patient was initially diagnosed with COVID-19, Moderate-Severe Bilateral Pneumonia, and Cardiomegaly. CRP yielded a high value of 15.42. D-Dimer revealed a high value of 1550. Real time Reverse Polymerase Transcription Chain Reaction (RT-PCR) had already been done on the tertiary hospital on February 11th which yielded positive result. We diagnosed the patient with Severe COVID-19, Bilateral Pneumonia, Acute Kidney Injury, Impending Respiratory Failure, and High Risk of Arterial Venous Thromboembolism (HR-AVTE) due to history of repeated stroke.

Initial therapy was commenced which included the following: Levofloxacin 750 mg IV s.i.d IV for 10 days, Cefobactam 2 gr IV b.i.d for 10 days, Methylprednisolone 40 mg IV b.i.d, Resfar (Acetylcysteine) 5 gr IV s.i.d, Combivent nebulization q.i.d, Pulmicort nebulization q.i.d, Pantoprazole 40 mg IV b.i.d, Vitamin C 1 gr IV s.i.d, Vitamin D 5000 U PO s.i.d, Ondancentron 4 mg IV t.i.d, Remdesivir 200 mg IV s.i.d on the first day and 100 mg IV s.i.d on the following days for 9 days.

Patient was then transferred into the Intensive Care Unit (ICU) and High Flow Nasal Cannula (HFNC) oxygen support was given. During the ICU stay, rox index was monitored to assess the need of intubation. We consulted the patient with multidisciplinary care of pulmonologist, cardiologist, neurologist, anesthesiologist, and internist. Starting the first day of the ICU stay, Patient received additional treatment of Aspilet 80 mg PO s.i.d, Clopidogrel 75 mg PO s.i.d, Simvastatin 20 mg s.i.d, Angintriz MR 35 mg PO b.i.d as a preventive measure due high risk of arteriovenous thromboembolism.

Upon arrival, heparin treatment was initiated due to high level of coagulative marker, with bolus dose of 5000 IU followed by drip infusion of 500 IU every hourly, then monitoring of APTT every 6-hours following the initiation. Creatinine and Urea were tested every 2 days to monitor the progression of kidney injury.

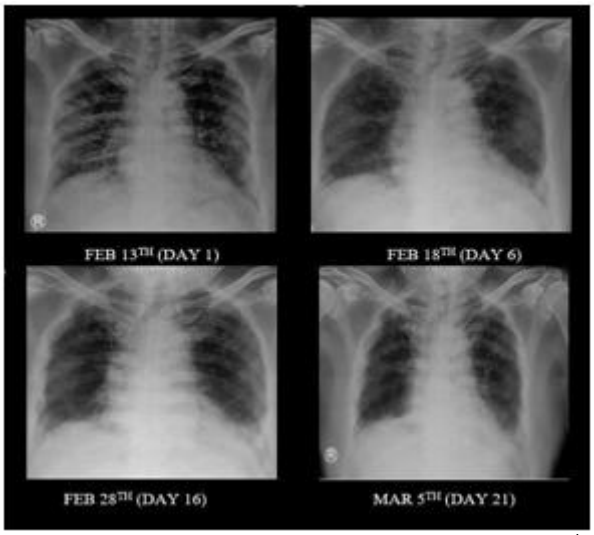

Figure 2.1: Chest x-ray comparisons of day 1 (Feb 13th),

day 6 (Feb 18th), day 16 (Feb 28th), and day 21st (March 5th). Reduction of infiltrate was best seen in day 6th, and slight improvement on day 16th and day 21st.

On February 15th, due to the condition of severe COVID-19 supported by a high inflammatory value (CRP), D-Dimer, and history of repeated cerebrovascular incident, we considered the patient to be given IVIG Administration, in hope of halting/preventing cytokine storms and thromboembolic incidents. The family was notified regarding the procedure, risks, and they agreed. The dose is 0.3g/kg/day. The treatment was given as a standalone infusion with the initial drips rate of 15-20 drops per minute for the first 30 minutes, followed by 30 drops per minute for the remainder once no hypersensitivity and hemodynamic instability ensued. IVIG infusion was given 7 vials/day for the duration of 3 days (February 15th – February 17th), with thoracal x-ray and CRP evaluation following the end of IVIG treatment.

On February 16th, patient received the second dose of another 7 vials of IVIG. Citicoline 500 mg IV b.i.d was initiated on February 16th as additional protective measure for the brain. Vital signs and allergic reaction were still strictly monitored.

On February 17th, the final IVIG dose is given. Heparin and clopidogrel treatment were deferred due patient presenting with melena, thus patient was given gastrointestinal medications (sucralfate PO t.i.d and antacid PO t.i.d) followed by fasting and temporal termination of oral administrations. Melena improved on February 20th thus oral administration of medications was resumed. The melena however, ensued again on February 23rd and tended to wax and wane for the remainder of the hospital stay hence some of the oral medications were having periods of being withdrawn multiple times, and we decided to perform nasogastric tube insertion during the period of melena (which persisted until February 28th). Similarly, tranexamic acid 500 mg PO t.i.d was intermittently given based on patient's report of whether he had dark stools.

Starting on February 18th, the patient started to slowly, yet steadily see improvement on his initial chief complaint shortness of breath. The complaint reemerged occasionally yet was never as severe as during admission. Chest x-ray revealed a slight decrease of pulmonary infiltrate and significant decrease of C-RP value (4.80 compared to the previous 15.42). As some lab test values began to improve, we spaced out the interval between each test, such as the Urea and Creatinine which already showed significant improvement.

On February 22nd, the patient was checked for sputum, urine, and blood culture, which yielded no bacterial growth for the urine and blood, and "multidrug resistant klebsiella pneumonia" for the sputum on February 26th. Hence, additional antibiotic therapy of meropenem 1 gr IV t.i.d was given for 10 days duration until March 7th, 2022.

On February 27th, patient's hemoglobin dropped to 8.4, which we heavily associated to his repeated melena, thus packed red cell transfusion was initiated from February 28th to March 1st with dose of 1 pack/day. Following the first transfusion, hemoglobin rose to 11.4.

During the ICU stay patient maintained a relatively stable vital sign and complaints, with day-by-day adjustments of flow and FiO2 for the HFNC support based on patient daily condition. We managed to maintain the peripheral oxygen (SaO2) above 90%. D-Dimer value was still above normal (850), but the amount was reduced to nearly half compared to during admission.

Patient's general condition improved further on early March. On March 5th, patient was transferred to the normal ward following negative results of COVID-19 RT-PCR on March 4th, 2022. Medicines given in the ward were mostly the same except for antibiotics and antiviral whose durations have been completed.

Oxygen support was shifted from HFNC to Non-Rebreathing Mask (NRM) 8 liters per minute. Urea and Creatinine routine tests were terminated on March 7th due to already normal levels, thus Acute Kidney Injury was removed from the diagnosis. Patient respiratory complaints such as shortness of breath, cough, phlegm have greatly decreased, yet the melena still waxed and waned. Due to the melena recurring repeatedly, we consulted the internist and esophagogastroduodenoscopy (EGD) was performed on March 10th, which revealed duodenitis and antrum-erosive gastritis. Gastrointestinal medicines consisting of pantoprazole 40 mg IV b.i.d, Sucralfate PO t.i.d, and Antacid PO t.i.d were initiated.

Oxygen support was slowly weaned to nasal cannula liters 4 per minute on March 8th, 3 liters per minute on March 9th, 2 liters per minute on March 11th, and 1 liter per minute on March 13th. Oxygen support was removed in early morning on March 14th. Patient no longer reported melena starting on March 12th.

Aside from the gastrointestinal problem, the patient saw more improvement and granted discharge on March 14th. Patient's final condition was Blood pressure 131/73 mmHg, heart rate 83x/minute, respiratory rate 19x/minute, temperature 36.1 C, and SaO2 93% on Room Air. Patient still had intermittent shortness of breath upon moderate exertion, and the Oxygen level did not fully raise above 95%, but we realize it was something that needed gradual recovery hence we didn't establish an overtly strict aim. Our take home medicine includes Symbicort puff b.i.d and Mixed capsule which contains: Theophylline, N-Acetylcysteine, Methylprednisolone, Mebhydrolin Napadisylate, and Salbutamol. The capsule is taken three times daily. We educated the patient to take portable oxygen therapy at home to slowly wean the oxygen requirement and visit the polyclinic 7 days later for the continuation of his gastrointestinal and lung problems.

Table 2.1 and **2.2** show patient's notable lab results during his hospital stay. Note some of the test's interval are adjusted based on patient's most recent clinical condition and previous lab results

FEBRUARY 2022															
Lab Results	13th	14th	15th	16th	17th	18th	19th	20th	21st	22nd	23rd	24th	25th	26th	27th	28th
WBC	16.49		15.84		12.77		15.49		19.06		12.45		13.2		12.4	
HGB	15.5		14.3		11.0		12.2		12.8		11.9		10.8		8.4	
HCT	43.1		41.9		30.4		34.2		35.5		33.1		31.7		33.1	
PLT	230		247		240		271		250		219		198		214	
RBG	139		141		192		168		156		159		144		-	
Urea	88		58		54		42		47		39		42		-	
Cr	1.35		0.95		0.90		1.00		1.01		0.9		1.03		-	
Na	135		139		135		137		-		-		-		133	
K	3.9		4.1		4.0		3.8		-		-		-		3.9	
CRP	34.02		15.42		4.80		-		-		-		-		-	
pH	7.505															
PO2	144															
PCO2	16.5															
HCO3	13.0															
APTT		40.2	31.9	40.8	24.8	28.5	21.0									
D-Dimer	1550															850

MARCH 2022														
Lab Results	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th
WBC	15.93		11.75		6.82		-	7.20						
HB	11.4		10.9		10.7		-	9.9						
HCT	23.6		24.8		31.7		-	29.3						
PLT	174		144		220		-	283						
RBG	115		123		128		-	113						
Urea	70		59		32		-	21						
Cr	1.18		1.01		0.94		-	0.87						
Na	134		-		-		130	-						
K	4.1		-		-		3.9	-						
CRP	-		-	-	-	-	-	-						

WBC: White Blood Cell in 10^3/ul, HGB: Haemoglobin in g/dl, HCT: Hematocrit in %, PLT: Platelet in 10^3/ul , RBG: Random Blood Glucose in mg/dL, Cr: Creatinine in mg/dL, Urea in mg/Dl, Na: Natrium in mmol/L, K: Kalium in mmol/L, CRP: C-Reactive Protein in mg/L, APTT: Activated Partial Thromboplastin time, in seconds. PO2: Partial pressure of oxygen in mmHg. PCO2: Partial pressure of carbon dioxide in mmHg. HCO3: Bicarbonate serum in mmol/L.

3.Discussion

The rationale of IVIG treatment on a critically ill COVID-19 patients remains a controversy in various studies.[6] Several case reports mentioned either immediate or gradual improvement upon IVIG administration shown by their inflammatory markers, yet not a few studies and articles elucidated how IVIG treatment didn't significantly shorten the hospital stay or even improve the overall outcome of critical patients.[10,11,14] It has been documented that the phase in which a patient starts to deteriorate becomes a crucial point that may change the patient outcome whenever adjunctive treatment such as IVIG is given, hence the earlier is better.[6,13,14]

Proposed mechanism of IVIG on severe-critical COVID-19 works by modulating the aggressive immune response in various levels, both cellular and humoral. IVIG has been reported to act on numerous immune cells.[6] On T Lymphocytes, IVIG inhibits the upregulation of Th1, which is mainly responsible to produce the proinflammatory IL-6 in triggering the cytokine storm. IVIG also upregulates the T-regulatory, which has anti-inflammatory properties.[6,9] On B lymphocytes, IVIG helps neutralizes the cytokines related to tumor necrosis factor families produced by B lymphocyte, such as APRIL, and fasten the apoptosis of the B cell through Fas mediated cell death. On macrophages, IVIG inhibits its differentiation, and amplifies the production of IL-10, an anti-inflammatory cytokine.[9,15] Several studies also proposed that IVIG reduces the expression of Neutrophil Extracellular Traps (NET), a substance thought to be heavily involved in triggering the cytokine storm by promoting proinflammatory and procoagulant environment, which ultimately leads to respiratory distress syndrome and rises the risk of endothelial damage.[6,9,15] In conclusion, IVIG works to upregulate the anti-inflammatory agents within immune system, all the while suppresses the half-life and action of pro-inflammatory mediators.

It should be noted that this treatment option offers minimum benefit on those presenting with mild or moderate cases, due to the treatment aim being to modulate a highly aggressive immune and inflammatory cascade. In mild and moderate cases, such ailment is commonly not found thus the expense of the treatment does not justify being used as a supplementary/replacement of standard treatment.

Unfortunately, in our case the patient had been diagnosed as a severely ill patient in the previous tertiary hospital for 3 days, hence we did not witness the progression in which the patient started to deteriorate. The scarce of the IVIG availability in our town, along with extended family discussion regarding the procedure also postponed the treatment to be given as soon as the patient arrived in the ICU. That being said, patient slow but steady improvement since February 18th (a day after the final dose of IVIG), along with decreasing inflammatory markers gave insight that the IVIG may indeed contribute in improving the critical condition which stem from an overly aggressive immune response.

In our case, we believe the IVIG improved the patient survival and outcome, but not length of hospital stay. This may stem from some reasons. First, patient presenting with repeated melena caused prolonged discharge, despite the initial chief complaint and lab results have improved. Second, patient had already been in relatively severe condition during his referral to our hospital, thus the adjunct treatment such as IVIG may not be as satisfactory as when said treatment is given very soon.

Xie et al reported a single center retrospective study of 58 patients treated with IVIG, which are divided into those receiving IVIG < 48 hours, and those > 48 hours. A total of 23 patients died within 28 days of admission, 7 in <48h group and 16 in >48h group. The result concluded that IVIG treatment initiated in the first 48 hours of admission reduced length of stay compared to >48h group (11.50 ± 1.030 vs 16.96 ± 1.620 days), mechanical ventilation usage (6.67% vs 32.14%), and 28 days-mortality (23.3% vs 57.1%).[10]

A case series reported by Mohtadi et al shown improvement of five critically ill COVID-19 patients in whom standard treatment failed were given the IVIG. All five patients had at least one comorbidity and were rapidly deteriorating during the hospital stay, with lung progression marked in CT scan and very significantly decreasing SaO2 level. IVIG treatment was given for 5 days; all five patients initially encountered either acute respiratory distress or shown pulmonary lesion on CT scan, but then saw improvement following the last day of IVIG administration. All patients managed to be discharged.[11]

Esen et al documented a retrospective study of critically ill COVID-19 patients which divided into two groups: the case group consisting of 51 patient given IVIG, and the control group consisting of 42 patients. This yielded a satisfactory result of case group vs control group survival (61% vs 38%) with OR 2.2 and 95% confidence interval. The study however had a noticeable weakness, in which the baseline of severity for the disease between case and control group was not balanced, with some of the latter group being more severe.[12]

In a randomized placebo-controlled double blind clinical trial conducted by Gharebaghi et al, 59 critically ill COVID-19 patients who failed to respond to standard treatment were included. The patients are divided into those receiving IVIG (n=30) and those receiving placebo (n=29). The result yielded that the treatment group had significantly lower in-hospital mortality rate (20%) compared to the control group (48.3%), yet longer hospital stay for the treatment group. The author concluded that the later might be because of the longer survival in treatment group, in comparison to the critically ill patient in control group who died earlier.

However, in another randomized control trial, Tabarsi et al reported there was no significant benefit in use of IVIG in terms of reducing mortality and the use of mechanical ventilation. This study included 52 patients in IVIG group and 32 patients in control group receiving standard of care. Intervention group received IVIG with dose of 0.4 gr/kg for 3 days. The author however remarked there was a positive relationship between time of admission to IVIG initiation and the length of hospital stay among survivors. Similarly, Salehi et al concluded no benefit of IVIG treatment in critically ill COVID-19 patients in a retrospective cohort study. This study evaluated 3 tertiary centers and divided the COVID-19 patients into two groups, standard treatment (n=109) and IVIG treatment (n=74), in which the IVIG group is further divided into small dose, medium dose, and large dose groups. The result concluded that there was no difference in terms of duration of ICU stay, mechanical ventilation, or mortality rate, and in fact, result yielded longer hospital stay for IVIG group.[8]

Despite the positive outcome from fairly large amount of studies, it is worth nothing that due to the heterogenicity of the methodological studies, baseline of disease severity and comorbidity, variation of doses, durations, and time initiation of the treatment, concurrence with other treatments, as well as differing sample sizes in those studies, it is hard to standardize the outcome and verify the robustness of the treatment option.[8,10-14] One thing generally accepted is that the use of IVIG in early phase of critical condition does improve some outcome variables such as length of hospital stay, mortality within 28 days, pulmonary lesions.[6,8,10-14] Nevertheless, with concordance of reports from different nations yielding positively, the role of IVIG in reducing the clinical burden should not be overlooked.

4.Conclusion

From the above discussion, we believe that IVIG treatment does play some role in severe-critically ill COVID-19 patients particularly if given in the early phase of deterioration. However, robust data and larger scale clinical trials are still scarce thus need further testing and research. This case report does further the already existing studies and data that postulate that IVIG treatment is an admissible option for those presenting with severe-critical cases and high inflammatory markers.

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