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Intravenous Immunoglobulin as a Therapeutic Option in Severe COVID-19 Patient: Case Report

Yulia Karolina Kurniawati[1], Ongky Aristian[2], Anak Agung Gde Upeksha[3]

[1]Intern of Pulmonology and Respiratory Medicine Department in Bali Mandara Regional General Hospital, Denpasar, Bali, Indonesia
yuliakarolina[at]gmail.com

[2]Intern of Internal Medicine Department in Bali Mandara Regional General Hospital, Denpasar, Bali, Indonesia
ongkyaristian[at]gmail.com

[3]Pulmonologist of Pulmonology and Respiratory Medicine Department in Bali Mandara Regional General Hospital, Denpasar, Bali, Indonesia
upekshagde[at]gmail.com

Abstract: ***Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent for the ongoing pandemic of coronavirus disease 2019 (COVID-19). Until now, no definite effective treatment has been identified. Case Report: This article reports a 41 year old male, diagnosed with Confirmed Pneumonia COVID-19 with hypertension, transaminitis and obesity. The patient received high-dose intravenous immunoglobulin (IVIg) therapy. Conclusion: Patient was treated by intravenous immunoglobulin (IVIg) showed satisfactory recovery. Based on observations, IVIg should be considered in deteriorating patients infected with COVID-19. However further investigations are needed to explain this further.***

Keywords: COVID-19, IVIg

1. Introduction

The outbreak of pneumonia caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously known as 2019-nCoV), has recently been assessed by the World Health Organization (WHO) as a pandemic. The disease it was later designated as coronavirus disease 2019 (COVID-19) by the WHO.[1,2] Rapid progression of lung involvement, relatively high infectivity, and lack of definite effective treatment make it urgent to develop efficient measures of management based on the pathogenesis of COVID-19. Although many empirical therapeutic options have been introduced on several recommendations, including existing and new generation of antivirals, steroids, the optimal strategy for severe COVID-19 remains unclear. [3]

The clinical spectrum of SARS-CoV-2 infection is wide. COVID-19 symptoms can be categorized into asymptomatic, mild, moderate, severe and critical. Patients with mild symptoms are symptomatic patients without hypoxia or evidence of viral pneumonia. Symptoms include fever, cough, fatigue, myalgia, anorexia, shortness of breath. Other non-specific symptoms such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, loss of smell (anosmia) or loss of taste (ageusia) that appear before the onset of respiratory symptoms are also frequently reported. Patients with moderate symptoms are patients with clinical signs of pneumonia (fever, cough, rapid breathing, shortness of breath) but no signs of severe pneumonia. In patients with severe symptoms there are clinical signs of pneumonia (fever, cough rapid breathing, shortness of breath) plus one of the following: respiratory rate> 30 bpm, severe respiratory distress, or SpO2 <93% in room air. Meanwhile, critical patients are patients with Acute Respiratory Distress Syndrome (ARDS), sepsis and septic shock.[2]

In patients who rapidly progressed to critical conditions, elevated inflammatory factors were observed, indicating an overwhelming immune response. Researches showed that the main pathogenesis of organ dysfunction lay in the overall cytokine dysregulation. Similarly, the point when status deterioration starts in patients with COVID-19 should be a critical window of opportunity for intervention. Until now, no definite effective treatment has been identified.[4,5]

Intravenous immunoglobulin (IVIG) is a product derived from the plasma of donors used for treatment of primary and secondary immunodeficiencies, autoimmune/ inflammatory conditions, neuroimmunologic disorders, and infection-related sequelae. IVIg provides passive immune protection against broad range of pathogens.[6,7] More evidence exists for the use of hyperimmune globulin in the treatment viral illnesses. A retrospective review revealed that convalescent plasma from SARS-CoV survivors administered to SARS-CoV patients with progressive disease resulted in significantly higher discharge rates and lower mortality rates, compared to historical controls. Retrospective study including patients from three hospitals, two from the United States of America and one from Germany provide valuable information regarding the use of IVIG for the treatment of COVID-19 in 12 patients (9 male) with an average age of 50 years (range 23–74 years) and severe COVID-19 was well tolerated. The promising result from this study is that all patients survived hospital discharge. In the context of COVID-19, the actual role of IVIG is not to boost the immune system, but through its immunomodulatory effect to suppress a hyperactive immune response that is seen in some patients. This overwhelming response, which is vaguely described as cytokine storm syndrome, ends up being the major cause of lung injury. This highlights the importance of

selecting the right patient and intervening at the right moment.

The rationale for the use of IVIg in SARS-CoV-2 infection is modulation of inflammation. Several anti-inflammatory mechanisms of IVIG may lessen the inflammatory response in severe SARS-CoV-2 infection, including the presence autoreactive antibodies that bind cytokines or binding to the variable domains of other antibodies. Additionally, the presence of IgG dimers in IVIG may block activating FcγR on innate immune effector cells.[8]

Here, we review the mechanism and utility of viral infections, and consider their usage in COVID-19 infection.

2. Case Illustration

A 41-year old male came to the ER on January 28, 2021 with main symptom of fever since a week before admission to hospital. Fever had characteristic of sudden onset fever. Fever was intermittent and did not improve with paracetamol administration. Patient also complained of dry cough that increasingly worse since 7 days prior to admission. Cough did not improve with cough medicine. Symptoms of breathlessness and losing ability to smell were denied. The patient had history of hypertension which was not controlled with antihypertensive medication. Patient denied having history of diabetes mellitus, and all other degenerative disease. The patient was obese with BMI of 31.1, with body weight of 90 kg, and height of 170 cm.

Physical examination revealed patient had compos mentis consciousness, with blood pressure 160/100 mmHg, pulse rate 90 beats per minute, respiratory rate 24 breaths per minute, patient was afebrile when patient came to ER, with axillary temperature: 36 ℃ and oxygen saturation 98% when breathing ambient air. On lung physical examination, tachypnea was observed, with rales in all fields of lungs. Other physical examinations were within normal limits.

Laboratory test results revealed a positive result of SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (rRT-PCR) assay. Complete blood count results revealed leukocyte count of 14,6 (4,10 – 11,00) X 10^3/µL, Hb 15,7 g/dL, HCT 44,7%, PLT 236 x 10^3/µL. Blood chemistry shown D-dimer : 770 ng/mL, GDS 162 mg/dL, SGOT 44 U/L, SGPT 42 U/L, BUN 39 mg/dL, Creatinine serum 1,41 mg/dL, Na : 131 mmol/L K 3,7 mmol/L, Procalcitonin 0,10 ng/mL, Ferritin > 1200,00 ng/mL, CRP 74,74 mg/L. Chest x-ray examination results showed severe grade bilateral pneumonia. Patient was diagnosed of moderate grade covid-19 with bilateral pneumonia, transaminitis, and stage II hypertension.

Patient was given intravenous fluid drip (IVFD) NaCl 0,9% 500 ml/24 hours, levofloxacin 1x750 mg (i.v.), methylprednisolone 2x40 mg (i.v.), N-acetylcysteine 2x600 mg (i.v.), Paracetamol 3x1 gram (i.v.), zinc 1x5 mg (p.o), vitamin C daily (i.v.), Cernevit daily (iv), curcuma daily (p.o), ondancenteron 3x4 mg (i.v.), pantoprazole 2x40 mg (i.v.), codeine 3x5 mg (p.o.), isoprenosin 4x 500 mg (p.o.), hepatin three times daily (p.o.), folic acid two times daily (p.o.), lovenox 1x 0.6cc (s.c.), Candesartan 1x8mg (p.o.).

After 5 days of hospitalization (4/2/2021), patient felt shortness of breath. Patient required breathing muscles during inspiration and expiration. Patient also had cough with mucous phlegm. Physical examination revealed patient had compos mentis consciousness, with respiratory rate 32 breaths per minute. Oxygen saturation decreased below 90% when breathing ambient air, oxygen saturation was 93% with NRM 15 liters per minute. Leukocyte level was 10, 36 (4,10 – 11,00) X 10^3/µL. CRP level was 68,77 (<5) mg/L. Chest x-ray examination revealed severe pneumonia. The diagnosis was modified with severe Covid-19, severe bilateral pneumonia. The patient was given IVIg at 0.5 g/kgBW on first day followed by 0.3 g/kgBW from second until fifth days. The patient was given given furosemide 20 mg (i.v) as post medication (if the systolic blood pressure > 100 mmHg). The patient weighs 90 kg, hence the dosage of IVIg on the first day is 45 grams and 27 grams from second until fifth days. On 5/2/2021, patient was given second dose of IVIg at 0.3 g/kgBW (27 grams). Patient complained of shortness of breath and cough with mucous phlegm. Oxygen saturation was 96% with NRM 10 liters per minute.

On 6/2/2021, patient was given third dose of IVIg at 0.3 g/kgBW. Patient felt there was improvement of his condition clinically, he did not feel the shortness of breath as worse as the day before. Oxygen saturation was 99% with NRM 8 liters per minute. CRP level was 40,94 (<5) mg/L, crp level was high but lower compared to 2 days before. Chest x-ray examination revealed severe pneumonia, there was no significant improvement when compared to latest chest x-ray [**Fig 1**]. On 7/2/2021, patient was given fourth dose of IVIg at 0.3 g/kgBW. Patient was making a clinical improvement gradually, with no productive cough. Oxygen saturation was 96% with facemask 7 litre per minute. Leukocyte level was 18.87 (4,10 – 11,00) X 10^3/µL. CRP level was 21.73 (<5) mg/L. Patient was given additional cefobactam 2x2 g iv.

On 8/2/2021 the patient was given fifth dose of IVIg at 0.3 g / kgBW. Patient was making a significant improvement clinically. Patient did not have any symptoms. Oxygen saturation was 97% with facemask 6 liters per minute.
On 5th day of IVIg administration, there was no adverse event reported. Over the next few days, his clinical status gradually improved. Next chest x-ray was performed on February 9, 2021. The result showed a decrease in paracardial infiltrate. CRP level was monitored on February 9 2021, the result was 7.53 (N<5) mg/L. After 10 days, CRP level on February 19 2021 was normal 1.25 (<5) mg/L. WBC level next examined on February 10, 2021 with result of 17,59 (4,10 – 11,00) X 10^3/µL. Unfortunately, oropharyngeal swabs on February 9 and February 19 still showed positive result
His oxygen saturation level returned to 97%–98% on February 21 when breathing ambient air, without supplemental oxygen. Patient was finally discharged on February 23.

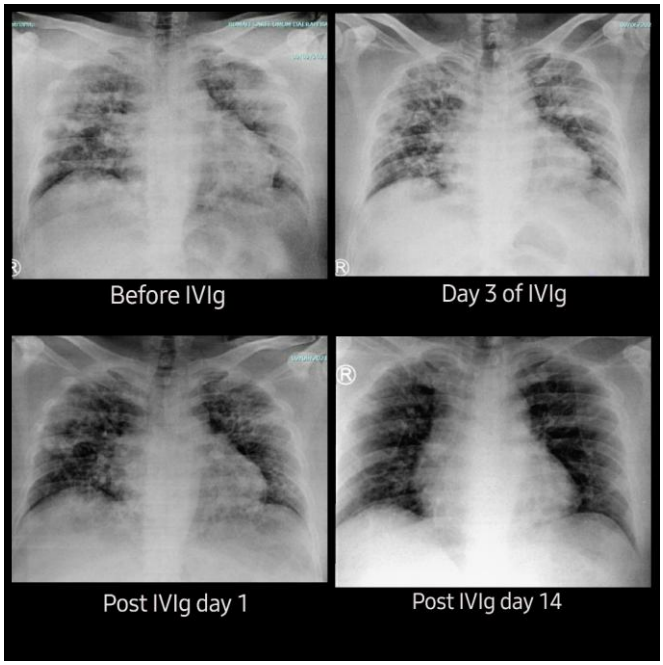

Figure 1: Chest X-ray during hospitalization

3. Discussion

Although confirmed cases of COVID-19 have accumulated during the past year, understanding of the pathophysiological changes of this infection still remains very limited. No definite treatment has been identified, which makes clinical management more difficult.[3] Here we report a case of patients with severe COVID-19, whom was successfully treated by Intravenous Immunoglobulin (IVIg) at the early stage of clinical deterioration. Based on observations, a high dose of IVIg administered at the appropriate point could successfully improve the outcome of COVID-19. The natural history of SARS-CoV-2 infection does not resemble that of any of the previously known coronaviruses. To date, we have noticed wide clinical spectrum of SARS-CoV-2 infection, including asymptomatic infection, mild respiratory tract illness, moderate, severe until critical manifestations. The infection often started with mild or moderate unspecific symptoms like low-grade fever, sore throat, coughing, fatigue, and malaise, similar to the symptoms of a common cold.[2] The initial symptoms usually persist for around 3–7 days, when high-grade fever developed and respiratory distress became more prominent. Some of patients would also complained of gastrointestinal symptoms during this period.

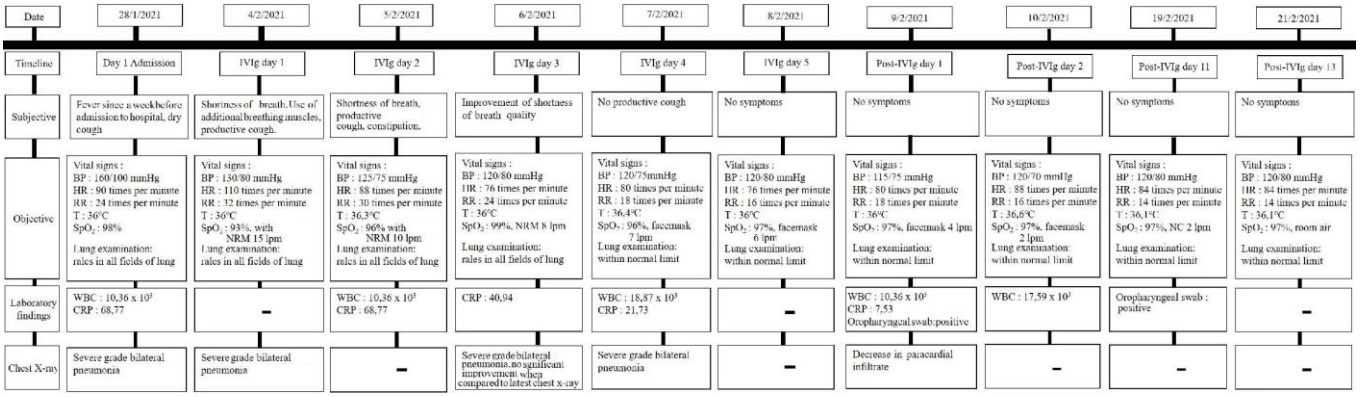

Figure 2: Timeline of patient's symptomps and laboratory results during administration of IVIg

When clinical deterioration begins, the first few days of deterioration may present a critical point when potent suppression of the inflammatory cascade could save the patients from fatal immune-mediated injuries, as shown above. High-dose IVIg at 0.3–0.5 g per kg weight per day for five days was used in our patient as a potent and safe immune modulator. The dose of IVIg was determined based on well-established practice in immune modulation therapy for other diseases, including autoimmune thrombocytopenic purpura, neuromuscular disorders, etc with a consideration of potential renal or cardiac impairment in severe COVID-19 patients.[6,7] The patient reported no adverse events. Patient was clinically improved after the administration, with breathing difficulties alleviating in 3–5 days. Confounding factors did exist, including the use of different antiviral, antibiotic and a short course of steroids in patient. Nevertheless, from the timeline and pattern of disease, it is most probable that high-dose IVIg played the role in their recovery. IVIg is a blood product containing polyclonal immunoglobulin G isolated from healthy donors, and it has been used over years. IVIg of higher dose has been a choice of immunomodulatory therapy for autoimmune or inflammatory disease and for prophylaxis and treatment of severe infections, especially in immunocompromised patients [9,10] Several theories have been proposed to explain its potential immunomodulatory mechanisms, including Fab-mediated Fc-mediated and approaches.[11,12] In previous studies of SARS and MERS, IVIg therapy has exhibited various clinical benefits with good tolerance.[13,14,15] Considering its efficacy in modulating immune inflammation, improving passive immunity, and the overall safety profile, IVIg could be considered a promising option at the early stage of clinical deterioration of patients with COVID-19. Our report is limited by the evidence is needed to confirm the conclusions. However, this report provides an important therapeutic clue to the current situation of rapid disease spreading. Patients might not receive much benefit when systemic damage has already happened.

4. Conclusion

We reported a patient with severe COVID-19 who received intravenous immunoglobulin (IVIg) at the time of initiation of respiratory distress showed satisfactory recovery. Considering its efficacy in modulating immune inflammation,

improving passive immunity, and the overall safety profile, IVIg could be considered a promising option at the early stage of clinical deterioration of patients with COVID-19. Based on observations, high-dose IVIg could successfully improve the outcome of COVID-19 and should be considered as a therapeutic option in severe COVID-19. However, further study is needed.

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