International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2019): 7.583

Successful Therapy of Critically Ill Coronavirus Disease-19 Patients with Intravenous Immunoglobulin (IVIg): A Case Series

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Abstract: ***Introduction: Coronavirus disease-19 (COVID-19) pandemic management strategyneeds therapy with proven safety profiles. Intravenous immunoglobulin (IVIg) has been used for decades in various immune disorders and infection. In COVID-19 context IVIg given mainly in severe to critically ill patients. Cases: We report 3 patients treated with IVIg in our hospital. 1) Male, 61 yo, critically ill COVID-19 and type II DM, had worsening of symptoms 8th day after admission and intubated, IVIg was then administered, ventilator use discontinued at the end of IVIg, recovery achieved in 9 days. 2) Female, 62 yo, admitted with moderate COVID-19 and hypertension. After 9 days, develop deterioration into critical disease. Negative swab results achieved in 10 days after IVIg. 3) Male, 37 yo, critically ill COVID-19, hypertension, and obese. IVIg therapy showed improvement in 3 days. Discussion: IVIg may act against hyperinflammatory state found in critical COVID-19.All patients in our case received IVIg dose 0,5 g/kgBW/day for 5 days. Time of administration before acceleration phase give greatest benefit. No mortality was observed at 28th and 60th days. Our result demonstrated successful therapy with IVIg as found in other studies. Conclusion: IVIg therapy in COVID-19 is increasingly used worldwide. Recent evidence shows improvement of clinical and supporting examination parameters. Underlying mechanism of IVIg in COVID-19 is still unclear. Further studies are needed.***

Keywords: IVIg, COVID-19, critically ill patients

1. Introduction

Coronavirus disease-19 (COVID-19) pandemic caused by *severe acute respiratory syndrome coronavirus* 2 (SARS-CoV-2) is still not completely under control worldwide. The morbidity and mortality rates continue to increase even though the route of transmission already known. This situation demands appropriate and effective management in order to improve patient outcomes.

World Health Organization (WHO) China reported there are about 20% cases of severe to critical COVID-19. As of April 2020, more than 2.3 million people were infected with SARS-CoV-2 and more than 150 thousand people died.[1]Mortality rate of COVID-19 at all degrees of severity is around 1–15%, while for critical patients, National Health Commission of China report a higher mortality of around 30-60%.[2]In Indonesia COVID-19 cases affect more than 349,000 people, with mortality more than 12,000.[1]The incidence of COVID-19 in Bali is also high, estimated 10,000 cases, with mortality more than 340.[2] These data support the fact that COVID-19 still causes significant morbidity and mortality. Thus, effective management strategy is needed.

A number of development and advancements have been reported on various aspects of pandemic management in order to find effective management of SARS-CoV-2 infection, which in implementation adjusts to the degree of disease.[3] A wise choice is to study the effectiveness of existing therapeutic options with an acceptable safety profile, for example administration of intravenous immunoglobulin (IVIg).

Intravenous immunoglobulin is a blood product made from serum collected from thousands of healthy donors. It has been shown for decades that IVIg has a pleiotropic immunomodulation action, involving innate and adaptive immunity, and used in variety of diseases such as autoimmune disorders, hematology, neuromuscular, rheumatology, ophthalmology, dermatology, as well as bacterial or viral infections. In the context of COVID-19, IVIG act as immunomodulator to suppress the hyperactive immune response known as cytokine storm syndrome, the main cause of lung injury. It is mediated by several mechanisms including interaction with T cell function, presentation / maturation of antigen presenting cells, combined with the capacity to decrease inflammatory reactions[4], inhibition of proinflammatory cytokines, and binding of Fc-gamma receptors from activated macrophages. In severe to critical degrees of COVID-19 there are multiorgan dysfunction, dysregulation due to the host's response to SARS-CoV-2 which is characterized by refractory hypoxemia, acute respiratory distress syndrome (ARDS), sepsis, and septic shock.

Numerous studies examined the use of IVIg for severe and critical COVID-19 in patients with mean age 50 years (range 23–74 years).[6] The IVIg dose ranged from 0.1 to 2.0 g/kg/day (median 1.25 g/kg) and given 1 - 15 days, with the most common regimen 0.5 g/kg/day for 1 - 5 days.[4,6]Other multicentre retrospective cohort study evaluate the effectiveness of IVIg in 325 severe and critical COVID-19

patients treated in southern China. Total 174 patients (64% male, mean age 61 years) received IVIg therapy. Additional therapy includes antibiotics, anti-viral, and steroids according to Chinese guidelines.[7,8]The results of these studies indicated that IVIg was well tolerated. All of the patients were successfully discharged from the hospital alive. IVIg initiation resulted in immediate and significant improvements of clinical symptoms, laboratory examinations, and imaging.[4,6]It can be seen that the properties of IVIg have significant potential for COVID-19 especially severe and critical degrees.

The appropriate time for IVIg administration is very important in order to be able to provide effective intervention and achieve good results. Early IVIg administration (within 3 days after admission) was associated with a significantly shorter length of stay (median 7 days, range 3-14 days). Meanwhile, delayed IVIg administration (> 7 days) was associated with significantly increased length of stay in hospital (median 33 days, range 8-48 days, p = 0.03). In another retrospective study of severe and critical COVID-19, early administration of IVIG was also associated with reduced ventilator use, length of stay, and intensive care units, and improved 28-day mortality.[9] High dose IVIg (> 15 g/day) and early administration (≤ 7 days) improved the prognosis of critical COVID-19 patients.[7] One study documented that short-term moderate-dose corticosteroids plus IVIg (20 g/day) may benefit patients who do not respond to low-dose therapy (10 g/day).[8] Low-dose IV glucocorticoid administration (1-2 mg/kg) for 5-7 days in critically ill patients and early IVIG administration (48 hours after admission to ICU) resulted in significant reduction in the use of mechanical ventilation, hospitalization, and clinical effectiveness.[10] These data indicate that the greatest benefit of IVIg in COVID-19 setting achieved by early administration. We present a case series regarding the administration of IVIgin three patients with confirmed critical COVID-19.

2. Case Illustration

Case 1

A 61-year-old male patient, married, Javanese, self-employed, admitted to Bali Mandara Hospital on July 24, 2020 with chief complaint dyspnea since 2 days before admission. It does not improve with position changes to the left or right and no use of additional respiratory muscles. Patient also complained history of fever 2 days ago. Fever with sudden onset and fluctuative. Patient lives in a local transmission area. History of type 2 diabetes mellitus (T2DM) controlled with insulin glulisine 3X 10 IU, and insulin glarginin 1X 14 IU.

From physical examination we found respiratory rate (RR) 28x/minute, temperature 38.5 ℃ and desaturation (SpO_2 96% with NRM 15 lpm). On lung examination, rhonchi were found in all areas of the right and left lungs.

Laboratory investigations on complete blood count showed an increase in leukocytes (13.13) with neutrophils predominance (12.12), increase in NLR (21.3), and decrease in lymphocytes (0.57). Blood chemistry results showed an increase in D-dimer (2045), BSA (196), procalcitonin (0.77), Ferritin (> 2045), and CRP (308,48). Oronasopharyngeal RT-PCR swab of SARS-CoV-2 on 24thJuly 2020 was found positive. Blood gas analysis revealed abnormalities in the form of respiratory alkalosis and metabolic acidosis, with PaO_2/FiO_2 71. AP chest X-ray imaging showed bilateral pneumonia. The patient was diagnosed with confirmed critical COVID-19, severe acute respiratory distress syndrome (ARDS), and type II DM.

Patients received initial IVFD therapy with NaCl 0.9% 12 dpm, O2 with NRM 15 lpm, remdesivir loading dose 200 mg iv every 24 hours on day 1 followed by 100 mg iv every 24 hours on days 2-10, paracetamol 1 gram iv every 8 hours, vitamin C 1000 mg iv every 24 hours, dexamethasone 6 mg iv every 24 hours, ranitidine 50 mg iv every 12 hours, azithromycin 500 mg po every 24 hours, enoxaparin 0.4 cc subcutaneously (SC) every 12 hours, acetylcysteine 600 mg po every 12 hours, insulin glulisine 10 IU every 8 hours, and insulin glarginin 14 IU every 24 hours.

After 8 days, on July 31, 2020 the patient developed worsening complaints of dyspnea, with the use of respiratory muscles during inspiration and expiration. Vital sign obtained tachypnea (RR 36x / minute) and desaturation (SpO2 83% with NRM 15 lpm + Nasal cannula (NK) 6 lpm). Rhonchi in all areas of the right and left lungs persist. Investigations for blood gas analysis showed worsening with the current PaO2 / FiO2 32.1. The patient then intubated with mechanical ventilator.

Patient received IVIg administration starting at a dose of 0.5 g/kgBW on the first day, followed by 0.3 g / kgBW on the second to fifth days. On August 5, 2020, the patient was successfully extubated, SpO2 96% with NRM 10 lpm, gradual tapering down of O_2 therapy, with a target saturation of 92-96%. On August 13, 2020 the patient was free from O_2 therapy. The evaluation swab on August 14, 2020 gave negative results, the patient was declared cured. Monitoring and observation on day 28 and 60, no mortality was found.

Case 2

Female, 62 years old, married, Balinese, and works as a lecturer, came to Bali Mandara Hospital on December 23, 2020 with chief complaint shortness of breath since 2 days before admission. Patient feel difficult to do deep inspiration and use accessory muscles to breath. History of fever also known. Other complaints were cough with white sputum and anosmia since 2 days ago. Patient lives in a local transmission area. History of hypertension since 10 years ago controlled with bisoprolol 1x 2.5 mg, clopidogrel 1x 75 mg, amlodipine 1x10 mg. Allergy to sulfa group.

Physical examination found blood pressure 160/100 mmHg, tachypnea (RR 28x / minute), and desaturation (SpO_2 97% with NK 4 lpm). On physical examination of the lungs, rhonchi were found in all left and right lung fields.

SARS-CoV-2RT-PCR oronasopharyngeal swab on December 23, 2020 was positive. Laboratory examination revealed increase in NLR (5,7), D-dimer 660, BSA 162, SGOT 44, SGPT 42, BUN 39, Creatinine 1.41, Procalcitonin 0.10, Ferritin>1200, and CRP 74.74. AP chest X-ray revealed bilateral pneumonia.

Patient was diagnosed with moderate degree COVID-19 and Stage II Hypertension. Manage with IVFD NaCl 0.9% 12 dpm, paracetamol 3x 1 gram iv, vitamin C 1x 1000 mg iv, favipiravir loading dose 2x 1600 mg po day 1 followed by 2x 600 mg po day 2-5, azithromycin 1x 500 mg po, dexamethasone 1x 6 mg iv, enoxaparin 2x 0.4 cc sc, pantoprazole 2x 40 mg iv, curcuma 3x 1 tablet po, acetylcysteine 2x 600 mg po, clopidogrel 1x 75 mg po, amlodipine 1x 10 mg po, bisoprolol 1x 2.5 mg po, and candesartan 1x 16 mg po.

After 9 days, on January 1st, 2021 the patient worsened. Physical examination revealed tachypnea (RR 34x / minute) and desaturation (85% SpO_2 with NRM 15 lpm). Rhonchi in all left and right lung fields were still found. Investigation of blood gas analysis revealed type 1 respiratory failure, with PaO_2 / FiO_2 141. AP chest X-ray of January 1, 2021 showed significant increase in infiltrates in both lung fields.

Patients diagnosed with COVID-19 had a confirmed critical degree, moderate ARDS, and stage II hypertension. The patient then received O_2 therapy using a high flow nasal cannula (HFNC) flow 60 lpm FiO_2 100%, and was given IVIG at a dose of 0.5 g/kgBW on the first day, followed by 0.3 g/kgBW on the second to fifth days. The next 10 days patient improves clinically and laboratory parameters and x-rays, until on January 22nd, 2021 the patient use no additional O_2. AP chest X-ray 21st January 2021 revealed reduced infiltrates. On January 21stand 22nd 2021 the patient got two negative swab results, patient declared cured. Monitoring and observation on days 28 and 60, no mortality was found.

Case 3

Male, 37 years old, married, Balinese, referred from Klungkung Regional Hospital on February 17th, 2020, with chief complaint dyspnea since 12 days before admission. Shortness of breath does not improve with position changes to the left or right. Cough with yellowish-brown phlegm. History of fever 12 days ago, got better with antipyretic. Exposure to confirmed COVID-19 patient, which is his wife, lives in local transmission area. History of hypertension since 10 years ago, controlled with amlodipine 1 x 10 mg po.

Physical examination revealed blood pressure 137/81 mmHg, tachypnea (RR 30x / minute), and desaturation (SpO_2 96% HFNC flow 45 lpm FiO_2 55%). Patient body weight 103 kg (ideal 63 kg), height 170 cm, and body mass index (BMI) 35.64 kg/m^2. On lung examination rhonchi were found in all left and right lung fields.

Complete blood count demonstrated increase in leukocytes (13.49), neutrophil dominance (90), and a decrease in lymphocytes (5.4%). Blood gas analysis revealed type 1 respiratory failure, with PaO2 / FiO2 65,45. The SARS-CoV-2 RT-PCR oronasopharyngeal swab on February 17th, 2020 was positive. Chest X-ray PA on February 16th, 2021 from Klungkung Hospital showed bilateral pneumonia (Figure 6).

Patient was diagnosed with confirmed critical COVID-19, severe ARDS, hypertension and grade II obesity. Therapy given was IVFD NaCl 0.9% 12 dpm, remdesivir loading dose 1x 200 mg iv day 1 followed by 1x 100 mg iv day 2-10, acetylcysteine 2x 600 mg po, vitamin C 1x 1000 mg iv, curcuma 3x 1 po, dexamethasone 1x 6 mg iv, enoxaparin 2x 0.4 cc sc, pantoprazole 2x 40 mg iv, and paracetamol 3x 500 mg po.

After 6 days, on 23rd February 2021 patient developed deterioration, use of additional respiratory muscles for inspiration and expiration. Physical examination revealed tachypnea (RR 32x / minute) and desaturation (SpO2 91% with NRM 15 lpm). Lung examination found crackles in all lung fields. Patient then given IVIg 0.5 g/kgBW on the first day, followed by 0.3 g/kgBW on second to fifth days. Patient use HFNC flow 55 lpm FiO2 95%

Monitoring for next 3 days patient shows clinical improvement as well as laboratory parameters and x-rays.On 2ndMarch 2021 patient use no O_2 supportive therapy. AP chest X-ray 2ndMarch 2021, revealed reduced bilateral pneumonia. Patients monitoring and observation on day 28 and 60, no mortality was found.

3. Discussion

Our case series present 3 patients who were successfully treated with intravenous immunoglobulin (IVIg). The COVID-19 pandemic has been going on for a year however, there is still no definitive therapy. On the other hand, supportive and adjuvant therapy is rapidly developing. Clinical trials and autopsy results suggest that inflammation and excessive immune response caused by viral infection are key factors for disease progression and poor prognosis. Immunotherapy based on neutralization of inflammatory cytokines and immunomodulation can reduce inflammation and lung damage.[7] IVIg is blood product containing polyclonal immunoglobulin G isolated and collected from healthy donors, and has been used for more than 30 years. Several theories have been proposed to explain the potential immunomodulatory mechanisms of IVIg, including the Fc-mediated and Fab-mediated approaches, but still unclear. In previous studies of SARS and Middle East Respiratory Syndrome (MERS) infection, IVIg has shown a variety of clinical benefits with good tolerance.[11] This theoretical basis forms the rationale for IVIg administration in our patients.

Table 1: Laboratory Parameter of 3 Patients in Our Study

Parameter	Patient 1		Patient 2			Patient 3			Normal
	Admission (24/7/2020)	Post-IVIg (D-2) (7/8/2020)	Admission (23/12/2020)	Worsening (1/1/2020)	Post-IVIg (D-8) (15/1/2020)	Admission (17/2/2021)	Worsening (23/2/2021)	Post-IVIg (D-7) (2/3/2021)	
WBC	13.13	8.29	8.26	9.54	19.68	13.49	16.61	18.41	(4.1 – 11) X 10^3/µL
RBC	4.69	4.50	4.39	4.27	4.62	5.5	5.35	4.89	(4.0 - 5.2) X 10^6/µL
HB	13.3	12.9	13.1	12.7	13.8	15.7	15.9	14.4	(12 – 16) g/dL
HCT	39.5	36.9	40.3	38.5	42.7	45.8	44.2	40.7	(35 – 47) %
PLT	230	341	277	253	409	294	477	409	(150 – 440) X 10^3/µL
NE#	92.3	7.65	6.23	8.53	16.97	90	15.37	15.61	(1.5 - 7.0) X 10^3/µL
LY#	4.3	1.71	1.1	0.61	1.71	5.4	0.64	1.73	(1.0 - 3.7) X 10^3/µL
CRP	308.48	1.21	84.06	169.59	1.8	20.2	56.64	0.58	< 5 mg/L

The effectiveness of IVIg therapy was also assessed based on chest X-rays. In case 1, on admission 24/7/2020, the chest X-ray showed bilateral pneumonia. Meanwhile, post IVIg, the infiltrates were significantly reduced (Figure 2).

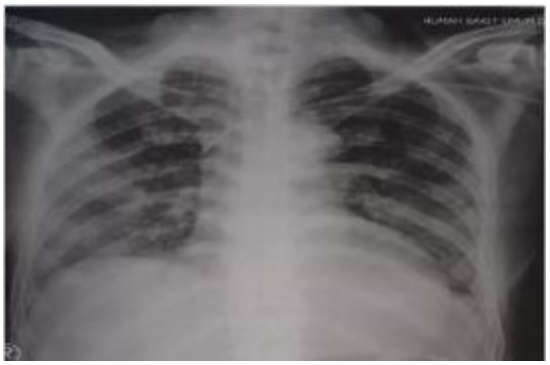

Figure 1: Bilateral pneumonia on day -1 (24/7/2020), case 1

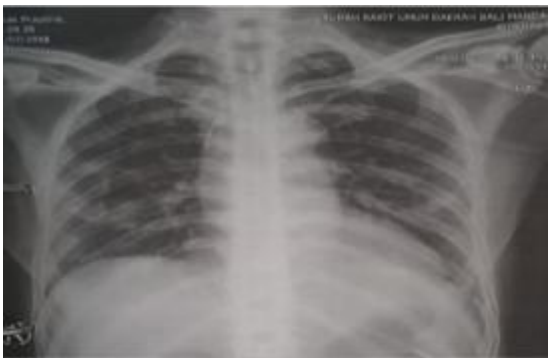

Figure 2: Infiltrates significantly reduced post IVIg day -2, case 1

In case 2 the effectiveness of IVIg therapy was also assessed by chest X-ray. On admission 23/12/2020, chest X-ray examination showed bilateral pneumonia. On 1/1/2021 (Figure 4), when the patient experienced clinical deterioration, the infiltrates increase. Meanwhile, on the 8th day post IVIg therapy, the infiltrates was reduced.

In case 3, on admission 16/02/2020, chest X-ray demonstrated bilateral pneumonia. Meanwhile, on 1/1/2021, patient developed deterioration, infiltrates also significantly increased. Chest X-ray on the 8th day post IVIg demonstrate pneumonia with reduced infiltrates (Figure 7-9).

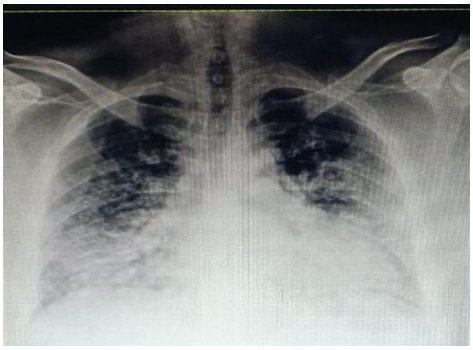

Figure 3: Bilateral pneumonia on day-1 (23/12/2020) of case 2

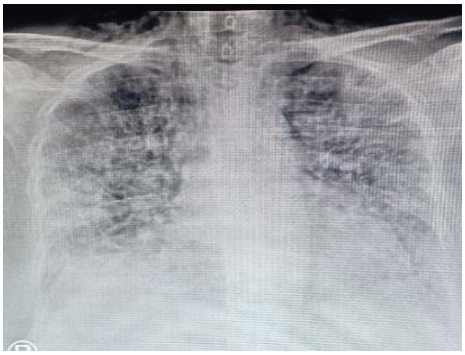

Figure 4: Infiltrates significantly increased on day-9 (1/1/2021), then IVIg initiated on case 2

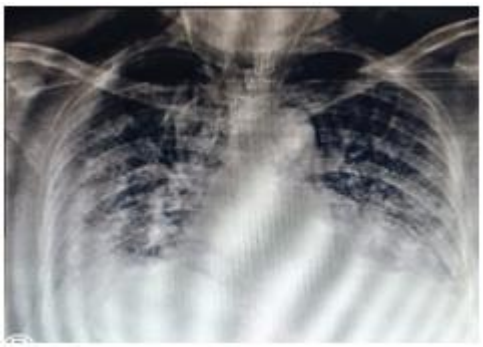

Figure 5: Infiltrates significantly reduced post IVIg D-14 (15/1/2021) on case 2

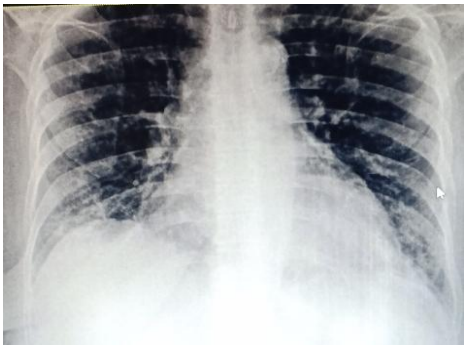

Figure 6: Polyclinic thorax evaluation on 4/2/2021 of case 2

COVID-19 mainly consists of 3 phases, (1) Initial phase which includes the acquisition of virus and subsequent viremia; (2) Acceleration phase, when secondary damage caused by the virus to target organs and tissues occurs (including lungs, heart, gastrointestinal tract), and the overall inflammatory storm, and (3) Final recovery phase. This is characterized not only by clinical features but also laboratory dynamics, including progressive lymphocytopenia, and inflammatory markers that increase on acceleration. Strategy against COVID-19 should be determined according to the course of the infection. The best time for antivirals may lie in the phase before acceleration. When clinical deterioration begins, first few days can become a critical point when strong suppression of the inflammatory cascade can save the patient from immune-mediated fatal injury. Initiation of a cytokine storm occurs 5–7 days after onset of symptoms and immunomodulation is likely to be most beneficial.[4] Based on our case series, IVIg were given at the appropriate time, thus producing favorable outcome.

Similar to our report, there is other case series regarding the use of IVIG in three patients infected with SARS-CoV-2 in China. All three patients were classified as severe COVID-19, and all had laboratory features of lymphopenia with high markers of inflammation. Patient received IVIg dose 0.3-0.4 g/kg/day for 5 days. Clinical improvement was found where all patients had normal body temperature within two days and respiratory symptoms reduced within five days. Confounding factors include simultaneous use of antiviral and steroid as well as the lack of control.[11] However, based on the COVID-19 management protocol in Indonesia, antiviral and steroid are mandatory standard therapy in every patient with confirmed COVID-19.

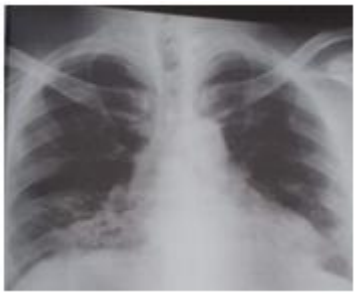

Figure 7: Bilateral pneumonia day-1 (16/12/2020) on case 3

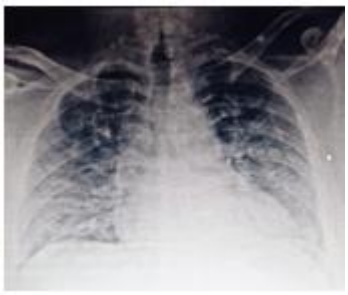

Figure 8: Infiltrates significantly increased on day-9 (1/1/2021), IVIg then initiated

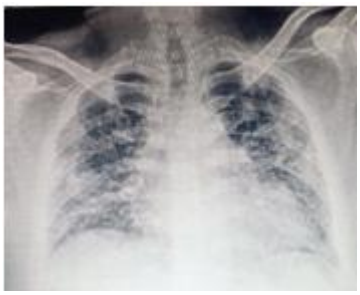

Figure 9: Infiltrates significantly reduced post IVIg day-14 (15/1/2021) on case 3

Based on experience, if the acceleration phase can be stopped, IVIG may play an essential role even though effective antiviral drug has not been found. High-dose IVIG 0.3-0.5 g/kg/day for five days was used, as in our patients. This dosage is determined based on established practice in immune modulation therapy for various diseases including neuromuscular disorders, autoimmune, etc.[4,5] Considering its effectiveness in enhancing passive immunity and modulation of inflammation as well as the overall safety profile, high dose IVIg can be considered as a promising option in the early stages of clinical deterioration patients with COVID-19.

After IVIg administration, none of our three patients reported side effects. All patients clinically improved immediately after administration, with temperature returning to normal within 1-2 days and respiratory symptoms diminished within 3-5 days. The therapeutic effects of IVIg alone can last from 2 weeks to 3 months. In these patients, IVIg caused immunity to be inactive and provide adequate level of antibodies to prevent infection.[12] In this report all patients required supplemental oxygen during hospitalization, but respiratory function (judged by PaO2 / FiO2 and SpO2) improved rapidly after IVIG initiation. The mean time to normalization of oxygen saturation and pO2 (> 80 mmHg) was 3.6 days. The number of lymphocytes increased until day 14, while the number of neutrophils normalized on day 3. The main inflammatory biomarkers (interleukin-6, C-reactive protein and fibrinogen) decreased on day 7, reaching normal values on day 14. However, D-dimers did not become normal in all individuals by day 14. None of the patients experienced a thrombotic event during the study or subsequent follow-up after discharge from hospital. Patient 1 also immediately discontinue ventilator use after IVIg. Overall, IVIg resulted in good recovery, resolution of various parameters including chest radiographs, normalization of inflammatory markers, lymphocyte count, reduce ventilator use, and length of stay

in hospital. The clinical and supporting parameters of improvement found in patients in our case report series are also consistent with other studies.[3]

Our report has several weaknesses, such as the study design in the form of serial case report, small number of patients, and limited access to IVIg. However, this report provides important therapeutic clues to current situation due to rapid spreading of COVID-19. Appropriate time of IVIg administration is crucial. Patients may not receive much benefit when systemic damage has occurred. Currently, a randomized controlled trial evaluating the efficiency of high-dose IVIg in severe and critical COVID-19 has been initiated (NCT 04261426). We hoped our case series can contribute as preliminary report regarding IVIg use in severe to critical COVID-19.

4. Conclusion

Coronavirus disease-19 (COVID-19) pandemic caused by *severe acute respiratory syndrome coronavirus* 2 (SARS-CoV-2) is still not completely under control worldwide. Administration of intravenous immunoglobulin (IVIg) is increasingly used in COVID-19 context because of existing acceptable safety profile and act as immunomodulator, especially in severe to critical patients. Recent evidence support findings in our case series. Improvement of clinical, supporting examination parameters, ventilator use, length of stay in hospital, and mortality rate has been reported in association with IVIg therapy in COVID-19 studies. We report serial case series consisting of 3 critically ill COVID-19 patients with successful outcome at discharge. No mortality was found in our cases. Underlying mechanism of IVIg in COVID-19 is still unclear. Further studies are needed.

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