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Intravenous immunoglobulin as adjuvant therapy for COVID-19: A case report and literature review

Carlos A Flores-Oria[1], Emilio Saturno[2], Supriya Ramanathan[3], Diana J Martinez Castillo[3], Roshni Kumar[4], Nelson Ferrer[5], Afnan Mossaad[6], Maria E Tellez[7], Cindy Jon[1], Sara C Waters[6] and Ricardo A Mosquera[1]

Abstract

Severe acute respiratory syndrome coronavirus 2 has infected and caused the death of an alarming number of individuals worldwide. No specific treatment has been internationally standardized for coronavirus disease 2019 (COVID-19); however, in some cases, intravenous immunoglobulin (IVIG) has been used as adjuvant treatment in critically ill patients with COVID-19 pneumonia. We report a case of a 50-year-old man with severe COVID-19 pneumonia who received 5 days course of IVIG as adjuvant therapy. Invasive respiratory support was avoided. The patient had a successful recovery and was discharged without supplemental oxygen. A high dose of IVIG may improve survival in patients with severe COVID-19 pneumonia. In the current report, we reviewed literature on how IVIG use may improve the early stages of the disease.

Keywords

Coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, intravenous immunoglobulin, IVIG, hypoxemia

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent for coronavirus disease 2019 (COVID-19), has infected more than 170 million people and has caused the death of more than 3.6 million globally, as of June 2021. In Panama, more than 379,000 total cases of COVID-19 and more than 6000 total deaths have been confirmed as of June 2021.[1]

No specific treatment has been internationally standardized for COVID-19. At the time of this case, current therapeutic regimens were in clinical trials. Empirical administration of intravenous immunoglobulin (IVIG) to patients with severe disease was used in a previous outbreak of SARS-CoV in 2002. Although there was no control group, it was believed that IVIG might be an effective therapy.[2] IVIG has been used as adjuvant treatment in critically ill patients with COVID-19 with unequal success.[3] We report a case of a patient with severe COVID-19 pneumonia who received 5 days course of IVIG as adjuvant therapy with successful outcomes and reviewed the literature on IVIG use in patients with COVID-19. The patient provided written informed consent for patient information and images to be published.

Case

Presentation

A 50-year-old man presented to a hospital in Panama with a history of dyspnea and oxygen saturation of 87%. He had a 1-week history of nasal congestion, cough, sore throat,

[1]Division of Pulmonology, Department of Pediatrics, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA
[2]West Jefferson Medical Center, Marrero, LA, USA
[3]Department of Pediatrics, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA
[4]Bellaire High School, Bellaire, TX, USA
[5]Hospital Pacifica Salud, Panama
[6]Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA
[7]School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX, USA

Corresponding Author:
Carlos A. Flores-Oria, McGovern Medical School, The University of Texas Health Science Center at Houston, 6410 Fannin St. Suite 470, Houston, TX 77030, USA.
Email: Carlos.A.FloresOria@uth.tmc.edu

Table 1. Patient's day of hospitalization, pertinent labs, and intervention.

DOH	1	3	4	5	6	7	8	9	10	11	13	16	18
Labs													
SARS-CoV-2 PCR	Detected										Not detected		Not detected
CRP		37.58	143.75		141.02		86.04		19.53				
Ferritin				1945.1						5127.9			
D-Dimer		311	694	1742							1123		
WBC (10^3/μL)	9.1	7.1		9.3		6.2	4.5	4.7	5.7		5.8	6.0	
Lymph (%)	5.9	19.5		9.7		9.4	20.0	29.6	29.1		26.5	30.3	
Lymph (10^3/μL)	0.50	1.40		0.91		0.60	0.90	1.40	1.70		1.50	1.80	
Intervention													
Supplemental O_2 (LPM)	4	15	15	15	15	15	15	15	12	7	4	Room air	Room air
IVIG				Day 1	Day 2	Day 3	Day 4	Day 5					

CRP: C-reactive protein; DOH: day of hospitalization; IVIG: intravenous immunoglobulin; LPM: litres per minute; Lymph: lymphocytes; PCR: polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; WBC: white blood cells.

rhinorrhea, and fever with chills, which developed 4 days after returning from New Orleans, Louisiana. During his trip, he had exposure to patients with fever and influenza-like symptoms. During this time, the first COVID-19 cases were reported in both Panama and LA.

Clinical course and treatment

Prior to hospitalization, he was treated with azithromycin 500 mg by mouth daily, prednisone 50 mg by mouth once daily, and budesonide/formoterol 160/4.5 μg two inhalations twice a day. In the emergency room, he was started on supplemental oxygen at 4 liters per minute (LPM) via nasal cannula but rapidly deteriorated upon transfer to the ward, requiring up to 15 LPM via a reservoir mask. Initial chest radiography demonstrated bibasilar infiltrates, and computerized tomography of the chest revealed a bilateral crazy-paving pattern. He tested positive for SARS-CoV-2 via nasopharyngeal polymerase chain reaction (PCR). He was started on hydroxychloroquine, oral azithromycin, and intramuscular ceftriaxone. He continued to be hypoxemic despite optimal noninvasive oxygen therapy and prone position. C-reactive protein (CRP), D-dimers, and ferritin were markedly elevated (Table 1). Mechanical ventilation was considered on day 5 of hospitalization, but the patient declined. IVIG was then initiated at 400 mg/kg/day for 5 days (total 25 g). The fever resolved 2 days later. However, he had persistent though less severe hypoxemia requiring 12 LPM of supplemental oxygen and infiltrates on chest radiography. The second course of antibiotics, vancomycin, and quinolone was initiated for suspected secondary bacterial pneumonia.

Resolution

The SARS-CoV-2 nasopharyngeal PCR test was repeated and found to be negative on days 12 and 17 of hospitalization. The patient was gradually weaned off oxygen after 2 weeks and discharged from the hospital after 18 days without supplemental oxygen and mild, but improving, dyspnea.

Discussion

Coronaviruses are enveloped, positive-stranded RNA viruses with spike proteins on their envelope, which resemble a crown under the electron microscope. Spikes are glycoproteins that confer viral identification and virulence and are essential for cellular tropism. SARS-CoV-2 spike protein binds to angiotensin-converting enzyme 2 as the primary host cell receptor, which is highly expressed in type II alveolar cells of the respiratory tract.[4] This interaction would serve as a target for a therapeutic approach such as neutralizing antibodies that could block receptor binding, viral fusion, and hence replication. It is of great curiosity why some people without apparent risk factors develop severe disease. Interestingly, a genome-wide study conducted in Europe implied that individuals with blood group A have high risks for severe respiratory illness.[5] Although our patient was identified with blood group A, this association was unknown at the time and may or may not fully explain our patient's clinical course.

The clinical entity is assumed to occur in three phases: the viremia phase (0–7 days), acute phase or pneumonia (7–14 days), and the recovery phase (beyond 21 days). Critical immune interaction is believed to occur in the phase of pneumonia. There may be an adequate immune response that suppresses the virus, or there may be dysregulation leading to the reduction of lymphocytes and an increase of pro-inflammatory cytokines and D-dimers.[6] Administration of IVIG during this early phase could halt the progression by enhancing the immune system. In our case, IVIG was administered just before the transition from acute to pneumonia phase, achieving a satisfactory outcome. The availability of IVIG among institutions and their potential effectiveness and safety in critically ill patients has encouraged their use in COVID-19. A review of reported cases is summarized in Table 2.

Table 2. Cases of IVIG use in COVID-19 in the literature.

Source		Age (years)	Gender	Comorbidities	Prior medications	HLOS (days)	IVIG				Outcome
							Time of administration	Dose	Duration	Concomitant use	
Cao et al.[7]	Patient 1	56	M		Oseltamivir Azithromycin Moxifloxacin	16	DOH 7	25 g/day	5 days		Afebrile on first day of IVIG. Improved clinically
	Patient 2	34	M	2 years' history of hypertension	Valsartan Felodipine	8	DOH 2	25 g/day	5 days		Afebrile on second day of IVIG. Improved clinically
	Patient 3	35	F		Lopinavir/ritonavir	17	DOH 6	25 g/day	5 days	Methylprednisolone 40 mg/day × 3 days	Afebrile on first day of IVIG. Improved clinically
Shi et al.[8]		50	F		Ceftriaxone Piperacillin/tazobactam Inhaled interferon alfa-2b Lopinavir/ritonavir Human granulocyte-colony stimulating factor (G-CSF)	15	DOH 3	20 g/day	6 days	Plasma exchange × 5 total doses on DOH 6,7,9 methylprednisolone 80 mg	Recovered after fourth day of plasma exchange and IVIG. Improved clinically
Ahmed et al.[9]	Patient 1	50	M	Possible ITP related to COVID-19				1 g/kg	×2 doses?		Platelet improved and bleeding stopped. Recovered
	Patient 2	49	F	Possible ITP related to COVID-19				1 g/kg	1 day		Improved platelet in 40 hours. Recovered
	Patient 3	96	F	History of Atrial fibrillation, ischemic heart disease, chronic kidney disease				0.4 mg/kg	5 days		Platelet improved. Clinical deterioration and Passed away
Moeinzadeh et al.[10]		25	M	Crescentic proliferative glomerulonephritis related to COVID-19	Hydroxychloroquine Levofloxacin	13	DOH 2	20 g/day	3 days	Plasma exchange and Methylprednisolone 1 g × 3 days, then cyclophosphamide	Recovered
Lanza et al.[11]		42	F	History of controlled hypothyroidism	Hydroxychloroquine Azithromycin	⩾ 11	DOH 6	450 mL 5 mL/kg	4 days		Respiratory function improved at the end of IVIG therapy
Mohtadi et al.[12]	Patient 1	66	F	History of hypertension and coronary artery bypass	Hydroxychloroquine Lopinavir/ritonavir Oseltamivir Vancomycin Levofloxacin Meropenem Tavanx ®			25 g/day	5 days	hydrocortisone	Improved and extubated on fifth day of IVIG. Discharged 2 weeks later

(Continued)

Table 2. (Continued)

Source		Age (years)	Gender	Comorbidities	Prior medications	HLOS (days)	IVIG				Outcome
							Time of administration	Dose	Duration	Concomitant use	
	Patient 2	57	F	History of kidney transplantation, hypertension, and heart disease	Hydroxychloroquine Lopinavir/ritonavir Ceftriaxone Azithromycin Vancomycin Meropenem		DOH 16	30 g/day	5 days		Pulmonary involvement improved on last day of IVIG therapy. Discharged 3 days later
	Patient 3	65	M	History of diabetes	Hydroxychloroquine Lopinavir/ritonavir Oseltamivir Vancomycin Imipenem		DOH 6	25 g/day	5 days		Pulmonary involvement and hypoxemia improved at the end of IVIG therapy. Discharged few days later
	Patient 4	50	F	History of hypertension	Hydroxychloroquine Lopinavir/ritonavir Vancomycin Imipenem		DOH 9	25 g/day	5 days		Pulmonary lesions improved after IVIG therapy. Discharged 1 day later
	Patient 5	64	F		Hydroxychloroquine Lopinavir/ritonavir Vancomycin Imipenem		DOH 6 ?	25 g/day	5 days		Pulmonary involvement and hypoxemia improved after IVIG therapy. Discharged 2 days later
Assini et al.[13]	Patient 1	55	M	Demyelinating disease associated with COVID-19 20 days after admission	Hydroxychloroquine Umifenovir Lopinavir/ritonavir		DOH 20	0.4 g/kg/day	5 days		Improved on fifth day of IVIG
	Patient 2	60	M	Demyelinating disease associated with COVID-19, 20 days after admission	Hydroxychloroquine Antiretroviral therapy Tocilizumab		> DOH 20	0.4 g/kg/day	5 days		Improved on fifth day of IVIG
Aljaberi et al.[14]		53	F	History of common variable immunodeficiency, hypothyroidism, bronchiectasis, Sjogren's syndrome	Hydroxychloroquine Ceftriaxone Doxycycline IVIG (routine infusions)	14	DOH 1 and DOH 14	40 g/day	× 2		Extubated on DOH 13 and discharged the following day after second dose of IVIG
Ikuyama et al.[15]		76	F	Diabetes mellitus, hypertension, and glaucoma	Lopinavir/ritonavir Moxifloxacin Piperacillin/tazobactam Peramivir	> 40	DOH 3	5 g/day	6 days		Continued deteriorating towards the end IVIG treatment. Improved with ECMO

DOH: day of hospitalization; HLOS: hospital length of stay; ITP: idiopathic thrombocytopenic purpura; IVIG: intravenous immunoglobulin.

A high dose of IVIG has improved survival in some patients with severe COVID-19 pneumonia. The majority of case reports have used a high dose of IVIG (25 g/day or 0.4 g/kg/day for 5 days), obtaining positive outcomes.[7–13] In case series, a high dose of IVIG infusion helped prevent progression of pulmonary involvement contrary to one case in which 5 g/day for 5 days was administered to a woman who further deteriorated, requiring extracorporeal membrane oxygenation.[12,15–17] Timing of administration seems to be crucial as well. According to one retrospective study, administration of IVIG within 48 hours of acute decompensation showed a reduction in ventilator use, hospital and intensive care unit length of stay, and mortality compared with past 48 hours.[3] Although a randomized controlled trial using a different protocol with a lower dose and longer time of administration demonstrated no benefits of IVIG therapy, it still supports safety since it did not show increased mortality with its use.[18]

The major component of IVIG is a relatively pure concentrate of polyclonal immunoglobulin G (IgG) derived from pooled human plasma of thousands of donors. In replacement therapy, the mechanism of action consists of neutralization of pathogen, inactivation of toxins, opsonization, boosting B and T cell functions, and complement activation. Anti-inflammatory effects involve neutralization of autoantibodies and pro-inflammatory cytokines, blocking of activated complement and/or adhesion molecules, interference with idiotypic/anti-idiotypic network, and increased autoantibody clearance, among others.[19] Further investigation is needed to see whether any of these functions apply to coronavirus, including SARS-CoV-2.

Various hypothetical mechanisms of IVIGs have been assumed to have therapeutic effects on COVID-19. Antibody-dependent enhancement (development of primed antibodies against prior coronavirus infection) has been proposed as a possible mechanism to explain disparities in severity among countries.[20] Commercial products of unmodified human IVIGs have demonstrated some in vitro cross-reactivity to SARS-CoV-2 and other coronaviruses. The tested preparations originated from donors in the United States and European countries. The presence of antibody reactivity against SARS-CoV-2 S1 protein has been identified in IVIG preparations.[21] Although, a following study revealed no cross-neutralization antibodies against SARS-CoV-2 detected in IVIG during pre-pandemic period,[22] a promising study demonstrated a rapid increase in the concentration of specific neutralizing antibodies among preparations developed during the pandemic year.[23] The functionality of neutralizing antibodies still needs additional investigation and other possible mechanisms, such as anti-inflammatory effects, may be involved. Ameliorating the inflammatory cascade by binding cytokines and other antibodies, complement scavenging, inhibition of innate immune cells and effector T-cell activation, and expansion of Tregs has been proposed but not demonstrated yet.[24,25]

Unquestionably, immunization would be the best approach to reduce transmission and occurrence of severe cases. However, high dose of IVIG may still play a beneficial role when the disease develops in people who are at risk of progressing to severe COVID-19 pneumonia.

Conclusion

In summary, this case report demonstrated that a high dose of IVIG given in the early stages may help patients with severe COVID-19 pneumonia. However, there is still an unknown universe regarding the functionality, effectiveness, and benefits of IVIG in patients with severe SARS-CoV-2 infection.

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Informed consent

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ORCID iD

Carlos A Flores-Oria https://orcid.org/0000-0002-9337-6175

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