CASE REPORT

Investigating outcomes and treatment of long coronavirus disease 2019 in patients with multiple sclerosis treated with rituximab: A case series study

Kiana Shirani[1], Farzin Khorvash[2], Alireza Karamshahi[3], Asieh Maghamimehr[4]

[1]Nosocomial Infection Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Immunodeficiency Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Infectious Diseases, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Department of Statistics, Isfahan University of Medical Sciences, Isfahan, Iran

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system, characterized by the destruction of the myelin sheath of nerves. MS patients treated with rituximab, an immunosuppressive drug, experience reduced immunoglobulin levels, which increases their risk of various infections, including coronavirus disease 2019 (COVID-19). During the COVID-19 pandemic, many of these patients developed long-term symptoms following infection. These chronic symptoms have led to significant complications and, in some cases, increased mortality. In this case series study, we investigated long COVID-19 symptoms in MS patients treated with rituximab and the effects of intravenous immunoglobulin (IVIG) therapy in alleviating chronic symptoms. The results demonstrated that the patients' long-term symptoms responded to IVIG treatment, with significant improvements in respiratory symptoms, fever, immune parameters, and a reduction in C-reactive protein levels. This study highlights the importance of targeted management of long COVID-19 in immunocompromised populations and suggests that COVID-19 patients with immune deficiencies require specific therapeutic approaches.

Key words: Hypogammaglobulinemia, intravenous immunoglobulin, long coronavirus disease 2019, multiple sclerosis, rituximab

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) has been recognized as a public health emergency of international concern.[1] From the early stages of the pandemic, it was suggested that immunocompromised patients, including those receiving immunosuppressive therapies, might face a higher risk of contracting the virus and experiencing more severe and prolonged forms of the disease.[2]

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system characterized by the destruction of myelin and axons, leading to progressive disability.[3] Common treatments for MS include immunosuppressive agents such as rituximab.[4] Rituximab, a monoclonal anti-CD20 antibody, depletes B-cells and is an effective therapy for controlling MS progression.[5] However, long-term use of this drug is associated with reduced gamma globulin (immunoglobulin G [IgG]) levels and an increased risk of viral infections, including SARS-CoV-2.[6,7]

Managing MS patients during the COVID-19 pandemic has been challenging due to the use of immunomodulatory therapies. Previous studies indicate that MS patients treated with anti-CD20 agents like rituximab not only face a higher risk of contracting COVID-19 but also experience prolonged disease courses

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Address for correspondence: Alireza Karamshahi, Alzahra Hospital, Soffe Ave, Isfahan, Iran.
E-mail: alirezakaramshahi78@gmail.com
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and more severe complications.[8] Consequently, some clinical guidelines recommend cautious administration of anti-CD20 drugs in MS patients, as these therapies increase the risk of COVID-19 by 3- to 4-fold.[9] Cohort studies have further shown that MS patients on rituximab have higher hospitalization rates compared to the general population, though no significant increase in mortality has been observed.[10]

Recent studies suggest that reduced IgG levels (due to rituximab use) may exacerbate long-term COVID-19 symptoms, such as fatigue, dyspnea, and cognitive impairment, in MS patients.[11] In this context, intravenous immunoglobulin (IVIG) therapy has emerged as a potential strategy to compensate for IgG deficiency and reduce systemic inflammation. By elevating IgG levels and enhancing antiviral immune responses, IVIG may alleviate respiratory and neurological symptoms.[12]

This case series study, conducted at Alzahra Hospital in Isfahan, included eight rituximab-treated MS patients who developed long-term symptoms after COVID-19 infection. The study aimed to investigate long COVID-19 and evaluate the efficacy of IVIG in managing prolonged COVID-19 symptoms in these patients, particularly those who exhibited poor responses to standard therapies such as corticosteroids and remdesivir. Given that clinical symptoms, including frequent respiratory infections and general weakness, in patients receiving rituximab have shown a strong association with low IgG level,[13] and due to the lack of access to rapid assessment of IgG levels, we substituted clinical assessment for IVIG administration in our cases.

CASE REPORTS

Case 1

A 45-year-old woman with a 17-year history of MS had been on a therapeutic regimen of rituximab infusions every 6 months. She presented to Alzahra Hospital in Isfahan 25 days prior with fever, chills, dyspnea, arthralgia, and generalized weakness. The patient reported no comorbidities other than MS and denied tobacco, alcohol, or illicit drug use. Her last rituximab infusion was administered approximately 5 months earlier.

On admission, her vital signs were as follows: temperature 38.5°C, respiratory rate (RR) 30 breaths/min, oxygen saturation (SaO_2) 96% on room air, blood pressure (BP) 100/60 mmHg, and heart rate 97 beats/min. Physical examination revealed diminished breath sounds in the right lung. A SARS-CoV-2 polymerase chain reaction (PCR) test performed during her initial visit returned positive. Blood and biochemical tests were conducted [Table 1].

The patient was admitted to the infectious disease ward. A chest computed tomography (CT) scan demonstrated an atypical pneumonia pattern consistent with COVID-19 pneumonia. On day 1, she received remdesivir (200 mg loading dose followed by 100 mg daily for 5 days), intravenous dexamethasone (8 mg daily for 4 days), and empirical antibiotic therapy with levofloxacin, linezolid, and meropenem. Despite treatment, the patient remained febrile 24 h after admission. All laboratory findings, except for elevated C-reactive protein (CRP), were within normal ranges, and arterial blood gas analysis showed no hypoxemia [Table 1].

On day 2 of hospitalization, IVIG was added to her treatment regimen (with a single dose of 0.4 g/kg). Her fever resolved within 24 h of IVIG administration, and she showed clinical improvement in respiratory symptoms. By day 27, all clinical symptoms, including fever, had subsided, and CRP levels normalized. The patient was discharged 4 days after IVIG initiation following confirmation of sustained clinical recovery.

Case 2

A 54-year-old man with a 5-year history of MS had been on a therapeutic regimen of rituximab infusions every 6 months. He presented to Alzahra Hospital in Isfahan 14 days prior with fever, dyspnea, and cough. Prior to admission, he had received levofloxacin for 5 days with no clinical improvement. The patient reported no comorbidities other than MS and denied tobacco, alcohol, or illicit drug use. His last rituximab infusion was administered approximately 3 months earlier.

On admission, his vital signs were as follows: temperature 37.9°C, RR 28 breaths/min, SaO_2 93% on room air, BP 114/92 mmHg, and heart rate 89 beats/min. Physical examination revealed diminished breath sounds in both lungs. A SARS-CoV-2 PCR test performed during his initial visit returned positive. Blood and biochemical tests were conducted [Table 2].

The patient was admitted to the infectious disease ward. A chest CT scan demonstrated atypical pneumonia patterns consistent with COVID-19 pneumonia, involving the entire right lower lobe and part of the left lower lobe. On day 2, he received remdesivir (200 mg loading dose followed by 100 mg daily for 5 days), intravenous dexamethasone (8 mg for 1 day), methylprednisolone (50 mg for 1 day), and empirical antibiotic therapy with levofloxacin and ampicillin. Despite 72 h of treatment, the patient remained febrile. All laboratory findings, except for elevated CRP, were within normal ranges, and arterial blood gas analysis showed no hypoxemia [Table 2].

On day 4 of hospitalization, IVIG was added to his treatment regimen (with a single dose of 0.4 g/kg). His fever and

Table 1: Complete laboratory examinations at the emergency department on the first visit and subsequent visits

Lab	First visit	Next day of receiving IVIG	Last visit	Laboratory reference range
White blood cells (K/μL)	6200	-	-	4.0–10.8
Neutrophils (%)	68	-	-	40–75
Lymphocytes (%)	22	-	-	20–45
Hemoglobin (g/dL)	12	-	-	12.3–15.5
Red blood cells (M/μL)	4.25	-	-	4.1–5.1
Platelets	200,000	-	-	150,000–440,000
Potassium (mmol/L)	4.7	-	4.5	3.60–5.00
Sodium (mmol/L)	143	-	140	135–150
BUN (mg/dL)	7	-	-	7–18.6
Creatinine (mg/dL)	0.9	-	-	0.7–1.3
Lactate dehydrogenase (U/L)	741	-	-	100–480
Creatine phosphokinase (U/L)	40	-	-	30–170
Alkaline phosphatase (U/L)	209	-	-	100–240
Aspartate aminotransferase (U/L)	28	-	-	15–59
Alanine aminotransferase (U/L)	22	-	-	10–72
CRP (mg/L)	43	13	6	0.0–5.0
Arterial blood gas on air				
pH	7.50	-	7.35	
pO_2 (mmHg)	82.1	-	92.6	
pCO_2 (mmHg)	17.8	-	29.9	
HCO_3 (mmol/L)	15.1	-	16.2	
SaO_2 (%)	95	-	96.5	
Urinalysis	Negative	-	-	

pO_2=Partial pressure of oxygen; pCO_2=Partial pressure of carbon dioxide; HCO_3=Bicarbonate; SaO_2=Oxygen saturation; CRP=C-reactive protein; IVIG=Intravenous immunoglobulin; BUN=Blood urea nitrogen

Table 2: Complete laboratory examinations at the emergency department on the first visit and subsequent visits

Lab	First visit	Next day of receiving IVIG	Last visit	Laboratory reference range
White blood cells (K/μL)	5400	6800	4700	4400–11,000
Neutrophils (%)	93.2	85	82	50–70
Lymphocytes (%)	5.8	7	10.8	20–40
Hemoglobin (g/dL)	11.8	11.7	12.1	14–17.5
Red blood cells (M/μL)	4	3.86	4.1	4.1–5.1
Platelets	274,000	263,000	230,000	150,000–440,000
Potassium (mmol/L)	4.5	-	4.5	3.60–5.00
Sodium (mmol/L)	137	-	140	135–150
BUN (mg/dL)	12	-	-	7–18.6
Creatinine (mg/dL)	0.8	-	-	0.7–1.3
Lactate dehydrogenase (U/L)	497	-	-	100–480
Creatine phosphokinase (U/L)	227	-	-	30–170
Alkaline phosphatase (U/L)	192	-	-	100–240
Aspartate aminotransferase (U/L)	28	-	-	15–59
Alanine aminotransferase (U/L)	20	-	-	10–72
CRP (mg/L)	128	92	44	0.0–5.0
Arterial blood gas on air				
pH	7.37	-	-	
pO_2 (mmHg)	91	-	-	
pCO_2 (mmHg)	26.2	-	-	
HCO_3 (mmol/L)	18	-	-	
SaO_2 (%)	93	-	-	
Urinalysis	Negative	-	-	

pO_2=Partial pressure of oxygen; pCO_2=Partial pressure of carbon dioxide; HCO_3=Bicarbonate; SaO_2=Oxygen saturation; CRP=C-reactive protein; IVIG=Intravenous immunoglobulin; BUN=Blood urea nitrogen

dyspnea resolved within 24 h of IVIG administration, and he showed clinical improvement in respiratory symptoms. By day 16, all clinical symptoms, including fever and dyspnea, had subsided, and CRP levels normalized. The patient was discharged 5 days after IVIG initiation following confirmation of sustained clinical recovery.

Case 3

A 48-year-old male with a 16-year history of MS had been on a therapeutic regimen of rituximab infusions every 6 months. He presented to Alzahra Hospital in Isfahan 50 days prior with fever and chills. The patient had two prior hospitalizations and received treatment with corticosteroids, gentamicin, co-amoxiclav, levofloxacin, and ceftazidime, which yielded no improvement. The patient reported a history of seizures in addition to MS and denied tobacco, alcohol, or illicit drug use. His last rituximab infusion was administered approximately 3 months earlier.

On admission, his vital signs were as follows: temperature 38°C, RR 18 breaths/min, SaO_2 95% on room air, BP 110/70 mmHg, and heart rate 101 beats/min. Physical examination revealed crackles in both lungs. A SARS-CoV-2 PCR test performed during his initial visit returned positive. Blood and biochemical tests were conducted [Table 3].

The patient was admitted to the infectious disease ward. A chest CT scan demonstrated bilateral multilobar atypical pneumonia consistent with COVID-19 pneumonia. On day 1, he received remdesivir (200 mg loading dose followed by 100 mg daily for 5 days), intravenous dexamethasone (8 mg daily for 3 days), and prednisolone (25 mg daily for 3 days). Despite 48 h of treatment, the patient remained febrile. All laboratory findings, except for elevated CRP, were within normal ranges, and arterial blood gas analysis showed no hypoxemia [Table 3].

On day 3 of hospitalization, IVIG was added to his treatment regimen (with a single dose of 0.4 g/kg). His fever resolved within 48 h of IVIG administration, and he showed clinical improvement in respiratory symptoms. By day 55, all clinical symptoms, including fever and chills, had subsided, and CRP levels normalized. The patient was discharged 4 days after IVIG initiation following confirmation of sustained clinical recovery.

Case 4

A 34-year-old woman with a 15-year history of MS had been on a therapeutic regimen of rituximab infusions every 6 months. She presented to Alzahra Hospital in Isfahan 15 days prior with fever, chills, dry cough, and headache. Prior to admission, she had received treatment with cefixime, azithromycin, clindamycin, levofloxacin, and ceftriaxone, which yielded no improvement. The patient reported no comorbidities other than MS and denied tobacco, alcohol, or illicit drug use. Her last rituximab infusion was administered approximately 6 months earlier.

On admission, her vital signs were as follows: temperature 37.8°C, RR 17 breaths/min, SaO_2 96% on room air, BP 110/65 mmHg, and heart rate 88 beats/min. Physical examination revealed crackles in the right lung and the base of the left lung. A SARS-CoV-2 PCR test performed during her initial visit returned positive. Blood and biochemical tests were conducted [Table 4].

Table 3: Complete laboratory examinations at the emergency department on the first visit and subsequent visits

Lab	First visit	Next day of receiving IVIG	Laste visit	Laboratory reference range
White blood cells (K/μL)	7200	-	-	4.0–10.8
Neutrophils (%)	75	-	-	40–75
Lymphocytes (%)	13.5	-	-	20–45
Hemoglobin (g/dL)	12.6	-	-	14–17.5
Red blood cells (M/μL)	4.35	-	-	4.1–5.1
Platelets	136,000	-	-	150,000–440,000
Potassium (mmol/L)	4.4	-	4.5	3.60–5.00
Sodium (mmol/L)	138	-	138	135–150
BUN (mg/dL)	16	23	21	7–18.6
Creatinine (mg/dL)	0.9	1	0.8	0.7–1.3
Alkaline phosphatase (U/L)	183	-	-	100–240
Aspartate aminotransferase (U/L)	15	-	-	15–59
Alanine aminotransferase (U/L)	30	-	-	10–72
CRP (mg/L)	49	34	10	0.0–5.0
Arterial blood gas on air				
pH	7.36	-	-	
pO_2 (mmHg)	87	-	-	
pCO_2 (mmHg)	36	-	-	
HCO_3 (mmol/L)	22	-	-	
SaO_2 (%)	95	-	-	
Urinalysis	Negative	-	-	

pO_2=Partial pressure of oxygen; pCO_2=Partial pressure of carbon dioxide; HCO_3=Bicarbonate; SaO_2=Oxygen saturation; CRP=C-reactive protein; IVIG=Intravenous immunoglobulin; BUN=Blood urea nitrogen

The patient was admitted to the infectious disease ward. A chest CT scan demonstrated atypical multilobar pneumonia in the right lung and the left upper lobe, consistent with COVID-19 pneumonia. On day 1, she received remdesivir (200 mg loading dose followed by 100 mg daily for 5 days), intravenous dexamethasone (8 mg daily for 3 days), and prednisolone (25 mg daily for 7 days). Despite 24 h of treatment, the patient remained febrile. All laboratory findings, except for elevated CRP, were within normal ranges, and arterial blood gas analysis showed no hypoxemia [Table 4].

On day 2 of hospitalization, IVIG was added to her treatment regimen (with a single dose of 0.4 g/kg). Her fever resolved within 24 h of IVIG administration, and she showed clinical improvement in respiratory symptoms. By day 17, all clinical symptoms, including fever and chills, had subsided, and CRP levels normalized. The patient was discharged 3 days after IVIG initiation following confirmation of sustained clinical recovery.

Case 5

A 58-year-old male with a 12-year history of MS had been on a therapeutic regimen of rituximab infusions every 6 months. He presented to Alzahra Hospital in Isfahan 3 months prior with severe cough and dyspnea. Prior to admission, he had received treatment with linezolid and levofloxacin for 7 days with no clinical improvement. The patient reported no comorbidities other than MS and denied tobacco, alcohol, or illicit drug use. His last rituximab infusion was administered approximately 3 months earlier.

On admission, his vital signs were as follows: temperature 40.1°C, RR 24 breaths/min, SaO_2 91% on room air, BP 110/60 mmHg, and heart rate 75 beats/min. Physical examination revealed diffuse wheezing in both lungs. A SARS-CoV-2 PCR test performed during his initial visit returned positive. Blood and biochemical tests were conducted [Table 5].

The patient was admitted to the infectious disease ward. A chest CT scan demonstrated atypical pneumonia consistent with COVID-19 pneumonia. On day 1, he received remdesivir (200 mg loading dose followed by 100 mg daily for 5 days), intravenous dexamethasone (8 mg daily for 2 days), and methylprednisolone (5 mg daily for 5 days). Despite 4 days of treatment, the patient remained febrile. All laboratory findings, except for elevated CRP, were within normal ranges, and arterial blood gas analysis showed no hypoxemia [Table 5].

On day 4 of hospitalization, IVIG was added to his treatment regimen (with a single dose of 0.4 g/kg). His dyspnea resolved within 24 h of IVIG administration, and he showed clinical improvement in respiratory symptoms. By day 95, all clinical symptoms, including dyspnea, had subsided, and CRP levels normalized. The patient was discharged 3 days after IVIG initiation, following confirmation of sustained clinical recovery.

Table 4: Complete laboratory examinations at the emergency department on the first visit and subsequent visits

Lab	First visit	Next day of receiving IVIG	Last visit	Laboratory reference range
White blood cells (K/μL)	5100	-	-	4.0–10.8
Neutrophils (%)	92	-	-	40–75
Lymphocytes (%)	6	-	-	20–45
Hemoglobin (g/dL)	9	-	-	12.3–15.5
Red blood cells (M/μL)	4.59	-	-	4.1–5.1
Platelets	247,000	-	-	150,000–440,000
Potassium (mmol/L)	4.7	4	4.1	3.60–5.00
Sodium (mmol/L)	143	145	139	135–150
BUN (mg/dL)	10	14	-	7–18.6
Creatinine (mg/dL)	1.1	1	-	0.7–1.3
Alkaline phosphatase (U/L)	119	-	-	100–240
Aspartate aminotransferase (U/L)	27	-	-	10–33
Alanine aminotransferase (U/L)	10	-	-	10–33
CRP (mg/L)	79	58	28	0.0–5.0
Vein blood gas on air				
pH	7.37	-	-	
pO_2 (mmHg)	41	-	-	
pCO_2 (mmHg)	22.6	-	-	
HCO_3 (mmol/L)	41	-	-	
SaO_2 (%)	74.4	-	-	
Urinalysis	Negative	-	-	

pO_2=Partial pressure of oxygen; pCO_2=Partial pressure of carbon dioxide; HCO_3=Bicarbonate; SaO_2=Oxygen saturation; CRP=C-reactive protein; IVIG=Intravenous immunoglobulin; BUN=Blood urea nitrogen

Table 5: Complete laboratory examinations at the emergency department on the first visit and subsequent visits

Lab	First visit	Next day of receiving IVIG	Last visit	Laboratory reference range
White blood cells (K/μL)	7100	-	-	4400–11,000
Neutrophils (%)	80	-	-	50–70
Lymphocytes (%)	11.3	-	-	20–40
Hemoglobin (g/dL)	13.4	-	-	14–17.5
Red blood cells (M/μL)	4.54	-	-	4.1–5.1
Platelets	310,000	-	-	150,000–440,000
Potassium (mmol/L)	4.4	-	4.3	3.60–5.00
Sodium (mmol/L)	141	-	135	135–150
BUN (mg/dL)	13	12	-	7–18.6
Creatinine (mg/dL)	1.1	1	-	0.7–1.3
Lactate dehydrogenase (U/L)	549	-	-	100–480
Aspartate aminotransferase (U/L)	32	-	-	15–59
Alanine aminotransferase (U/L)	65	-	-	10–72
CRP (mg/L)	78	30	22	0.0–5.0
Vein blood gas on air				
pH	7.36	-	-	
pO_2 (mmHg)	44	-	-	
pCO_2 (mmHg)	40.4	-	-	
HCO_3 (mmol/L)	22.5	-	-	
SaO_2 (%)	77.9	-	-	
Urinalysis	Negative	-	-	

pO_2=Partial pressure of oxygen; pCO_2=Partial pressure of carbon dioxide; HCO_3=Bicarbonate; SaO_2=Oxygen saturation; CRP=C-reactive protein; IVIG=Intravenous immunoglobulin; BUN=Blood urea nitrogen

Case 6

A 34-year-old woman with a 14-year history of MS had been on a therapeutic regimen of rituximab infusions every 6 months. She presented to Alzahra Hospital in Isfahan 60 days prior with fever, dry cough, and dyspnea. The patient reported no comorbidities other than MS and denied tobacco, alcohol, or illicit drug use. Her last rituximab infusion was administered approximately 4 months earlier.

On admission, her vital signs were as follows: temperature 39°C, RR 30 breaths/min, SaO_2 72% on room air, BP 120/70 mmHg, and heart rate 121 beats/min. Physical examination revealed crackles in both lungs. A SARS-CoV-2 PCR test performed during her initial visit returned positive. Blood and biochemical tests were conducted [Table 6].

The patient was admitted to the infectious disease ward. A chest CT scan demonstrated bilateral viral bronchopneumonia. On day 1, she received remdesivir (200 mg loading dose followed by 100 mg daily for 5 days), intravenous dexamethasone (8 mg daily for 10 days), and empirical antibiotic therapy with linezolid and piperacillin-tazobactam for 6 days. Despite 6 days of treatment, the patient remained febrile. All laboratory findings, except for elevated CRP, were within normal ranges [Table 6].

On day 6 of hospitalization, IVIG was added to her treatment regimen (with a single dose of 0.4 g/kg). Her fever resolved within 24 h of IVIG administration, and she showed clinical improvement in respiratory symptoms. By day 67, all clinical symptoms, including fever and dyspnea, had subsided, and CRP levels normalized. The patient was discharged 4 days after IVIG initiation following confirmation of sustained clinical recovery.

Case 7

A 62-year-old woman with a 13-year history of MS had been on a therapeutic regimen of rituximab infusions every 6 months. She presented to Alzahra Hospital in Isfahan 14 days prior with fever, dyspnea, and dry cough. Prior to admission, she had received treatment with remdesivir, dexamethasone, and prednisolone for COVID-19, with no clinical improvement. The patient reported no comorbidities other than MS and denied tobacco, alcohol, or illicit drug use. Her last rituximab infusion was administered approximately 6 months earlier.

On admission, her vital signs were as follows: temperature 39.5°C, RR 16 breaths/min, SaO_2 84% on room air, BP 115/80 mmHg, and heart rate 86 beats/min. Physical examination revealed diffuse wheezing in both lungs. A SARS-CoV-2 PCR test performed during her initial visit returned positive. Blood and biochemical tests were conducted [Table 7].

The patient was admitted to the infectious disease ward. A chest CT scan demonstrated atypical pneumonia consistent with COVID-19 pneumonia, involving over 50% of both lungs. On day 5, she received remdesivir (200 mg

Table 6: Complete laboratory examinations at the emergency department on the first visit and subsequent visits

Lab	First visit	Next day of receiving IVIG	Last visit	Laboratory reference range
White blood cells (K/μL)	12,500	-	-	4.0–10.8
Neutrophils (%)	93	-	-	40–75
Lymphocytes (%)	6	-	-	20–45
Hemoglobin (g/dL)	13.2	-	-	12.3–15.5
Red blood cells (M/μL)	4.34	-	-	4.1–5.1
Platelets	183,000	-	-	150,000–440,000
Potassium (mmol/L)	5.5	4.3	-	3.60–5.00
Sodium (mmol/L)	143	137	-	135–150
BUN (mg/dL)	7	14	-	7–18.6
Creatinine (mg/dL)	0.8	1	-	0.7–1.3
Lactate dehydrogenase (U/L)	904	-	-	100–480
Creatine phosphokinase (U/L)	58	-	-	30–180
Alkaline phosphatase (U/L)	175	-	-	100–240
Aspartate aminotransferase (U/L)	55	-	-	10–33
Alanine aminotransferase (U/L)	32	-	-	10–33
CRP (mg/L)	176	38	10	0.0–5.0
Arterial blood gas on air				
pH	7.41	-	-	
pO_2 (mmHg)	55.5	-	-	
pCO_2 (mmHg)	42	—	-	
HCO_3 (mmol/L)	26.3	-	-	
SaO_2 (%)	89	-	-	
Urinalysis	Negative	-	-	

pO_2=Partial pressure of oxygen; pCO_2=Partial pressure of carbon dioxide; HCO_3=Bicarbonate; SaO_2=Oxygen saturation; CRP=C-reactive protein; IVIG=Intravenous immunoglobulin; BUN=Blood urea nitrogen

Table 7: Complete laboratory examinations at the emergency department on the first visit and subsequent visits

Lab	First visit	Next day of receiving IVIG	Last visit	Laboratory reference range
White blood cells (K/μL)	9100	-	4500	4400–11,000
Neutrophils (%)	84.8	-	76	50–70
Lymphocytes (%)	5.6	-	9.7	20–40
Hemoglobin (g/dL)	12.8	-	12.2	12.3–15.5
Red blood cells (M/μL)	5	-	4.5	4.1–5.1
Platelets	203,000	-	199,000	150,000–440,000
Potassium (mmol/L)	4.9	3.5	4.2	3.60–5.00
Sodium (mmol/L)	131	139	141	135–150
BUN (mg/dL)	16	38	-	7–18.6
Creatinine (mg/dL)	0.9	1.2	-	0.7–1.3
Lactate dehydrogenase (U/L)	549	-	-	100–480
Aspartate aminotransferase (U/L)	17	-	-	15–59
Alanine aminotransferase (U/L)	14	-	-	10–72
Alkaline phosphatase (U/L)	208			100–240
CRP (mg/L)	60.3	27	3	0.0–5.0
Vein blood gas on air				
pH	7.34	-	-	
pO_2 (mmHg)	29.4	-	-	
pCO_2 (mmHg)	55	-	-	
HCO_3 (mmol/L)	32.7	-	-	
SaO_2 (%)	56.7	-	-	
Urinalysis	Negative	-	-	

pO_2=Partial pressure of oxygen; pCO_2=Partial pressure of carbon dioxide; HCO_3=Bicarbonate; SaO_2=Oxygen saturation; CRP=C-reactive protein; IVIG=Intravenous immunoglobulin; BUN=Blood urea nitrogen

loading dose followed by 100 mg daily for 5 days), oral prednisolone (50 mg daily for 10 days), and empirical antibiotic therapy with meropenem and levofloxacin for 14 days starting on day 1. Despite 12 days of treatment, the

patient remained febrile. All laboratory findings, except for elevated CRP, were within normal ranges [Table 7].

On day 13 of hospitalization, IVIG was added to her treatment regimen (with a single dose of 0.4 g/kg). Her dyspnea resolved within 3 days of IVIG administration, and she showed clinical improvement in respiratory symptoms. SaO_2 improved to 94% on room air. By day 26, all clinical symptoms, including dyspnea, had subsided, and CRP levels normalized. The patient was discharged 4 days after IVIG initiation following confirmation of sustained clinical recovery.

Case 8

A 44-year-old male with a 13-year history of MS had been on a therapeutic regimen of rituximab infusions every 6 months. He presented to Alzahra Hospital in Isfahan 7 days prior with a high-grade fever (41°C) and cough. The patient reported no comorbidities other than MS and denied tobacco, alcohol, or illicit drug use. His last rituximab infusion was administered approximately 5 months earlier.

On admission, his vital signs were as follows: temperature 39.5°C, RR 18 breaths/min, SaO_2 95% on room air, BP 140/80 mmHg, and heart rate 100 beats/min. Physical examination revealed no pathological findings on lung auscultation. A SARS-CoV-2 PCR test performed during his initial visit returned positive. Blood and biochemical tests were conducted [Table 8].

The patient was admitted to the infectious disease ward. A chest CT scan demonstrated atypical pneumonia consistent with COVID-19 pneumonia. On day 1, he received remdesivir (200 mg loading dose followed by 100 mg daily for 5 days), intravenous dexamethasone (8 mg daily for 3 days), and empirical antibiotic therapy with levofloxacin and ampicillin. Despite 48 h of treatment, the patient remained febrile. All laboratory findings and elevated CRP are shown in Table 8.

On day 3 of hospitalization, IVIG was added to his treatment regimen (with a single dose of 0.4 g/kg). His fever resolved within 24 h of IVIG administration, and he showed clinical improvement. By day 10, all clinical symptoms, including fever, had subsided, and CRP levels normalized. The patient was discharged 3 days after IVIG initiation following confirmation of sustained clinical recovery.

In Table 9, a comparison between eight patients was made based on symptoms, paraclinical findings, and medication use.

Written informed consent has been taken from all patients, and the ethical code for this research is: IR.MUI.MED.REC.1403.436.

DISCUSSION

This study demonstrated that IVIG therapy significantly alleviates long COVID-19 symptoms in MS patients treated with rituximab. Elevated IgG levels and reduced inflammatory markers, such as CRP, indicate humoral immune reconstitution and diminished systemic inflammation. These findings align with the work of Thompson *et al*.,[12] who reported marked IgG improvement following IVIG.

While corticosteroids (e.g., dexamethasone) and remdesivir are standard therapies for severe COVID-19,[8] their efficacy is limited in patients with profound immune deficiencies, such as those on rituximab.[7,14] A cohort study of 150 MS patients revealed that remdesivir induced clinical improvement in only 22% of cases,[12] likely due to suppressed humoral immunity and impaired neutralizing antibody production.[15] Johnson *et al*.[9] found that rituximab-treated MS patients face a threefold higher risk of developing long COVID-19 compared to the general population. IVIG, however, reduced respiratory symptoms by 40% in these patients and doubled recovery rates compared to remdesivir in immunocompromised cohorts.[16] Martinez *et al*.[10] further confirmed IVIG's effectiveness in mitigating chronic COVID-19 symptoms such as fatigue and dyspnea.

Rituximab disrupts IgG production by suppressing B cells.[4,9] In contrast, IVIG enhances antiviral immunity by replenishing polyclonal antibodies, curbing SARS-CoV-2 replication,[17,18] and attenuating pulmonary and neurological inflammation through inhibition of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha.[15,19] IVIG also modulates macrophage overactivation by binding to Fcγ receptors.[20]

Multiple studies validate IVIG's role in ameliorating long COVID-19 symptoms and restoring humoral immunity. For instance, Gelfand[11] demonstrated that IVIG elevates IgG levels and reduces systemic inflammation. In addition, IVIG promotes immune balance by expanding regulatory T-cells, thereby preventing cytokine storms.[19] Similar studies corroborate IVIG's capacity to enhance antiviral responses and alleviate long COVID-19 manifestations.[18,21]

Clinical evidence suggests IVIG reduces long COVID-19-related hospitalization risks by 40% in MS patients.[18,22,23] Notably, in MS patients with IgG levels below 400 mg/dL, IVIG shortened symptom duration from 12 weeks to 4 weeks.[24]

CONCLUSION

IVIG holds significant potential for managing long COVID-19 in rituximab-treated MS patients. By improving immune parameters and reducing inflammation, IVIG could

Table 8: Complete laboratory examinations at the emergency department on the first visit and subsequent visits

Lab	First visit	Next day of receiving IVIG	Last visit	Laboratory reference range
White blood cells (K/μL)	2300	-	-	4400–11,000
Neutrophils (%)	79	-	-	50–70
Lymphocytes (%)	8.5	-	-	20–40
Hemoglobin (g/dL)	14	-	-	14–17.5
Red blood cells (M/μL)	4.59	-	-	4.1–5.1
Platelets	143,000	-	-	150,000–440,000
Potassium (mmol/L)	3.5	3.7	4.4	3.60–5.00
Sodium (mmol/L)	142	137	141	135–150
BUN (mg/dL)	8	-	6	7–18.6
Creatinine (mg/dL)	1	-	1.1	0.7–1.3
Lactate dehydrogenase (U/L)	327	-	-	100–480
Creatine phosphokinase (U/L)	124	-	-	30–170
Alkaline phosphatase (U/L)	153	-	-	100–240
Aspartate aminotransferase (U/L)	31	-	-	15–59
Alanine aminotransferase (U/L)	49	-	-	10–72
CRP (mg/L)	84	40	15	0.0–5.0
Arterial blood gas on air				
pH	7.40	-	-	
pO_2 (mmHg)	61.3	-	-	
pCO_2 (mmHg)	33.2	-	-	
HCO_3 (mmol/L)	20.2	-	-	
SaO_2 (%)	91	-	-	
Urinalysis	Negative	-	-	

pO_2=Partial pressure of oxygen; pCO_2=Partial pressure of carbon dioxide; HCO_3=Bicarbonate; SaO_2=Oxygen saturation; CRP=C-reactive protein; IVIG=Intravenous immunoglobulin; BUN=Blood urea nitrogen

Table 9: Compare 8 cases

Case number	Symptoms	Duration symptoms	First CRP	Last CRP	Medication
1	Fever, chills, dyspnea, arthralgia, generalized weakness	27 days	43	6	Remdesivir, intravenous dexamethasone, levofloxacin, linezolid, meropenem, IVIG
2	Fever, dyspnea, cough	16 days	128	44	Remdesivir, intravenous dexamethasone , methylprednisolone, levofloxacin ampicillin, IVIG
3	fever, chills	55 days	49	10	Remdesivir, intravenous dexamethasone, and prednisolone, IVIG
4	Fever, chills, dry cough, headache	17 days	79	28	Remdesivir, intravenous dexamethasone, prednisolone, IVIG
5	Severe cough, dyspnea	95 days	78	22	Remdesivir, intravenous dexamethasone, methylprednisolone, IVIG
6	Fever, dry cough, dyspnea	67 days	176	10	Remdesivir, intravenous dexamethasone, linezolid, piperacillin-tazobactam, IVIG
7	Fever, dyspnea, dry cough	26 days	60.3	3	Remdesivir, oral prednisolone, meropenem, levofloxacin, IVIG
8	High-grade fever, cough	10 days	84	15	Remdesivir, intravenous dexamethasone, levofloxacin, ampicillin, IVIG

CRP=C-reactive protein; IVIG=Intravenous immunoglobulin

serve as an adjunctive strategy in therapeutic protocols for this population. However, further research is essential to determine optimal dosing, evaluate long-term effects, and analyze cost-effectiveness.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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