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Case Series

Anaesthesia Section

Antibody Cocktail in Moderate to Severe COVID-19 Infection: A Series of 10 Cases

ROHIT HANMANTA BHANDARI[1], SONALI GUPTA[2]

ABSTRACT

In the wake of the Coronavirus Disease-2019 (COVID-19) pandemic, scientists all over the world are in a relentless search for a cure. None of the therapies advised till date have shown significant benefit in treating COVID-19 infection. An antibody cocktail consisting of a combination of casirivimab and imdevimab is the newest weapon in the armamentarium against the disease. Currently, it has shown great promise in treating mild non hospitalised cases. The authors present the results of a series of 10 cases aged 31-76 years that demonstrate the efficacy of this cocktail in treating moderate to severe cases as well. All the patients received Roche's Antibody cocktail© on admission and standard treatment protocol comprising of remdesivir, methylprednisolone and low molecular weight heparin was given. Oxygen supplementation was titrated to achieve a target oxygen saturation (SpO_2) of 88-92%. Majority (70%) of the patients demonstrated an improvement in SpO_2/Fraction of Inspired Oxygen (FiO_2) ratio and a decline in the inflammatory marker levels 3-5 days after receiving the cocktail. Eight out of the 10 patients could be discharged home after 10-14 days of admission. The remaining two had severe disease with Computed Tomography Severity Index (CTSI) >17/25 and died despite receiving all the available therapies. Antibody cocktail is an effective adjuvant therapy against moderate to severe COVID-19 pneumonitis, demonstrating rapid improvement in SpO_2/FiO_2 ratio, inflammatory markers and a shortened duration of hospital stay.

Keywords: Casirivimab, Coronavirus disease-2019, Imdevimab, Remdesivir, Roche's antibody cocktail

INTRODUCTION

Coronavirus Disease-2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a novel coronavirus was first identified in November 2019. The large number of cases reported worldwide has put immense burden on the healthcare infrastructure. The spectrum of the disease encompasses a constellation of symptoms ranging from mild flu to potentially life-threatening Acute Respiratory Distress Syndrome (ARDS) and systemic complications. Seeing no definitive cure at hand, a fervent search began for an effective treatment. First use of immunotherapeutic strategies was seen in the form of convalescent plasma.

However, it was not specific and demonstrated an unpredictable response due to variability in the sera from different patients. On the other hand, targeted monoclonal antibodies, which were tailored to specific sequences on the viral genome, have shown great promise as an adjunctive therapy by preventing viral attachment to the host cells and thus, reducing the viral load [1]. An antibody cocktail consisting of a combination of casirivimab and imdevimab is an upcoming antiviral therapy in treating mild non hospitalised cases [2]. The authors present a series of 10 cases demonstrating efficacy of Roche's antibody cocktail© consisting of casirivimab and imdevimab in severe cases as well [3].

CASE SERIES

A total of 10 cases admitted from September 2021 to October 2021 were included in this series, the details of which are listed in [Table/Fig-1]. The patients were between 31 to 76 years of age, with a Male:Female ratio of 1.5:1. Half of them had significant co-morbidities such as diabetes mellitus, hypertension or cardiac disease. The most common symptoms were fever, cough, shortness of breath and bodyache, lasting between 3 to 8 days. Consent was obtained from all patients for publication of clinical data.

On admission, baseline vital signs including SpO_2 was recorded, and a High Resolution Computed Tomography (HRCT) chest was done. Arterial blood gas, complete blood count, kidney function test, serum electrolytes were done along with COVID-19 Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test. Testing for inflammatory markers included D-dimer, ferritin and C-Reactive Protein (CRP) levels, which were repeated on day 4. All the patients

Case	Age/ Sex	Co-morbidities	Admission on day of illness	CT severity score	SpO_2/FiO_2 ratio				D-dimer (ng/mL)		Ferritin (ng/mL)	CRP (mg/L)	Outcome
					On admission	Day 3	Day 5	Day 7	Day 1	Day 4			
1	31/F	None	Day 4	12/25	184	153	230	383	410	326	47	3	Discharged
2	32/M	HTN	Day 3	15/25	184	184	230	255	1554	1340	750	116	Discharged
3	54/M	DM/HTN/IHD	Day 5	12/25	153	184	184	184	322	4072	510	156	Discharged
4	69/M	None	Day 6	18/25	100	131	92	92	724	1408	864	52	Expired
5	73/F	None	Day 8	14/25	92	230	383	438	1583	1309	21	53	Discharged
6	76/M	DM/HTN/IHD	Day 8	22/25	92	92	92	85	787	1422	1318	66	Expired
7	55/F	None	Day 5	15/25	92	94	230	328	1106	635	148	7	Discharged
8	67/M	DM/HTN	Day 4	13/25	219	255	383	402	702	289	604	103	Discharged
9	55/F	None	Day 7	17/25	95	153	230	367	800	152	727	221	Discharged
10	68/M	DM	Day 6	20/25	153	153	153	230	1162	781	1290	141	Discharged

[Table/Fig-1]: Case details.
F: Female; M: Male; HTN: Hypertension; DM: Diabetes mellitus; CT: Computed tomography; CRP: C-reactive protein; IHD: Ischaemic heart disease

required Intensive Care Unit (ICU) admission as their SpO_2/FiO_2 ratio, respiratory rate and HRCT were suggestive of moderate to severe disease [4].

They received Roche's Antibody cocktail© (caserivimab 600 mg+ imdevimab 600 mg Intravenous (i.v.) diluted in 250 mL normal saline over 2 hours) on the day of admission after testing positive for COVID-19 along with a standard treatment protocol comprising of Inj. remdesivir 200 mg i.v. loading followed by 100 mg i.v. once daily for 5 days and Inj enoxaparin 0.6 mL SC 12 hourly. Inj. methylprednisolone 40 mg i.v. 12 hourly was started for 5 days and then tapered-off. Adjuvant measures like prone positioning and chest physiotherapy were also instituted. Oxygen supplementation was titrated to achieve a target SpO_2 of >92%. Drop in SpO_2 <90% or increase in respiratory rate >35/min was used as targets to step up the oxygen therapy. Conversely, SpO_2 >95% and Respiratory Rate (RR) <25/min were used to de-escalate the oxygen support. Serial chest X-rays and blood investigations were done to monitor the progress of the patients. SpO_2/FiO_2 ratio was monitored daily, and D-dimer and other inflammatory markers were sent every 4th day. Blood glucose was maintained between 140-180 mg/dL.

Except for two, all patients were shifted to the ward once oxygen requirement was less than 2 L/min with a SpO_2 >92%. They were then discharged home without any oxygen support. Telephonic follow-up was done upto a period of two weeks for the possibility of recurrence of respiratory distress.

DISCUSSION

Coronaviruses are enveloped, positive-sense, single-stranded Ribonucleic Acid (RNA) viruses. They are largely divided into four genera; α, β, γ, and δ based on their genomic structure. The α and β coronaviruses infect only mammals. Human coronaviruses responsible for common cold and croup belong to α coronavirus. In contrast, SARS-CoV-2, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV-2 are classified to β coronaviruses [5].

Angiotensin Converting Enzyme-2 (ACE-2) has been identified as a functional receptor for SARS-CoV and is highly expressed on the pulmonary epithelial cells. It is through this host receptor that the Spike (S) protein binds initially to start the host cell invasion by the virus. The virus invades the type 2 alveolar epithelial cells, to undergo replication. The virus-laden pneumocytes then release cytokines and inflammatory markers. This 'cytokine storm' acts as a chemo attractant for neutrophils and T-cells which are responsible for fighting-off the virus, but in doing result in inflammation and lung injury [6]. Symptoms typically appear 7-10 days after infection and Immunoglobulin M (IgM) antibodies develop by 8-12 days after the onset of symptoms. Spectrum of clinical disease comprises of asymptomatic cases; mild disease with fever, sore throat, dry cough, malaise and body aches or Gastrointestinal (GI) symptoms; moderate disease with involvement of lower respiratory tract without hypoxemia and severe disease where hypoxemia and complications like ARDS, heart failure, shock etc., are prominent. Risk factors for developing severe disease include diabetes mellitus, age >60 years, cardiovascular diseases like hypertension and coronary artery disease, immunocompromised state and cerebrovascular disease [3].

Since its emergence in November 2019, SARS-CoV-2, has evolved into an even stronger and superior variant as compared to other coronaviruses. Its more virulent, transmissible and mutates rapidly making effective antiviral treatment available herculean task. Current treatment strategies are divided into antivirals (remdesivir) and immunotherapy (dexamethasone, tocilizumab, baricitanib, convalescent plasma and monoclonal antibodies) but none except dexamethasone have produced significant mortality reduction in severe cases [7]. Convalescent plasma from recovered individuals was first used to provide short term, passive immunity to susceptible individuals. Benefits included ready availability, antibody mediated viral suppression, resolution of lung consolidation and excellent safety profile. However, it was non specific and only provided short-term immunity [1]. Other strategies include use of specific monoclonal antibodies against Vascular Endothelial-derived Growth Factor (VEGF) and IL6 receptor (tocilizumab, siltuximab). These too, failed to prove effective and some were associated with severe side-effects [8].

Roche's antibody cocktail© consists of casirivimab and imdevimab, which belong to IgG1 class of immunoglobulins, that targets the spike protein of the virus and was effective in mild, non hospitalised cases. Upto 1000 times higher neutralising antibody titres are achieved with the cocktail as compared to convalescent plasma. It prevents virus attachment to the host via the ACE2 receptors and acts as an interim defense till the time the host is able to mount its own antibody response against the virus. It is particularly effective in patients in whom an endogenous immune response has not been initiated. It demonstrates a reduction in the viral load, rate of hospitalisation and progression to severe disease in patients infected with SARS-CoV-2 [2]. The cocktail appears to be effective in reducing the rate of symptomatic infection and risk of transmission in household contacts of COVID-19 infected patients [9]. It has an excellent safety profile and is devoid of any major adverse effects with the exception of hypersensitivity reaction. While data on its use in inpatients or severe disease is limited, cases have been reported demonstrating its efficacy in the same [10]. Studies have also shown that the combination of two monoclonal antibodies is more effective than a single one as it prevents escape mutations [11]. This is particularly important in determining the future course of viral evolution and subsequent susceptibility to treatment.

The 10 patients analysed included five patients over 60 years old, six males and five with co-morbidities like diabetes, hypertension and ischaemic heart disease, putting them at a higher risk for developing moderate or severe disease [12]. Five patients had a SpO_2/FiO_2 ratio <100 on admission and required Non Invasive Ventilation (NIV). Based on the CT severity score, seven patients had moderate disease while three had severe disease. Clinical experience has shown that patients with CT severity score >10/25 required enhanced oxygen supplementation in the form of NIV or High Flow Nasal Cannula (HFNC) for a prolonged duration and also had a longer hospital stay [4].

There was clinical improvement within 3-5 days after administration of the cocktail. Those on NIV or HFNC could be weaned-off positive pressure ventilation with improvement in SpO_2/FiO_2 ratios. Most of them (70%) had declining D-dimer levels. Improvement in these parameters corresponded with a subjective feeling of well-being. Eight patients were discharged home on room air within 10-14 days of admission. Two patients died despite all interventions. Both were >60 years age, presented on day 6 and 8 of illness respectively, had HRCT score >18/25 and raised inflammatory markers with rising D- dimer levels. Previous studies have demonstrated that old age, raised inflammatory markers and high CT severity score are all predictors for poor clinical outcome [12,13].

One of the limitations of this case series is that, it was done during the 2nd wave of COVID-19 pandemic in India, where the delta variant was the predominant one. Whether the cocktail is equally effective against the other variants remains to be seen.

CONCLUSION(S)

Monoclonal antibody cocktail is an effective adjuvant antiviral therapy even in severe cases of COVID-19 infection.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Registrar, Department of Neurotrauma Unit, Ruby Hall Clinic, Pune, Maharashtra, India.
2. Registrar, Department of Critical Care Unit, Sahtyadri Superspeciality Hospital, Pune, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Sonali Gupta,
B3-504, Ganga Constella, Kharadi, Pune, Maharashtra, India.
E-mail: drsonaligupta88@gmail.com

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