DOI: 10.7860/JCDR/2023/59143.17392

Original Article

Internal Medicine Section

Efficacy of Antibody Cocktail Drug in COVID-19 Positive Patients: A Retrospective Single-centered Study

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ABSTRACT

Introduction: Neutralising monoclonal antibodies (mABs) have been proposed and developed for the treatment of Coronavirus Disease-2019 (COVID-19) patients with mild to moderate diseases and to prevent further progression. The combination of Casirivimab and Imdevimab blocks the entry of virus into cells by attaching to receptor binding domain of Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) spike glycoprotein. The mABs are utilised as a pre-emptive strategy in certain high-risk groups such as those suffering from chronic liver, kidney and respiratory disease, malignancies and other immunocompromised states where efficacy of vaccines may be suboptimal.

Aim: To evaluate the clinical outcomes in COVID-19 patients who were treated with Antibody Cocktail drug (casirivimab and imdevimab).

Materials and Methods: A retrospective observational study was conducted in patients confirmed positive for SARS-CoV-2 from June 2021 to January 2022 and subsequently, the collected data was analysed from May 2022 to June 2022. The study was conducted in a tertiary care referral hospital in eastern India. All eligible patient subsequently received casirivimab and imdevimab at COVID-19 facility. Monitoring of patients was done upto 12 hour postinfusion. Demographic parameters, routine investigations and clinical outcomes were assessed. Data entry was done using Microsoft excel. Data was entered, coded and analysed using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 21.0. All analysis was done at a preset alpha error of 5% and results expressed at confidence levels of 95%.

Results: Total 104 eligible cases were taken in present study. Nearly, 93% of those patients who had not been vaccinated were at higher risk for having severely elevated levels of C-Reactive Protein (CRP) as compared to 48% of those with COVID-19 vaccination. Nearly, 9 out of 10 patients with moderate-severe CRP levels were at nine times more risk for longer duration of hospitalisation as compared to normal levels of CRP. All patients having moderate-severe CRP levels required mechanical ventilation in comparison to mild CRP levels. Patients with co-morbidities were more likely to get severe COVID-19 infections (p-value ≤0.05). Unvaccinated subjects were more likely to have severe infections than vaccinated subjects. (p-value ≤0.05). Prolonged hospitalisation (>7 days) was statistically significant in severe COVID-19. Unvaccinated subjects had a statistically significant rise in CRP over vaccinated subjects. The majority of the patients receiving antibody cocktail did not require prolonged hospitalisation while a minor fraction required invasive ventilation. Antibody cocktail was safe, well tolerated and had good efficacy and low mortality rate as compared to other modalities of treatment in this study.

Conclusion: The duration of hospitalisation and outcomes were superior in patients having mild to moderate COVID-19 who received antibody cocktail without any serious side-effects.

Keywords: Casirivimab, Clinical profile, Coronavirus disease-2019, Imdevimab, Monoclonal antibodies, Outcomes

INTRODUCTION

On March 11, 2020, the World Health Organisation (WHO) declared that COVID-19 caused by SARS-CoV-2 as a global pandemic [1]. As of August 12, 2021, there have been more than 203 million confirmed cases of COVID-19, including more than 4.3 million deaths globally [2]. Although the newly developed vaccines can provide effective protection against SARS-CoV-2 infection [3], many new COVID-19 cases have been reported in mid 2021 and early 2022 because of new and emerging variants of the SARS-CoV-2 virus. Therefore, the increasing number of COVID-19 patients remains a critical public health concern. The clinical spectrum of COVID-19 can range from asymptomatic, Severe Acute Respiratory Illness (SARI), pneumonia to Acute Respiratory Distress Syndrome (ARDS) [4-6]. Currently, the recommended treatment options for COVID-19 patients depend on the stage and severity of the disease [5-7]. For hospitalised COVID-19 patients, antiviral agents such as remdesivir is suggested, however anti-inflammatory agents such as corticosteroids and Interleukin-6 antagonist are recommended for patients requiring high-flow oxygen/non invasive ventilatory therapy with evidence of clinical progression or increased biomarkers of inflammation [7-9].

In addition to this, patients with severe to critical COVID-19 infection, a significant number of patients are classified as having mild or moderate illness. Some patients having mild to moderate illness may progress to severe illness or require hospitalisation, particularly those with older age, multiple co-morbidities, obesity and/or immunocompromised status [6]. Therefore, disease progression or hospitalisation in patients with mild or moderate COVID-19 is another important issue. To address this issue, neutralising mABs have been proposed and developed for the treatment of patients with mild to moderate diseases and to prevent further progression [10].

An antibody cocktail is defined as a combination of two SARS-CoV-2 non competing neutralising or monoclonal human Immunoglobulin G1 (IgG1) antibodies that target the receptor-binding domain of the SARS-CoV-2 spike protein. The mABs have been found to be safe and effective in treating viral infections by blocking virus entry into the host cells thereby preventing complications [11]. Antibody cocktail the receptor-binding domain of the spike glycoprotein of SARS-CoV-2 virus is the main target for neutralising antibodies [12]. Casirivimab and Imdevimab are two IgG1 anti-SARS-CoV-2 mABs, for ceasing progression of COVID-19 [7]. A combination of

antibodies that bind to non overlapping epitopes, rather than a single antibody, is intended to minimise the likelihood of loss of antiviral activity due to naturally circulating viral variants or development of escape mutants under drug pressure [3]. In a clinical study in adult outpatients with SARS-CoV-2 infection and risk factors for severe COVID-19, the combination of casirivimab and imdevimab was well tolerated with reduced viral load in the upper airway, shortened the time to symptom resolution and reduced the composite outcome of COVID-19 related admission to hospital or all-cause mortality [4,5]. The combination of casirivimab and imdevimab has also been shown to prevent SARS-CoV-2 infection in previously uninfected household contacts of infected individuals [6]. In this study, authors report the outcomes of casirivimab-imdevimab among high-risk population with mild to moderate COVID-19. There have been various studies in the western part of world on antibody cocktail (casirivimab and imdevimab) for the prevention, and its safety and efficacy in COVID-19 [13-16].

Despite recording one of the highest COVID-19 cases in the world very few studies have been done in Indian population regarding safety, efficacy, and outcomes of the antibody cocktail in COVID-19. This study aims to evaluate the clinical outcome in COVID-19 patients admitted to dedicated COVID-19 hospital-4 of SCB MCH, Cuttack, a tertiary referral medical institution of Odisha, India who were treated with casirivimab and imdevimab. This study is one of the largest retrospective studies evaluating outcomes of patients treated with antibody cocktail.

MATERIALS AND METHODS

This retrospective observational study was conducted on 104 COVID-19 positive patients admitted to dedicated COVID-19 hospital-4 of SCB MCH, Cuttack between June 2021 to January 2022 after getting approval from Institutional Ethics Committee (IEC) stated by letter no. 1047. Data of the patients were collected by past records and telephonically in some cases and the collected data was analysed between May 2022 to June 2022. All consenting patient received Inj. casirivimab (600-mg dose) and Inj. imdevimab (600 mg dose) in 250 mL 0.9% saline infused intravenously over one-hour at our COVID-19 facility. Monitoring of patients vitals was done for 12 hour postinfusion.

Inclusion criteria:

- Age ≥18 years
- Patients diagnosed with COVID-19 from nasopharyngeal swab (both by antigen and Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) test).
- High-risk group patients (Age ≥65 years, Body Mass Index (BMI) ≥35 kg/m^2, diabetes mellitus, chronic kidney disease, hypertension, cardiovascular disease, chronic lung disease, immunosuppressive medication use, or an immunocompromising condition).
- Should be hospitalised within seven days of onset of COVID-19 symptoms.
- Mild to moderate in severity.

Exclusion criteria:

- Age <18 years.
- Severe COVID-19 infection.
- >7 days of onset of COVID-19 symptoms.
- Pregnant and lactating women.

Study Procedure

All participants of the study who fulfilled the eligibility criteria were explained the objectives and protocols of the study. Informed written consent was taken from the patient or legal guardian of the patient (those unable to give consent due to sickness). In this study, six-basic principle of medical ethics like; beneficence, non maleficence, autonomy, justice, dignity and truthfulness and honest was followed. Patient data were collected from their past medical records, prescriptions, investigation reports and telephonic conversations. Proper care was taken for those patients developing any form of reaction from the treatment. The study protocol was approved by IEC. All eligible patients of COVID-19 were approached for counselling and consenting. Demographic parameters (age, sex, BMI), other characteristics (co-morbidity, disease severity and vaccination status) were obtained from the past medical records and by questioning. All routine investigations including CRP-Quantitative, D-Dimer done during initiation of treatment were recorded. Clinical outcomes (duration of hospitalisation, discharge and mortality) were assessed from the medical records. Values of D-Dimer were expressed quantitatively in mg/L FEU (Fibrinogen equivalent units). Patients were stratified into two groups (>1 mg/L FEU n=79) and <1 mg/L;(n=26) FEU) based on quantitative D-DIMER values [17]. Based on elevation of CRP levels expressed in mg/L patients were classified into normal, mild, moderate and severe group {mild (n=54), moderate-severe(50)} [18].

STATISTICAL ANALYSIS

Data entry was done using Microsoft excel. Data was entered, coded and analysed using IBM SPSS version 21.0. Proportions were calculated for categorical variables and compared using Chi-square test. Mean and standard deviations were estimated for continuous variables as the measures of central tendency and dispersion, respectively. All analysis was done at a preset alpha error of 5% and results expressed at confidence levels of 95%.

RESULTS

Total 104 eligible cases were taken in the study. The mean age of patients in this study was 53.55±13.92 years. Elderly subjects (>60 years) were 40 (38.5%) in this study while 64 (61.5%) were non elderly [Table/Fig-1]. Majority of the subjects were males 68 (65.4%) while females constituted around 36 (34.6%). Majority of the patients of the study group were vaccinated 90 (86.5%). This is explainable due to the massive vaccination drive launched by Government of India. Majority of the cases were classified as mild 94 (90.4%) and rest were moderate 10 (9.6%). Few patients required Low flow oxygen 5 (4.8%) and non invasive ventilation 4 (3.8%) while most of them were at room air 95 (91.4%). Majority of the patients had shorter duration of hospital stay i.e., <1 week 94 (90.4%) and some required prolonged hospitalisation 10 (9.6%) indicating the effects of antibody cocktail in reducing duration of hospitalisation. CRP levels were mildly elevated in 51 (49%) patients, while severe elevation was found in 3 (2.9%) of cases. Majority of the patients had mild elevation of D-dimer 79 (76%) while moderate to severe elevation was found in approximately one quarter of the cases [Table/Fig-2]. There were four deaths (3.8%) who are having high titre of CRP demonstrating it as an adverse prognostication marker. Adverse effects of the drugs were recorded in two subjects (1.92%). Vaccinated group had more severe elevation in CRP as compared to unvaccinated group. Subjects with elevated CRP levels were more likely to have prolonged hospitalisation than with normal CRP levels. All patients having moderate-severe elevation of CRP levels required mechanical ventilation in comparison to mild CRP levels. Patients with co-morbidities are more likely to get severe COVID-19 infections than those not having co-morbidties (p-value ≤0.05). Unvaccinated subjects had more likely to have severe infections than vaccinated subjects (p-value ≤0.05). Prolonged hospitalisation (>7 days) was statistically significant in severe COVID-19. Unvaccinated subjects had a statistically significant rise in CRP over vaccinated subjects [Table/Fig-3]. To summarise the duration of hospitalisation, and outcomes were superior in patients having mild to moderate elevation of CRP as compared to severe elevation of CRP. Most of the patients did not have any co-morbidites while

S. No.	Parameters		Frequency (n)	%
1	Age (years)	≤60	64	61.5
		>60	40	38.5
2	Gender	Male	68	65.4
		Female	36	34.6
3	Co-morbidity	Type 2 DM	3	2.9
		Type 2 DM with HTN	11	10.6
		Others	12	11.5
		NIL	78	75
4	Vaccination status	Taken	90	86.5
		Not taken	14	13.5
5	Vaccine type	Covishield	86	82.7
		Covaxin	4	3.8
		No vaccine	14	13.5
6	Severity	Mild	94	90.4
		Moderate	10	9.6
7	O_2 requirement status	RA	95	91.4
		LF	5	4.8
		NIV, IV	4	3.8
8	Duration of hospitalisation (days)	≤7	94	90.4
		>7	10	9.6
9	Outcome	Discharge	100	96.2
		Death	4	3.8
10	CRP levels	0-6 (Normal)	24	23.1
		≤25 (Mild)	51	49
		25.00-100 (Moderate)	26	25
		>100.00 (Severe)	3	2.9
11	D-dimer levels	<1 (Mild)	79	76
		>1 (Mod-Severe)	25	24
12	Side-effects	No	102	98.1
		Yes	2	1.9

[Table/Fig-1]: Baseline and hospitalisation parameters (N=104).
DM: Diabetes mellitus; HTN: Hypertension; RA: Room air; LF: Low flow oxygen; NIV: Non invasive ventilation; Others (data not available)

S. No.	Parameters	Status	Severity			Chi-square test	Odds ratio
			Mod N (%)	Mild N (%)	Total N (%)	p-value	
1	Co-morbidity	Present	4 (15.4)	22 (84.6)	26 (100)	0.01	6.9
		Absent	2 (2.6)	76 (97.4)	78 (100)		
2	Vaccination status	Not taken	4 (28.6)	10 (71.4)	14 (100)	<0.001	17.6
		Taken	2 (2.2)	88 (97.8)	90 (100)		
3	Duration of hospitalisation (days)	>7	2 (20)	8 (80)	10 (100)	0.04	5.62
		≤7	4 (4.3)	90 (95.7)	94 (100)		
4	D-Dimer levels	>1	5 (20)	20 (80)	25 (100)	<0.001	19.5
		<1	1 (1.3)	78 (98.7)	79 (100)		
5	CRP levels	Mod-Severe	48 (88.9)	6 (11.1)	54 (100%)	0.01	1.96
		Mild	0 (0)	50 (100)	50 (100%)		

[Table/Fig-2]: Association of severity of COVID-19 infection with various parameters.

Type 2 DM combined with hypertension was the single largest co-morbidity found. Malignancies both solid and haematolymphoid malignancies comprised the next major group [Table/Fig-4].

S. No.	Parameters	Status	CRP level Sev-Mild-Mod		p-value	Odds ratio
			N (%)	N (%)		
1	Vaccination status	Not taken	13 (92.9)	1 (7.1)	0.002	14.20
		Taken	43 (47.8)	47 (52)		
2	O_2 requirement status	NIV, IV	4 (100)	0 (0)	0.05	1.92
		Room Air	52 (52)	48 (48)		
3	Duration of hospitalisation (days)	>7	9 (90)	1 (10)	0.01	9.0
		≤7	47 (50)	47 (50)		
4	Outcome	Death	4 (100)	0 (0)	0.05	1.92
		Discharge	52 (52)	48 (48)		

[Table/Fig-3]: Association of CRP levels of COVID-19 infected patients with various parameters.
Others; (data not available)

S. No.	Co-morbidity	Frequency (N)	%
1	Type 2 DM	3	2.9
2	Type 2 DM+Hypertension	11	10.6
3	Hypothyroidism	3	2.9
4	Chronic obstructive pulmonary disease	2	1.9
5	Sickle cell disease	2	1.9
6	Solid malignancies	4	3.8
7	Chronic lymphocytic leukaemia	1	1.0
8	Nil	78	75

[Table/Fig-4]: Freqency and co-morbidities in the study population.

DISCUSSION

This retrospective study evaluated the outcomes of casirivimab and imdevimab in symptomatic COVID-19 patients and those with co-morbidities. Wood SN reported that COVID-19 fatality has been lowered drastically and are far away from its benign phase [19]. Seasonal resurgence of various mutant strains has been a matter of concern especially those elderly and with co-morbidities. The dose recommended varies between 1200 mg-8000 mg (600 mg-4000 mg each antibody) [20,21]. The agents are preferred for mild to moderate COVID-19 patients. In present study population had Type 2 DM and hypertension as the most common morbidities which was also found in similar study by Wang Z et al., which showed hypertension (severe: 33.4%, 95% CI: 25.4%-41.4%; non severe 21.6%, 95% CI: 9.9%-33.3%), followed by diabetes (severe: 14.4%, 95% CI: 11.5%-17.3%; non severe: 8.5%, 95% CI: 6.1%-11.0%) as the major co-morbidity in a systematic review of 4881 cases of COVID-19 [22]. Further vaccination status was an important predictor of severity in this study where majority of the patients were vaccinated. This is explainable due to the massive vaccination drive launched by Government of India. This has been also established in other studies done by Freund O et al., which concluded that subjects in the vaccinated group had a significantly low severity, significantly decreased ICU admission and significantly decreased oxygen requirement as compared to the unvaccinated subjects while death and hospital stay were not significantly different in between vaccinated and unvaccinated subjects in a series of 349 patients while Li M et al., in a large retrospective observational study concluded that COVID-19 vaccines were associated with 50-60% reduced risk of severe pneumonia and 70-80% lower risk of severe COVID-19 infection [23,24].

In a study by Joy AP et al., patients did not showed significant difference of rate of hospitalisation between monoclonal antibody treated group and control group [25]. Present study did not have a control group however the majority of subjects on monoclonal antibody did not required prolonged hospitalisation (90.4%). Few

patients required Low flow oxygen (4.8%) and NIV (3.8%) while most of them were at room air (91.4%). In the study by Joy AP et al., 6.3% required mechanical ventilation while another study by Bhagyanath T et al., in a series of 201 patients (control group (n=101), test group (n=100) having diabetes with a 10 days follow-up period from India demonstrated a significantly less requirement of oxygen in the test group receiving monoclonal antibody cocktail as compared to standard treatment [26]. Joy AP et al., in a comparative observational study of 152 patients (test; casirivimab and imdevimab treated patients, n=79) and control (non casirivimab and imdevimab treated individuals, n=73) observed noticed lesser requisite for mechanical ventilation (6.3%; p-value <0.001), high flow oxygen (5.1%; p-value <0.001) and no death during casirivimab and imdevimab therapy [25,26]. From these two studies one can infer that the requirement of invasive ventilation requirements is much less in the casirivimab and imdevimab treated patients as compared to the general population. The WHO guidelines recommend the antibody cocktail in those group who are likely to have a high rate of hospitalisation and in selective group of patients including elderly age and those suffering from chronic diseases, and unvaccinated subjects [21]. The panel also recommends offering antibody cocktail if no detectable SARS-CoV-2 antibodies are detected (seronegative status). NICE guidelines (UK) recommend against using antibody cocktail against Omicron variant [24].

Evidence gathered from one of the largest randomised clinical trial (recovery) suggest a significant reduction in progression to non invasive ventilation in the seronegative group receiving antibody cocktail as compared to other group receiving standard treatments while no difference was observed in the seropositive group [27,28]. The mortality rate in present group was 4% which was higher as compared to similar study conducted by Razonable RR et al., which compared 696 subjects having mild to moderate COVID-19 with high risk features (hypertension (52.4%), BMI ≥35 (31.0%), diabetes mellitus (24.6%), chronic lung disease (22.1%), chronic renal disease (11.4%), congestive heart failure (6.6%), and compromised immune function (6.7%)) receiving antibody cocktail to a propensity matched control of equal number of cases and concluded that patients who received casirivimab imdevimab had significantly lower all-cause hospitalisation rates at day 14 (1.3% vs 3.3%; absolute difference: 2.0%; 95% Confidence Interval (CI):0.53.7%), day 21 (1.3% vs 4.2%; absolute difference: 2.9%; 95% CI: 1.24.7%), and day 28 (1.6% vs 4.8%; absolute difference: 3.2%; 95% CI: 1.45.1%). Rates of intensive care unit admission and mortality at days 14, 21 and 28 were similarly low for antibody-treated and untreated groups [12]. This could be explained due to larger number of patients having elevated CRP at baseline. No case of anaphylaxis or serious adverse effects was observed. On the contrary, casirivimab and imdevimab are not recommended for COVID-19 patients with hypoxia [29]. Overall with monoclonal antibody cocktail, the duration of hospitalisation and overall outcome were superior as compared to general population. Vaccination status was an important predictor of severity of disease requiring prolonged hospitalisation and mechanical ventilation.

Limitation(s)

Limitations of the study include absence of control group, retrospective nature of the study, limited sample size and heterogenous nature of the population.

CONCLUSION(S)

The sudden arrival and devastating spread of the COVID-19 pandemic has stimulated an accelerated programme of international research to identify effective ways to limit the spread of infection and to reduce the morbidity and mortality associated with COVID-19. Neutralising mAbs, particularly in combination with other medications, are an attractive approach with potential utility in both prophylactic and treatment settings in high-risk population. Present study demonstrated superior outcomes with antibody cocktail with regards to hospitalisation, requirement of non invasive ventilation or invasive ventilation. On evaluating the post COVID-19 status of each patient in the study, majority of those on the antibody cocktail were healthy and were quite satisfied with the treatment. It will also be important to determine the optimum timing for administration of neutralising mAbs on the basis of viral load, serology and other potential clinical factors. More randomised studies with a greater sample size are required to confirm the findings and prove the efficacy of casirivimab-imdevimab combination.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 20, 2022
- Manual Googling: Oct 29, 2022
- iThenticate Software: Nov 01, 2022 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 18, 2022**
Date of Peer Review: **Aug 20, 2022**
Date of Acceptance: **Nov 02, 2022**
Date of Publishing: **Feb 01, 2023**