Research Article

Casirivimab/Imdevimab for Management of Mild to Moderate COVID 19: An Indian Experience

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ABSTRACT

Background: The antibody cocktail (Casirivimab and Imdevimab) has been approved in India for the treatment of mild to moderate coronavirus disease in adolescents and adults in specified high-risk groups. There is a paucity of experience published about its use in Indian patients with mild to moderate COVID-19.

Objectives: The primary objectives of the study were time to COVID-19 symptoms resolution and proportion of patients with disease progression defined in terms of oxygen requirement. The effect of BMI on outcomes of treatment was also assessed. The chief secondary objectives were to evaluate the safety and all-cause mortality in patients treated.

Methodology: In this retrospective study, patients with mild to moderate COVID-19 were enrolled. They were treated with the antibody cocktail 1.2 gm intravenously either on the day of diagnosis or within 24 hours of testing positive. The parameters of assessment included: time to symptom resolution, duration of hospitalization, need for oxygen, need for ventilator support and outcomes of hospitalization were evaluated

Results: Sixty three patients (mean age: 54.87 years ± 17.83 years) were enrolled in the study. Patients most commonly presented with symptoms of fever (52.4%) and cough (66.7%). Symptoms resolution occurred earliest for fever, (1.41 days ± 0.74 days) followed by sore throat (1.59 days ± 0.80 days). BMI had no impact on symptom resolution hospitalization and O2 support regardless of the presence or absence of comorbidities .

Conclusion: Casirivimab/imdevimab improves outcomes in Indian patients.The efficacy of casirivimab/imdevimab remains unaffected regardless of the age of the patient, body weight of the patient and the presence of comorbid diseases.

Keywords: Casirivimab/Imdevimab; COVID-19

Introduction

The quest for effective therapies to prevent and treat coronavirus disease 2019 (COVID-19) is still ongoing. Infection by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is known to have the highest mortality rate among the elderly and those with pre-existing medical conditions [1]. The viral load has a direct correlation with an increased risk of mortality in hospitalized patients. Once infected, Immunoglobulin-M (IgM) antibodies appear 8 days-12 days after the onset of clinical symptoms [2].

On May 5, 2021, the Central Drugs Standards Control Organization (CDSCO) provided an Emergency Use Authorization (EUA) for the antibody cocktail (Casirivimab and Imdevimab) in India for the treatment of mild to moderate coronavirus disease in adolescents and adults in specified high-risk groups. Monoclonal antibodies exhibit specific binding to specific surface proteins on SARS-CoV-2 and this helps to neutralize its pathogenic effects. Deb et al. noted that monoclonal antibodies are safer and more specific in targeting SARS-CoV-2 surface proteins [3].

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Casirivimab and imdevimab are monoclonal antibodies which bind to two distinct sites on the receptor binding domain of the SARS-CoV-2 spike glycoprotein. This results in blocking of the viral entry into host cells. Casirivimab and imdevimab must be administered together in a single intravenous infusion or, alternatively, administered consecutively by subcutaneous injection. For the treatment of COVID-19, the recommended dose is casirivimab 600 mg plus imdevimab 600 mg [4].

In vitro studies and clinical trials have indicated that Casirivimab plus imdevimab works optimally in lowering viral loads in patients who are serum antibody-negative at baseline. Weinrich, et al. demonstrated that patients who were not seronegative at baseline had a 2-log greater viral load at day seven post-infusion. In patients admitted to hospital with COVID-19, the monoclonal antibody combination of casirivimab and imdevimab reduced 28-day mortality in patients who were seronegative [5].

The variants of concern of SARS-CoV-2 have been changing over a matter of months. In mid 2021 Delta was the predominant variant of concern while towards the end of 2021 and by early 2022 the Omicron variant was the predominant variant [6].

Casirivimab and imdevimab has been used to treat patients with SARS-CoV-2 infection in India and found highly effective against SARS-CoV-2 delta and have shown good clinical outcomes [7].

There is a paucity of experience published about use in Indian patients with mild to moderate COVID-19. Hence, the effect of casirivimab and imdevimab in Indian patients needs to be studied in the real world setting. The real world experience needs to be documented and discussed, and hence this retrospective study was conducted.

Objectives of the study

The primary objectives of the study were time to COVID-19 symptoms resolution and proportion of patients with disease progression defined in terms of oxygen requirement in patients who received (or treated with) the antibody (Im/Cas). The effect of BMI on outcomes of treatment was also assessed. The chief secondary objectives were to evaluate the safety and all-cause mortality in patients treated with the monoclonal antibody cocktail therapy in the real world setting.

Methodology

The retrospective study on use of antibody cocktail was conducted in two tertiary care COVID centres in a metro city in India (Mumbai). The inclusion Criteria were RT-PCR confirmed mild to moderate COVID-19 patients (≥ 12 years) who were stable on room air and patients who have received single dose IV administration of Casirivimab and Imdevimab during treatment. Database of the two hospitals containing patients' demographic information, COVID-19 related information including but not limited to RT-PCR test outcome, laboratory investigations, concomitant medications, comorbid disease conditions, adverse drug reactions was used for analysis.

Patients with COVID positive report (RT-PCR) categorized as mild to moderate COVID diagnosed during the period from June 2021-January 2022 were enrolled in the study. They were treated with the antibody cocktail 1.2 gm intravenously either on the day of diagnosis or within 24 hours of testing positive. Patients were admitted if necessary. Patients received additional treatment as per the ICMR guidelines.

■ Parameters of assessment

Patient demography, comorbidities, vaccination status, number of doses of vaccine given were chronicled. Time to symptom resolution, duration of hospitalization, need for oxygen, need for ventilator support and outcomes of hospitalization were evaluated. Any adverse effects to the antibody cocktail (Casirivimab and Imdevimab) were also noted.

■ Statistical analysis

For parameters that were not normally distributed, non-parametric tests (Kruskal Wallis Test) were used to make group comparisons. Fisher's exact test was used to explore the association between 'BMI' and 'Symptom.The Chi-squared test was used to explore the association between 'BMI' and 'Comorbidities.

Results

Sixty three of patients were enrolled in the study. All the patients had been vaccinated with two doses. The mean age of the patient was 54.87 years ± 17.83 years .There was no difference in the number of males and females enrolled in the study (31 males vs 32 females) . Thirty one patients had BMI ≥ 25 Kg/m^2. Of these, 11.1% patients had BMI ≥ 30 Kg/m^2. Only 3.2%

patients were underweight and had BMI<18.5 Kg/m² (**Table 1**). Patients most commonly presented with symptoms of fever (52.4%) and cough (66.7%) (**Figure 1**).

The most common comorbid diseases were hypertension and cardiovascular diseases (36.5%) followed by diabetes (25.4%) (**Figure 2**).

Symptoms resolution occurred earliest for fever (1.41 days ± 0.74 days) followed by sore throat (1.59 days ± 0.80 days). Bodyache resolved after 4.35 days ± 1.70 days while weakness took longest time to resolve (6.33 days ± 2.74 days) (**Table 2**).

Only 11 patients (17.5%) patients needed hospitalization. The total duration of hospitalization was 5.00 ± 2.00 days. None of the patients enrolled in the study need oxygen support. None of the patients had any adverse effects after treatment with the antibody cocktail therapy and no mortality was reported. (**Table 3**).

BMI had no impact on prevalence of symptoms, duration of symptoms or on resolution outcomes, hospitalization and O_2 support (**Tables 4 and 5**). Similarly, there was no effect on outcomes in the patients with or without comorbidities such as hypertension, cardiovascular disease, diabetes, chronic lung diseases, chronic kidney disease.

Table 1: Demographics.

Baseline characteristics	Mean ± SD
Age (Years)	54.87 ± 17.83
Age Group	
≤ 40 Years	16 (25.4%)
41-50 Years	13 (20.6%)
51-60 Years	6 (9.5%)
>60 Years	28 (44.4%)
Gender	
Male	31 (49.2%)
Female	32 (50.8%)
Height (cm)	168.13 ± 8.53
Weight (kg)	72.26 ± 12.
BMI (Kg/m²)	25.55 ± 3.73
BMI	
<18.5 Kg/m²	2 (3.2%)
18.5 Kg/m²-24.9 Kg/m²	30 (47.6%)
25 Kg/m²-29.9 Kg/m²	24 (38.1%)
≥ 30 Kg/m²	7 (11.1%)
Both Doses of Vaccine Taken	63 (100.0%)

Association between comorbid diseases and outcomes

There was no statistically significant correlation between BMI and Time to Symptom Resolution such as cough (p=0.819) or fever or the need for hospitalization (Tables 6-8).

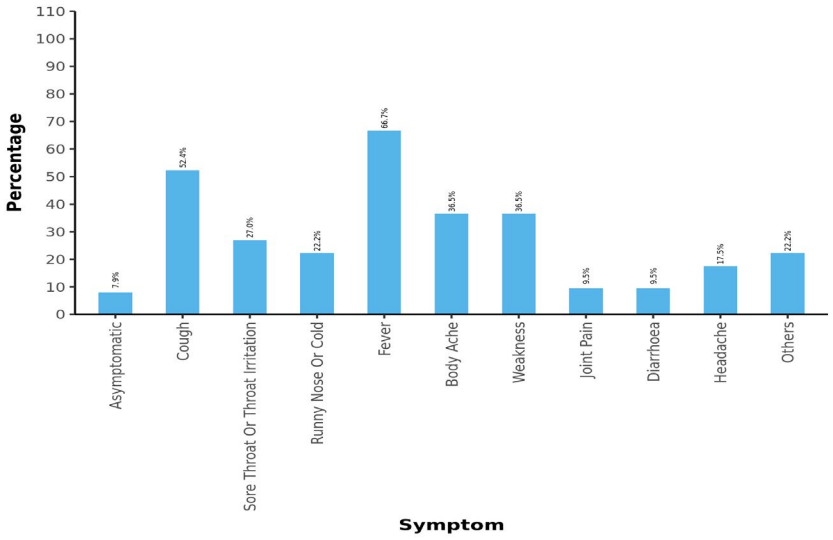

Figure 1: Most common presenting symptoms of the patients.

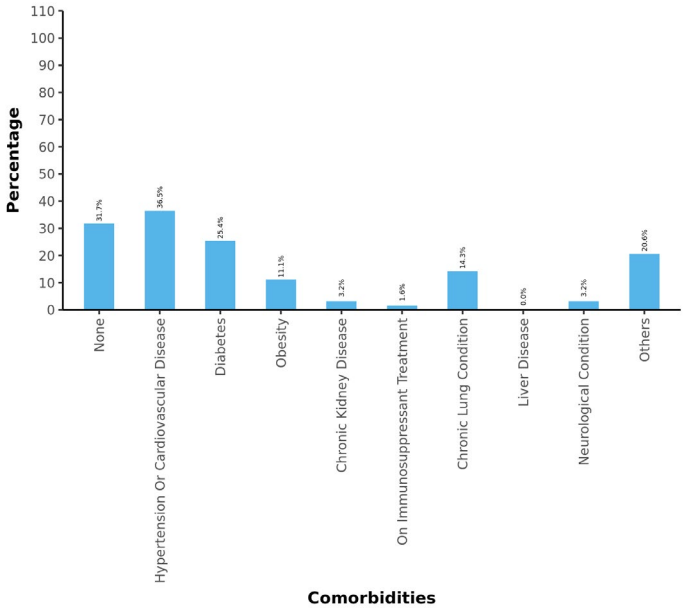

Figure 2: Comorbidities.

Table 2: Time to Symptom Resolution.

Time to Symptom Resolution (Days)	Mean ± SD
Cough	3.15 ± 1.42
Sore Throat Or Throat Irritation	1.59 ± 0.80
Runny Nose Or Cold	3.21 ± 1.58
Fever	1.41 ± 0.74
Body Ache	4.35 ± 1.70
Weakness	6.33 ± 2.74
Joint Pain	4.67 ± 1.37
Diarrhoea	2.00 ± 0.89
Headache	2.82 ± 1.99

Table 3: Summary of Outcomes.

Outcomes	Mean ± SD
% patients who needed Hospitalization (%)	11 (17.5%)
Days of Hospitalization (Days)	5.00 ± 2.00
Need for O_2 Support (Yes)	0 (0.0%)
Reaction/Side Effect After Infusion (% patients)	0 (0.0%)
RT-PCR Positivity from Second Dose (Days)	216.49 ± 47.85

Table 4: Association between BMI and symptom resolution.

Time to symptom resolution	BMI				p value
	<18.5 Kg/m²	18.4 Kg/m²- 24.9 Kg/m²	25 Kg/m²- 29.9 Kg/m²	≥ 30 Kg/m²	
	(n=2)	(n=30)	(n=24)	(n=7)	
Resolution of Cough	3.00 ± 0	3.29 ± 1.33	2.64 ± 1.39	4.50 ± 1.29	0.158[1]
Resolution of Fever	1.00 ± 0	1.32 ± 0.72	1.64 ± 0.84	1.25 ± 0.50	0.346[1]
Resolution of Body Ache	6.00 ± 1.41	3.67 ± 1.58	4.73 ± 1.68	3.00 ± 0	0.197[1]
Resolution of Weakness	7.00 ± 0	5.50 ± 1.90	7.29 ± 3.64	6.67 ± 3.51	0.649[1]
Resolution of Diarrhoea	-	1.67 ± 1.15	2.00 ± 0.00	3.00 ± 0	0.435[1]
Resolution of Headache	1.00 ± 0	3.00 ± 2.71	3.00 ± 1.73	3.00 ± 2.00	0.722[1]
Need For Hospitalisation (Yes)***	0 (0.0%)	2 (6.7%)	5 (20.8%)	4 (57.1%)	0.021[2]
Days of Hospitalization	-	6.00 ± 4.24	4.60 ± 1.82	5.00 ± 1.41	0.908[1]
Need for O_2 Support (Yes)	0 (NaN%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000[3]

***Significant at p<0.05, [1]: Kruskal Wallis Test, [2]: Fisher's Exact Test, [3]: Chi-Squared Test

Table 5: Correlation of BMI on hospitalization and O_2 support.

	BMI				p value
	<18.5 Kg/m²	18.5 Kg/m²- 24.9 Kg/m²	25 Kg/m²- 29.9 Kg/m²	≥ 30 Kg/m²	
	(n=2)	(n=30)	(n=24)	(n=7)	
Days of Hospitalization* **	-	6.00 ± 4.24	4.60 ± 1.82	5.00 ± 1.41	0.908[1]
Need for O_2 Support (Yes)	0 (NaN%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000[2]

***Significant at p<0.05, [1]: Kruskal Wallis Test, , [2]: Chi-Squared Test

Table 6: Resolution of cough.

Parameters	Time to Symptom Resolution of cough in patients with comorbidities	NO comorbidites	p value
Comorbidities: Diabetes	3.89 ± 1.62	2.88 ± 1.26	0.083[1]
Comorbidities: Obesity***	4.50 ± 1.29	2.97 ± 1.35	0.059[1]
Comorbidities: Chronic Kidney Disease	4.50 ± 0.71	3.06 ± 1.41	0.165[1]
Comorbidities: Chronic Lung Condition	4.00 ± 0.71	3.00 ± 1.47	-
Comorbidities: Neurological Condition	4.00 ± 1.41	3.10 ± 1.42	0.375[1]

***Significant at p<0.05, [1]: Chi-Squared Test

Table 7: Correlation of resolution of fever and presence of comorbidities.

Parameters	Symptom Resolution: Fever	Symptom Resolution: Fever	p value
	YES	NO	
Comorbidities: Hypertension Or Cardiovascular Disease	18 (43.9%)	5 (22.7%)	0.096[3]
Comorbidities: Diabetes	13 (31.7%)	3 (13.6%)	0.116[3]
Comorbidities: Obesity***	4 (9.8%)	3 (13.6%)	0.687[2]
Comorbidities: Chronic Kidney Disease	1 (2.4%)	1 (4.5%)	1.000[2]
Comorbidities: On Immunosuppressant Treatment	1 (2.4%)	0 (0.0%)	1.000[2]
Comorbidities: Chronic Lung Condition	7 (17.1%)	2 (9.1%)	0.476[2]
Comorbidities: Liver Disease	0 (0.0%)	0 (0.0%)	1.000[3]
Comorbidities: Neurological Condition	1 (2.4%)	1 (4.5%)	1.000[2]

***Significant at p<0.05, [2]: Fisher's Exact Test, [3]: Chi-Squared Test

Table 8: Correlation between Need for hospitalization and presence of comorbid diseases.

Comorbidities	Need for hospitalization	Need for hospitalization	p value
	YES	No	
Diabetes	4 (36.4%)	12 (23.1%)	0.448[2]
Obesity***	4 (36.4%)	3 (5.8%)	0.014[2]
Chronic Kidney Disease	0 (0.0%)	2 (3.8%)	1.000[2]
On Immunosuppressant Treatment	1 (9.1%)	0 (0.0%)	0.175[2]
Chronic Lung Condition	2 (18.2%)	7 (13.5%)	0.650[2]
Liver Disease	0 (0.0%)	0 (0.0%)	1.000[3]
Neurological Condition	1 (9.1%)	1 (1.9%)	0.321[2]

***Significant at p<0.05, [2]: Fisher's Exact Test, [3]: Chi-Squared Test

Discussion

Casirivimab/imdevimab antibody cocktail is composed of two SARS-CoV-2 neutralizing antibodies against distinct, non overlapping epitopes present on the spike protein. *In vitro* studies showed that this antibody cocktail, retains activity against current variants of concern and variants of interest, including B.1.1.7 (or alpha), B.1.429 (or epsilon), B.1.617.2 (or delta), and E484K-containing variants such as B.1.351 (or

beta), P.1 (or gamma), and B.1.526 (or iota) [7].

In early clinical trials, Casirivimab/imdevimab reduced the risk of Covid-19 related hospitalization or death from any cause, and it resolved symptoms and reduced the SARS-CoV-2 viral load more rapidly than placebo [5]. There was a significant 20% reduction in all-cause mortality .The casirivimab/imdevimab plus usual care group had a 17% lower relative risk of progressing to invasive mechanical ventilation or death (composite endpoint) as compared to the group on usual care only (30% of patients *vs* 37% of patients). A shorter duration of hospitalization was observed in the casirivimab/imdevimab treated group (13 days *vs* 17 days). A greater proportion of patients were discharged alive by day 28 (64% *vs* 58%) [8]. Early treatment with casirivimab/imdevimab was effective in preventing asymptomatic SARS-CoV-2 infection from progressing to symptomatic COVID-19 in a cohort of 314 subjects [9].

Two recent studies reported that a combination of the two monoclonal antibodies is more effective than a single monoclonal antibody in the treatment of the COVID-19 disease [10-12]. The efficacy of casirivimab plus imdevimab is likely due to casirivimab and imdevimab both targeting the spike protein on distinctly separate epitopes [5,12,13]. Baum et al. further suggested that the combination of the cocktail casirivimab plus imdevimab prevents rapid mutational escape, which is an important consideration as mutant SARS-CoV-2 strains arise globally [11]. Recent studies have noted that the monoclonal antibody combination of casirivimab and imdevimab (REGN-COV2) effectively reduces viral load in infected seronegative non-hospitalized patients [14-16].

The current study was undertaken in Indian patients with mild to moderate COVID-19, in order to study their response to the antibody cocktail therapy. In the study, fever was the symptom which resolved the earliest(1.41 days ± 0.74 days) while weakness persisted for a longer period of time and took longer time to resolve (6.33 days ± 2.74 days). Only 17.5% patients needed hospitalization. The total duration of hospitalization was 5.00 days ± 2.00 days. None of the patients enrolled in the study need oxygen support. None of the patients had any adverse effects after treatment with the antibody cocktail therapy. There was no effect on outcomes in patients with or without comorbidities such as hypertension, cardiovascular disease, diabetes, chronic lung condition , chronic kidney disease. There was no significant correlation between BMI and Time to Symptom Resolution such as cough or fever or the need for hospitalization regardless of the type of comorbidity present.

Another important aspect observed was that the presence of comorbidity did not have a negative impact on the resolution of symptoms such as cough or fever. The need for hospitalization was not negatively affected by the presence of comorbidity. The results of the current study indicate that the outcomes of treatment with monocloncal antibody are consistently seen across patient populations regardless of BMI, presence or absence of comorbidities.

Another fact to consider is that the population included during the study may have been infected with the Delta variant (early part of the study) or the Omicron variant (later part of the study in December 2021 and January 2022). Yet, the results were consistent throughout the study. No increased need for hospitalization was observed during the early or late part of the study

The findings of our study corroborate the findings published across the world. The findings demonstrate the safety and efficacy of the antibody cocktail therapy in Indian patients with mild to moderate COVID-19.

Limitations of the Study

We did not perform genotyping for identification of the variants.

Conclusion

The current study has demonstrated the efficacy and safety of casirivimab/imdevimab in preventing hospitalization and deaths in COVID 19 patients. Casirivimab/imdevimab improves outcomes in Indian patients.The efficacy of casirivimab/imdevimab remains unaffected regardless of the age of the patient, body weight of the patient and the presence of comorbid diseases.

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Conflict of Interest

None.

Ethical Approval

Study was approved by the Ethics committee of Nanavati Hospital, Mumbai.

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