International Journal of Research in Medical Sciences
Bhagyanath T et al. Int J Res Med Sci. 2022 Sep;10(9):1983-1987
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20222277

Original Research Article

Effect of casirivimab-imdevimab on mild COVID-19 patients with diabetes in reducing oxygen supplementation at 28 days: an observational study

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Received: 23 July 2022
Accepted: 12 August 2022

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ABSTRACT

Background: Monoclonal antibody therapy is one of the most promising treatments for COVID-19 infection. Casirivimab-imdevimab is a monoclonal antibody cocktail which is approved for high-risk patients with mild to moderate COVID-19 infection. The aim of the study was to determine the safety and efficacy of casirivimab-imdevimab on diabetic patients with COVID-19.
Methods: This was an observational study conducted on diabetic patients admitted with mild to moderate COVID-19 infection. The patients were divided into 2 groups. While 101 patients were administered with casirivimab-imdevimab (test group), 100 of them were provided with standard treatment (control group). Regular follow-ups ensued for 10 days during the period of their hospitalization and finally on the 28th day through a telephonic enquiry. Apart from this, safety of administering the drug was assessed in all patients who belonged to the test group.
Results: One of the patients who were administered casirivimab-imdevimab developed anaphylactic reaction. Three fourth of the patients who participated in the study were vaccinated and the oxygen requirement up to 10 days of admission was significantly lower in the vaccinated group (p=0.018). Oxygen requirement, mechanical ventilation and death up to 10 days of admission were less for patients who were administered monoclonal antibody, but it was not statistically significant. Oxygen requirement, and death after 10 days up to 28 days were also less for patients who were administered monoclonal antibody, even though not statistically significant.
Conclusions: Casirivimab-imdevimab was not found to be beneficial in diabetic patients with mild COVID-19. More studies with higher sample size are required to prove the clinical benefit of casirivimab-imdevimab beyond doubt.

Keywords: COVID-19, Diabetes mellitus, Casirivimab, Imdevimab, Monoclonal antibody, Oxygen requirement

INTRODUCTION

COVID-19 is a highly contagious viral infection which is inflicted by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. It has profound implications on the world's demographics resulting in the death of more than 6 million people to date.[1] Although there was a rapid development of drugs for COVID-19, only few drugs have proven to have clear cut benefit.

A new approach in the quest to find a new drug for COVID-19 infection involves use of monoclonal antibodies, which target the spike protein of SARS-CoV-2. Monoclonal antibody cocktail which binds different regions of the viral target helps in combating mutational escape seen when a single monoclonal antibody is given.[2] Casirivimab-imdevimab is an investigational monoclonal antibody cocktail which is given together as a single intravenous infusion.[3]

Casirivimab and imdevimab administered together in non-hospitalized COVID-19 patients with mild to moderate symptoms who were at high risk of developing severe illness was shown to have reduced hospitalisations and emergency visits within 28 days after treatment. In November 2020 United States food and drug administration (FDA) issued emergency use authorisation (EUA) for casirivimab and imdevimab to be administered together for the treatment of mild to moderate COVID-19 in adults and paediatric patients (12 years of age or older weighing at least 40 kilograms) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19.[4] The central drugs standards control organisation (CDSCO), on 05 May 2021, granted an emergency use authorization to Roche and Regeneron for use of the casirivimab-imdevimab cocktail in India.[5]

There are several risk factors for the development of severe illness in patients with COVID-19. Diabetes is one among the most common comorbidity seen among COVID-19 patients. Those with diabetes or hyperglycaemia have a two- to four-fold increase in mortality and severity of COVID-19 than those without diabetes.[6] This study aims to find the efficacy of casirivimab-imdevimab on mild COVID-19 patients with diabetes.

METHODS

This was an observational study done at Kinfra COVID Hospital, Palakkad, Kerala which mainly caters to the patients of the district. Patients with type 2 diabetes mellitus who were admitted with mild COVID-19 infection during the study period from August 2021 to January 2022 were enrolled in to the study.

The inclusion criteria were patients aged 18 years or more, patients positive of SARS-CoV-2 either by antigen test or molecular diagnostic test (RT-PCR or other molecular diagnostic assay) within ≤72 hours of admission, patients with symptoms consistent with COVID-19, with onset ≤10 days before admission, and was willing and able to provide informed consent signed by study patient or legally acceptable representative. The exclusion criteria were patients requiring supplemental oxygen at the time of screening, pregnant and breast-feeding women, has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma or monoclonal antibodies against SARS-CoV-2, within 3 months, and had known (recorded) allergy or hypersensitivity to components of study drug.

Sample size was calculated using the formula

$$N = \frac{4pq}{d^2} = \frac{4 \times 30 \times 70}{9 \times 9} \approx 103$$

Where p is prevalence of hospitalisation in treatment group of 30 based on previous study, $q = 100 - p$, d=precision=9.[7]

Patients who gave consent and fulfilled the inclusion criteria were taken up for the study. Complete physical examination was carried out on all patients. SpO_2 was measured at the time of admission and daily during hospital stay. Investigations including complete blood count (CBC), renal function test (RFT), liver function test (LFT), C-reactive protein (CRP), general random blood sugar (GRBS), and glycosylated hemoglobin (HbA1C) were done on all patients at the time of admission and as and when required. Patients were divided into two groups, test group and control group. There were 101 participants in the test group and 100 participants in the control group. Test group received casirivimab-imdevimab injection and standard treatment. Control group received standard line of treatment like paracetamol for fever. After infusion of study drug, patients were observed for 1 hour for adverse events. Subsequently, the patients were followed up in hospital for 10 days and telephonically after 28 days. Safety was assessed in all patients who were administered casirivimab and imdevimab.

Data management and statistical analysis

Data were de-identified, coded and entered in Microsoft excel 2020. Analysis was done using statistical package for the social sciences (SPSS) software. Continuous variables were summarized using mean and standard deviation. Categorical variables were summarised as proportion or percentage. Comparisons between quantitative variables were tested using student's t test. Comparison of proportion was done using Chi square test/Fisher's exact test.

RESULTS

A total of 201 patients were enrolled in the study with 101 in the test group and 100 patients in the control group. One patient in the test group developed anaphylactic reaction while administration of casirivimab-imdevimab and the drug was stopped immediately and patient was removed from further study. The mean age of the study population was 61.23±12.36 years. Out of the 200 patients, 114 were males and 86 were females. Casirivimab-imdevimab was administered to patients after a mean 1.18±1.08 days and a maximum of 5 days from testing positive for COVID-19. The mean days of antibody administration from the symptom onset was 3.05±1.95 days. No patients were administered the drug after 10 days of symptom onset.

147 patients in the study population received COVID-19 vaccination while 53 patients were unvaccinated. Out of the 147 patients who were vaccinated, 78 patients took single dose of the vaccine and 69 patients took double dose. 138 patients received covishield and 9 patients received covaxin (Table 1). Systemic hypertension was the most common comorbidity among study participants apart from diabetes mellitus. 93 patients had systemic hypertension. Coronary artery disease and dyslipidaemia were the next common comorbidities (Table 2).

Table 1: Vaccination status of the patients.

Vaccination status	Antibody given		Total (%)
	Yes	No	
Vaccinated	73	74	147 (73.5)
Unvaccinated	27	26	53 (26.5)
Single dose	43	35	78 (53.06)
Double dose	30	39	69 (46.93)
Covishield	67	71	138 (93.87)
Covaxin	6	3	9 (6.12)

Table 2: Comorbidities present among patients.

Comorbidities	Antibody		Total
	Yes	No	
Systemic hypertension	41	52	93
Coronary artery disease	18	12	30
Chronic kidney disease	9	2	11
Hypothyroidism	3	2	5
Dyslipidemia	11	11	22
COPD	5	8	13
Carcinoma	3	4	7
Stroke	5	3	8

The mean duration of diabetes mellitus among the study population was 8.39±7.27 years. There was no statistically significant difference in duration of diabetes mellitus between patients who received and did not receive antibody (Table 3).

A total of 189 patients where on treatment for diabetes mellitus, and 11 patients were not on treatment at the time of presentation. Out of the 189 patients, 164 patients were on oral hypoglycaemic agents (OHA) and the rest were on either insulin or combination of insulin and OHA. The mean SpO_2 at the time of admission was 97.82±1.13 for patients who received antibody and 97.73±1.27 for patients who did not receive antibody. There was no significant difference in the baseline investigations carried out on both groups except for HbA1c which was higher in the antibody administered group (Table 4).

Table 3: Duration of diabetes mellitus.

Antibody	Mean duration of diabetes mellitus	Standard deviation	P value
Yes	8.74	7.89	0.514
No	8.06	6.64	
Total	8.39	7.27	

It was noticed that oxygen requirement, mechanical ventilation and death up to 10 days of admission were less among the patients who were administered monoclonal antibody, but it was not statistically significant. Oxygen requirement, and death after 10 days up to 28 days were also less for patients who were administered monoclonal antibody, but it was not statistically significant. There were 2 deaths in the antibody treated patients. One of them was due to complication of cirrhosis liver which the patient already had. Among the patients who did not receive antibody, 4 patients died. Out of the 100 patients who were administered monoclonal antibody, 94 were stable after 10 days and 93 were stable after 28 days. Whereas among patients who were not administered monoclonal antibody, 88 patients were stable at 10 days and 91 were stable at 28 days. Oxygen requirement up to 10 days was significantly lower in the vaccinated patients compared to unvaccinated patients (Table 5).

Table 4: Investigations at the time of admission.

Investigation	Antibody	No antibody	P value
Haemoglobin (g/dl)	12.85±9.22	12.23±1.77	0.547
Total count (cells/mm^3)	7152±2835	7085±3335	0.886
Platelet count (10^3 cells/mm^3)	272±118	266±140	0.736
Urea (mg/dl)	30.86±33.25	27.95±17.48	0.479
Creatinine (mg/dl)	1.46±3.65	0.96±0.56	0.220
AST (IU/l)	36.98±25.78	33.63±15.74	0.312
ALT (IU/l)	32.65±29.65	33.54±20.37	0.822
CRP (mg/l)	28.87±41.31	28.26±34.67	0.920
GRBS (mg/dl)	291.44±129.01	265.78±113.21	0.140
HbA1c (%)	9.87±3.01	8.92±2.38	0.038

Table 5: Outcome of the patients.

Outcome	Antibody (n=100) %	No antibody (n=100) %	P value	Vaccinated (n=147) %	Unvaccinated (n=53) %	P value
O_2 requirement up to 10 days	6 (6)	12 (12)	0.138	9 (6.12)	9 (16.98)	0.018
ICU stay up to 10 days	2 (2)	2 (2)	1.00	2 (1.36)	2 (3.77)	0.286
Mechanical ventilation up to 10 days	0	1 (1)	1.00	0	1 (1.88)	0.265

Continued.

Outcome	Antibody (n=100) %	No antibody (n=100) %	P value	Vaccinated (n=147) %	Unvaccinated (n=53) %	P value
Death up to 10 days	0	1 (1)	1.00	0	1 (1.88)	0.265
Stable up to 10 days	94 (94)	88 (88)	0.138	138 (93.87)	44 (83.01)	0.018
Hospital stays after 10 days up to 28 days	6 (6)	7 (7)	0.774	8 (5.44)	5 (9.43)	0.312
Oxygen requirement after 10 days up to 28 days	2 (2)	5 (5)	0.248	4 (2.72)	3 (5.66)	0.385
ICU stay after 10 days up to 28 days	2 (2)	2 (2)	1.00	2 (1.36)	2 (3.77)	0.286
Mechanical ventilation after 10 days up to 28 days	1 (1)	1 (1)	1.00	2 (1.36)	0	1.00
Death after 10 days up to 28 days	2 (2)	3 (3)	0.651	4 (2.72)	1 (1.88)	1.00
Stable after 10 days up to 28 days	93 (93)	91 (91)	0.602	137 (93.19)	47 (88.67)	0.299

DISCUSSION

This study was conducted during the period of delta variant surge in Kerala. This observational study evaluated the oxygen requirement, mechanical ventilation, intensive care unit (ICU) stay, and mortality in mild COVID-19 patients who were on casirivimab and imdevimab. Majority of the patients were vaccinated either with a single dose or double dose of the vaccine. Systemic hypertension followed by coronary artery disease was the most commonly associated comorbidities in our study. In another study conducted in India, systemic hypertension followed by rheumatologic diseases were the most common comorbidities in diabetic patients.[8] Zhufeng et al in a systematic review found that systemic hypertension and diabetes are the major comorbidities in COVID-19 patients.[9]

The recovery trial was a multicentre randomized control trial evaluating the efficacy and safety of casirivimab 4 gm and imdevimab 4 gm on patients above 12 years of age admitted in hospital with clinically suspected or laboratory confirmed SARS-CoV-2 infection. They found that the 28-day mortality was significantly low in patients who received monoclonal antibody combination of casirivimab and imdevimab and were seronegative at baseline but no mortality benefit was seen in patients who were seropositive. In that study, 8% of the participants were vaccinated with at least a single dose of COVID-19 vaccine.[10] In a retrospective study conducted at Mayo clinic on 696 patients who were given casirivimab-imdevimab, it was seen that the all-cause mortality was significantly lower in the group that received the antibody as compared to the group that did not receive antibody. Similarly in that study, the all-cause ICU admissions were low in the casirivimab-imdevimab treated group but it was not significant. In their study 4 patients who did not receive antibody died and only one patient who received antibody died.[11] Similarly in our study also, total of 4 patients died in the control group and 2 patients died in the antibody treated group. In another study conducted by Ganesh et al between November 2020 and February 2021, it was seen that casirivimab-imdevimab treated patients had lesser rates of all cause and COVID related hospitalizations when compared to bamlanivimab monotherapy. There were 3 deaths among the 849 patients who were treated with casirivimab-imdevimab.[12] As per the state government guidelines prevailing at the time of our study, all symptomatic patients with comorbidities or age more than 60 years were admitted to hospitals/COVID treatment centres even if there was no fall in oxygen saturation. So casirivimab-imdevimab was administered to hospitalised patients at the time of admission, and hospitalisation rate following antibody administration was not studied. However, the rate of hospitalisation/rehospitalisation after 10 days of admission was studied and it was not significantly different between the two groups. In a study conducted at Mayo clinic during the SARS-CoV-2 delta surge, it was seen that the rate of hospitalization was significantly lower in both vaccinated and unvaccinated patients who were treated with casirivimab-imdevimab. They also found that the proportion of patients who developed hypoxia was lower among patients who received the antibody cocktail.[13]

In our study there was no significant difference between the two groups in terms of oxygen requirement, ICU stay and need for mechanical ventilation. This could probably be because of the effect of vaccine which reduces these end points. Aneesh et al in a retro-prospective study showed that need for mechanical ventilation and high flow oxygen requirement were significantly low in casirivimab-imdevimab treated patients when compared to patients with standard treatment.[14]

There was a case of anaphylaxis in one of the patients who received the drug and it was promptly treated. We recommend giving casirivimab-imdevimab at hospital setup where adequate facilities for resuscitation are available. No anaphylaxis or serious side effects was seen in another study conducted in India with a small sample size of 29 patients.[15]

CONCLUSION

Even though the oxygen requirement and mortality were lower among patients treated with casirivimab-imdevimab, it was not statistically significant. No other

studies have been carried out yet to find the effectiveness of casirivimab-imdevimab on diabetic patients with COVID-19. More randomised studies with higher sample size are required to prove the efficacy of casirivimab-imdevimab on diabetic patients.

ACKNOWLEDGEMENTS

Authors would like to thank all the staff of Kinfra COVID Hospital for their help in data collection. They would also like to thank Dr. Reshma Rajan for helping in data analysis.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Bhagyanath T, Remitha KR, Akshay CR, Aswin P, Deepak S, Jithesh R. Effect of casirivimab-imdevimab on mild COVID-19 patients with diabetes in reducing oxygen supplementation at 28 days: an observational study. Int J Res Med Sci 2022;10:1983-7.