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A RETROSPECTIVE COMPARATIVE STUDY ON THE OUTCOME OF CASIRIVIMAB -IMDEVIMAB ANTIBODY COCKTAIL TREATMENT IN COVID-19 PATIENTS

[1]Dr. Reshma T. S. PHARM D., [2]Dr. Praise Mariam Abraham PHARM D., [3]Dr. Swetha Joju MBBS, *[4]Dr. Hari Lakshmanan P. MD, [5]Dr. Siby Joseph PhD, [6]Dr. Muhammed Jasim Abdul Jalal DNB, [7]Dr. Mohammed Iqbal MBBS, MRCP UK, FRCP(London), FRCP(Edin), FRCP(Glasgow), [8]Dr. Joseph K. Joseph MD

[1,2&5]Department of Pharmacy Practice, St. Joseph's College of Pharmacy, Cherthala, Kerala-688524, India.
[3&4]Department of Pulmonary Medicine VPS Lakeshore Hospital Kochi, Kerala, India.
[6&8]Department of Internal Medicine VPS Lakeshore Hospital Kochi, Kerala, India.
[7]Department of Internal Medicine VPS Lakeshore Hospital Kochi, Kerala, India.

***Corresponding Author: Dr. Hari Lakshmanan P. MD**

Department of Pulmonary Medicine VPS Lakeshore Hospital Kochi, Kerala, India.

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ABSTRACT

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus which causes respiratory illness. Monoclonal antibodies have been widely used as a prophylaxis or treatment for managing this viral infection. Our research aims to compare the outcome of covid patients who were treated with and without Antibody Cocktail therapy. This will help physicians to get an insight into antibody cocktail therapy in covid patients in the Indian population.The research shows that antibody cocktail treatment is associated with faster remission of covid symptoms and provides up to 3 months of covid free interval in the Indian population. But it is indifferent to the development of post covid symptoms However the severity is found to be less in the test group compared to the control group.

KEYWORDS: Covid 19, Antibody Cocktail Therapy, Regen Cov.

INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. A greater proportion of people infected with the virus will undergo mild to moderate respiratory illness.[1] Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein has been proclaimed to have a clinical prerequisite in treating SARS-CoV-2 infection. The antedated activity of the different anti-SARS-CoV-2 mAb therapies varies greatly depending on the circulating variant.[2] Monoclonal antibodies have been denoted to be safe and effective in managing viral infections when used for prophylaxis (respiratory syncytial virus) or treatment (Ebola virus disease). These two man-made antibodies are termed Casirivimab and Imdevimab.[3] Adult and pediatric patients of age 12 years and above, with mild to moderate COVID-19, weighing at least 40 kg, who are confirmed to have been infected with the disease and who are at high risk for progressing to severe disease and do not require oxygen are to be treated with antibody cocktail (Casirivimab and Imdevimab).[4] Phase 3 trial of Casirivimab and Imdevimab demonstrated better results on high-risk COVID-19 patients, minimized the risk of hospitalization and mortality by 70%, and reduced the coronavirus symptoms by 4 days. The authorized combined dosage of the antibody cocktail is 1200 mg where, 600 mg of Casirivimab and 600 mg of Imdevimab, provided together by intravenous (IV) infusion or subcutaneous route as soon as possible after the positive viral test for SARS-CoV - 2 and within 10 days of symptoms onset.[5,6]

SARS-CoV-2 infection is initiated by binding the viral transmembrane spike glycoprotein to angiotensin-converting enzyme 2 on the surface of host cells. The receptor-binding domain of the spike glycoprotein is the main target for neutralizing antibodies. The two non-competing, high-affinity human IgG1 anti-SARS-CoV-2 monoclonal antibodies, bind specifically to the receptor binding domain of the spike glycoprotein of SARS-CoV-2, hindering the viral entry into host cells. A combination of antibodies that bind to non-overlapping epitopes, rather than a single antibody, is expected to lessen the likelihood of loss of antiviral activity due to naturally circulating viral variants or the spread of escape mutants under drug pressure.[3] Its direct bind would neutralize the antigen and stimulate anti-body mediated phagocytosis. The growth of drug-resistant virus strains would be minimized by using two antibodies together instead of one alone. These two IgG1 anti-SARS-CoV-2 monoclonal antibodies are given emergency use authorization by the US Food and Drug Administration-Federal Agency (FDA), European Medical Agency (EMA), and Central Drug Standard Control Organization (CDSCO) for ceasing the progression of COVID-19. As

per recent studies performed by the pharma company that developed this cocktail, those who received the injection were 81% less likely to become ill with COVID-19 than those who received a placebo.[7] While vaccines remain the best approach to prevent COVID-19, mAbs could potentially aid certain vulnerable populations before or after exposure to SARS-CoV-2, such as the unvaccinated or newly vaccinated high-risk patients.[8]

MATERIALS AND METHODS

Study settings

The retrospective comparative study on Antibody Cocktail therapy was carried out in the covid treatment unit of VPS Lakeshore Hospital Kochi, Kerala. It is a 650 bedded multi super-specialty hospital with over 30 clinical departments.

Study duration

July 2021 – January 2022.

Inclusion criteria

- Patients of either gender.
- Patients who tested positive for covid-19 by ANTIGEN/TrueNat/RT-PCR /CB-NAAT tests and meet eligibility criteria for cocktail therapy as per ICMR recommendations.
- Eligibility criteria for cocktail therapy.
- OP patients and selected IP patients with mild covid who were admitted for other disease indications.
- Chronic kidney disease stage with eGFR <60ml/min especially in those on MHD.
- Diabetes mellitus [HBA1C >10] or diabetes with end-organ damage.
- Chronic liver disease
- Immunocompromising conditions.
- Currently receiving immunosuppressive treatment
- Cardiovascular disease
- Chronic respiratory diseases.
- Body mass index (BMI) ≥35
- Malignancies with a chance of survival

Exclusion criteria

- Patients with Incomplete data.
- Patients admitted to ICU.
- Patients less than 18yrs of age / Pregnancy.

Study design

The study was conducted after obtaining the approval of the Institutional ethics committee and scientific committee. Patients were randomly selected based on inclusion and exclusion criteria during the study period and were assigned to each study arm.

Sample size

$$n \geq (Z)^2 pq / N^2$$

n = sample size
Z= confidence level at 95% (std value of 1.96)
pq = variance of population
N = allowable error

The sample size was calculated with the help of a statistician, a total of 156 patients were included in the study, 78 patients from each group.

Data collection tool

A specially designed data collection form and Questionnaire were prepared to obtain patient data. Relevant details were also collected from the Medical records and hospital information system, ELLIDER (version 2.1.0.1881).

Data collection and analysis

Patients who received a dose of an intravenous casirivimab-imdevimab cocktail, a combination of two monoclonal antibodies (casirivimab 600 mg and imdevimab 600 mg), were allocated to the test group (n=78). The other COVID-19 patients (n=78) who met the inclusion requirements but did not receive cocktail therapy were allocated to the control group. Both arms were matched with age and commodities. After allocating patients to the Test group and control group the baseline data were subsequently collected through the hospital information system and added to the specially designed data collection form. The details regarding the symptom, treatment, and outcome were collected through telephonic assistance with the aid of a specially prepared questionnaire. After obtaining the telephonic consent the questionnaire was read out to the patient over the phone and the response was recorded. Details collected include vaccination status, covid symptoms and their time of recovery, time for antigen negativity, post covid symptoms and its duration, adverse effect of mAB therapy, and re-covid data. Available sources such as medical records and the ELLIDER information system were also used to obtain the patient's data. The outcome including, Progression to severe disease/hospitalization, Effect on post covid symptoms, and time to recovery were analyzed and compared between the Test group and control group. Adverse events of cocktail therapy were also independently assessed. The collected data were compiled using Microsoft Excel and SPSS (26.0.0.0) and presented using tables and graphs. Calculations of mean, SD, and t-test were done by using statistical software and SPSS. The significance of the study results (<0.05) was assessed using the chi-square test.

OBSERVATION

The study evaluated a total of 156 COVID-19 patients. The sample consisted of 90 (57.7%) males and 66 (42.3%) females. The Mean age of the patients was 56.2 ± 1.34 ranging, from 18 to 87 years. The major comorbidity observed was diabetes and hypertension followed by Dyslipidemia and CAD.

Covid symptoms

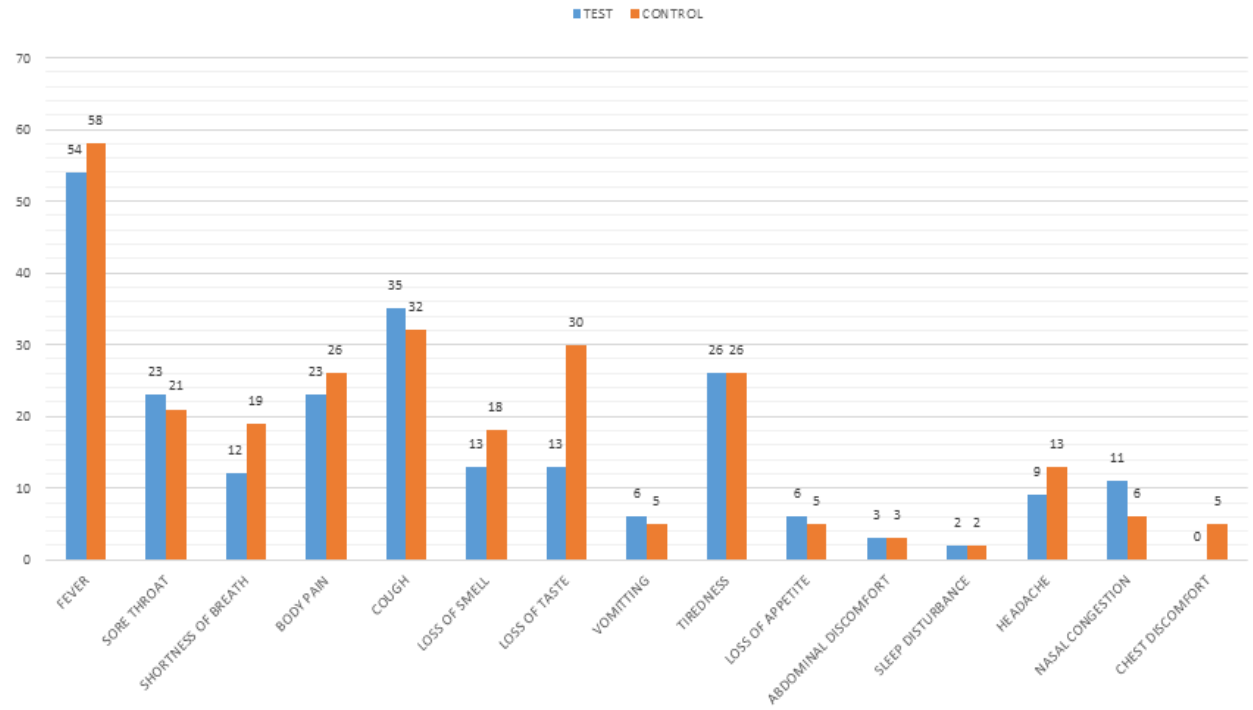

Fig. 1: Covid symptoms in Test and Control group.

The graph shows covid symptoms that were reported by both the Test and Control group. Before receiving any treatment, both groups displayed nearly identical symptoms. In which fever was the most common symptom displayed by both group.

RESULTS AND DISCUSSION

Remission of symptoms in covid-19 patients

Table 1: Remission of symptoms.

Group	Mean (day)	S.D	Difference in mean	n	*t*	*df*	*P*-value
TEST	3.21	2.973	1.564	78	3.129	154	*P*<0.01
CONTROL	4.77	3.263					

In the test group, the average days of symptom remission are 3.21 days compared to the control group which is 4.1 days. The p-value was found to be statistically significant. The symptom remission in the test group is significantly higher than that of the control group. Thus, we can conclude that cocktail therapy is significantly more effective than other conventional therapy for symptom remission in covid-19 patients.

Post covid symptoms

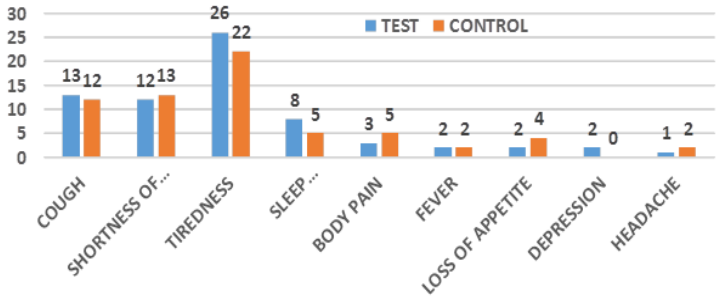

Fig. 2: Post covid symptoms in Test and Control group.

The post covid symptoms reported by the test and control groups were similar. 50% of patients (n=39) in each group had post-covid symptoms with tiredness being the most common one.

Post covid symptom duration

Table 2: Post covid symptom duration.

Post-covid symptoms duration	GROUP		Total	P value
	Test	Control		
No post covid symptom	37	40	77	0.058
< 50 days	23	25	48	
50- 100 days	3	8	11	
>100 days	15	5	20	
Total	78	78	156	

It was paradoxically found that post covid symptoms in the test group lasted longer, more than 100 days. The exact reason for the paradoxical occurrence cannot be explained. While analyzing the selected variables using chi-square test, the p-value was found to be more than 0.05 which indicates that there is no significant association between the duration of post covid symptoms and cocktail therapy. Therefore, cocktail therapy is indifferent to post covid symptoms.

The severity of post covid symptoms

Table 3: Level of care for post covid symptoms.

Level of care	GROUP		Total	P value
	Test	Control		
No post covid symptoms	39 (50%)	39 (50%)	78 (50%)	0.358
No treatment	25 (32.1%)	20 (25.6%)	45 (28.8%)	
IP Care	0 (0%)	1 (1.3%)	1 (0.6%)	
OP Care	14 (17.9%)	18 (23.1%)	32 (20.5%)	
Total	78 (100%)	78 (100%)	156 (100%)	

The 2.6% (n=1) of patients from the symptomatic control group required IP care while none from the test group required IP care. It was interesting to note that more number of patients who had post covid symptoms (32.1%) from the test group compared to (25.6%) of patients from the control group, required no treatment for post covid symptoms. The number of patients who required no treatment for post covid symptoms was greater in the test group (32.6%) compared to the control group (25.6%).

Based on the study, antibody cocktail therapy does not have any significant effect on the development of post covid symptoms. However, the severity is found to be less in the test group compared to the control group.

Similarly, a study carried out by A.P. Joy et al. 2022 revealed that only a restricted number of patients administered the antibody cocktail demonstrated medical attention within 29 days.[9]

Re-covid data

Table 4: Re-covid data in test and control group.

Re-covid	Test	Control	Total	P value
No	63 (80.8%)	66 (84.6%)	129 (82.7%)	0.404
Yes	15 (19.2%)	12 (15.4%)	27 (17.3%)	
Total	78 (100%)	78 (100%)	156 (100%)	

Out of 156 patients, 27 patients experienced recurrent covid, of whom 15 patients belonged to the test group and 12 to the control group. Since the p-value was found to be more than 0.05, the statistical analysis using chi-square, reveals that there is no significant correlation between cocktail therapy and re-covid infection.

The time gap for recovid

Table 5: Time gap for re-covid.

	<= 90 days	>90 days	Total	P value
Test	1	14	15	0.026
	6.7%	93.3%	100.0%	
Control	6	6	12	
	50.0%	50.0%	100.0%	
Total	7	20	27	
	25.9%	74.1%	100.0%	

The data shows that the patients in the control group got re-infected from the coronavirus within a short span of time compared to the test group. About 50% of patients from the control group showed re-infection within 3 months of initial illness, on the other hand, only 6.7% of patients from the test group showed re-infection within that particular time period. Hence, cocktail therapy and covid-free interval show a significant correlation as the p-value is less than 0.05. According to the findings, the cocktail therapy offers the Indian population protection against the COVID virus for up to three months. The antibody cocktail therapy is insufficient to prevent covid re-infection after three months.

Data based on the serology of patients

There were 3.8 % (n=3) of unvaccinated patients in the test group and 10.25% (n=8) in the control group. None of the unvaccinated individuals in both groups had post covid symptoms. But 37.5% (n=3) of unvaccinated patients in the control group developed re-covid whereas none of the patients in the test group developed re-covid.

LIMITATIONS OF THE STUDY

- This is a retrospective study where the data collection is typically constructed utilizing existing databases from healthcare records.
- The outcome measures were assessed using patient recollection.
- One month of the data collection coincides with the omicron variant.

CONCLUSION

Our results demonstrate that the Casirivimab-Imdevimab antibody cocktail treatment is associated with immediate remission of covid symptoms and provides up to 3 months of covid free interval in the Indian population. The cocktail therapy was found to be indifferent to post covid symptoms however the severity is found to be less in the test group compared to the control group.

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