Life Sci. Res. Commn., 2025; 1(1):21-30.
https://lifesci.com.sg

Original Article

Comparing the Efficacy of Remdesivir, Favipiravir, and Casirivimab and Imdevimab on Duration of Hospitalization and ICU Stay of Hospitalized COVID-19 Patients

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ABSTRACT

Objectives: The coronavirus disease of 2019 (COVID-19) disease advances science's ability to address this catastrophe. Additionally, there have been numerous therapeutic advances against COVID-19. Antibody combination against COVID-19, casirivimab and imdevimab, is used in antiviral therapy. Remdesivir and Favipiravir are the two antiviral medications typically used to treat COVID-19. The aim is to compare the effect of remdesivir, favipiravir, and casirivimab and imdevimab on the duration of hospital and ICU stay of COVID-19 patients. **Materials and Methods:** In this study, 265 COVID-19 patients with Polymerase Chain Reaction (PCR) confirmation and indications for antiviral medication were allocated into one of three groups in a ratio of (2:2:1) Remdesivir (REM group); Favipiravir (FAV group), and casirivimab and imdevimab (REG group) respectively. Single-blind non-Randomized Controlled Trial (non-RCT) was the study design. The study's medication is owned by Mansoura University Hospital (MUH). Following ethical permission. The duration of the study was six months from November 2021 to March 2022. **Results:** Casirivimab and imdevimab decrease hospital and ICU stay than favipiravir and remdesivir. **Conclusion:** Although casirivimab and imdevimab lack activity against the omicron variant of COVID-19, they cause better clinical parameters than the standard antiviral drugs.

Keywords: COVID-19, Remdesivir, Favipiravir, Casirivimab and imdevimab, Antivirals.

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Received: 28-11-2023;
Revised: 18-01-2024;
Accepted: 27-02-2024.

INTRODUCTION

COVID-19 definition and severity

COVID-19 is a viral disease that causes a high mortality rate. It is predisposed by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and has infected numerous people worldwide (Okonji *et al*., 2021). According to severity, patients with COVID-19 infection are classified into:

Patients with Mild illness exhibit any of COVID-19's many symptoms (such as coughing, fever, malaise, headache, diarrhea, nausea, and vomiting, loss of smell and taste), but without abnormal chest imaging, shortness of breath, or dyspnea. Patients with moderate disease have lower respiratory disease by imaging or clinical evaluation and have SpO_2 above 94% in normal ambient air at sea level.

Patients with severe illness include those whose SpO_2 on room air at sea level is below 94%, whose PaO_2/FiO_2 is less than 300 mm Hg, whose respiratory rate is more than 30 breaths per minute, or whose lung infiltrates are higher than 50%.

Patients who have multiple organ dysfunction, septic shock, and/or respiratory failure are considered to have a critical illness (NIH, 2019). Since 2020 till now, the COVID-19 epidemic has sparked several efforts to put an end to this problem. By 2021, a few developments in COVID-19 medication have emerged (Umakanthan *et al*., 2021).

Standard and unapproved antiviral agents for COVID-19 Remdesivir is a conventional COVID-19 antiviral that has been approved by the Food and Drug Administration (FDA) for the COVID-19 treatment in severe, moderate, mild and patients who are hospitalized (Aleem and Kothadia, 2021). Other medications with dubious antiviral efficacy include ribavirin, favipiravir, hydroxychloroquine, nitazoxanide, and ivermectin. For the COVID-19 treatment in outpatients (mild and moderate cases), favipiravir became a standard antiviral (De Almeida *et al*., 2020). Development of immunotherapy in management of COVID-19.

Immunotherapy was developed to target viruses by the end of 2020. As shown in Figure 1, active immunotherapy helps the body manufacture more antibodies to viruses than it would otherwise.

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DOI: 10.5530/lsrc.1.1.7

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Direct delivery of antibodies specifically, against a virus or the administration of an antibody-containing preparation, such as plasma, are both examples of passive immunotherapy (Owji *et al*., 2020).

Antibody cocktail against COVID-19

The focus of the current investigation is casirivimab and imdevimab which target the spike glycoprotein to by Angiotensin-Converting Enzyme 2 (ACE2) receptor prevent the virus entry into human cells (Baum *et al*., 2020; Hansen *et al*., 2020). Although these antibodies have demonstrated promising antiviral activity, more research is necessary to establish their value in COVID-19 patients (Weinreich *et al*., 2020).

There is a study that is conducted on this antibody combination. This study has concluded that their efficacy is confirmed, when compared to placebo, in treatment of COVID-19 outpatients in both high (8.0 g of antibodies), or low (2.4 g of antibodies) doses, Efficacy is classified into two types: virological efficacy and clinical efficacy. Virological efficacy is calculated as time-dependent change in viral counts from baseline to day 7, while Clinical Efficacy is measured as offset of symptoms on day 7 and the percentage of COVID-19 cases with ≥ 1 clinically related visit.

This research concluded that the efficacy is higher, and more prominent in outpatients with high baseline viral load, and outpatients who are seronegative (whose immunity is not mature yet to provide antibodies against the virus).

Data for these new antibody combinations, is currently accessible. The Food and Drug Administration (FDA) has granted an Emergency Use Authorization (EUA) for this combination for the treatment and post-exposure prophylaxis of COVID-19 in mild and moderate adults and pediatric outpatients (over 12 years old and weighing more than 40 kg) with a positive COVID-19 swab, and who are at high risk for progressing to severe COVID-19 that causes death or requires hospitalization.

Casirivimab and imdevimab are not approved for use in COVID-19 patients who require an increase in rate of baseline oxygen flow due to COVID-19 in patients requiring chronic oxygen therapy due to causes not related to COVID-19, in patients requiring hospitalization because of COVID-19, and in case of need for oxygen therapy because of COVID-19.

Casirivimab and imdevimab have linear pharmacokinetics, and the half- life of both antibodies is around 30 days. Regarding elimination, neither kidneys nor liver cytochrome enzymes eliminate them (FDA, 2021).

Limitations of the previous studies involve not studying the effect of antiviral agents on inflammatory markers, not using much clinically related outcomes as rate of mortality, study not including hospitalized patients and conducted on only non-hospitalized patients (trials are conducted on outpatients and not inpatients), and short follow up duration of the study. The objective of this research is to evaluate the effectiveness of casirivimab and imdevimab compared to remdesivir, and favipiravir in reducing the duration of hospital and ICU stay in hospitalized critical, severe, or moderate COVID-19 patients.

This research is a large clinical trial because it contains several aims, data, and outcomes to investigate efficacy and safety of Casirivimab and imdevimab and the other two antiviral agents, so this research is divided into five parts (of the same interventions and demographic data) and is published in five stages as described in study protocol due to size limitation in journal publishing.

MATERIALS AND METHODS

Study design (Trial design)

The design of the study is single blind non-RCT (Phase IV Clinical trial).

Patients and population (Participants).

In this study, 265 PCR-verified COVID-19 patients with a need for antiviral medication were included, and they were non-randomly assigned (2:2:1) into 3 groups respectively:

Remdesivir in REM group, Favipiravir in FAV group, and Antibodies cocktail in REG group (casirivimab and imdevimab).

Patients with COVID-19 hospitalized at the University of Mansoura- isolation hospital represented the study's population.

Inclusion criteria

Inclusion criteria involve patients who supplied written informed consent in a computer file (paper was not an effective tool for obtaining consent from patients or relatives to prevent the spread of infection), Patients who weigh more than 40 kg, age greater than 12 years, and PCR-confirmed positivity of patients prior to inclusion, and critical, severe, or moderate COVID-19 disease as defined by WHO.

Exclusion criteria

Exclusion criteria involve history of hypersensitivity after administration of antibodies, prior use of standard antiviral therapy (remdesivir or Favipiravir), current use of controversial antiviral therapy (ivermectin, semipirvir, ribavirin, lopinavir/ritonavir, hydroxychloroquine sofosbuvir, oseltamivir, acyclovir, nitazoxanide, azithromycin, daclatasvir), and patients expected to die within 48 hr Interventions The patients included in this trial were divided into 3 arms (REM, FAV, REG groups) with 2:2:1 ratio and given either remdesivir, favipiravir, or casirivimab and imdevimab, as illustrated in Figures 2 and 3.

REM group patients had been administered Remdesivir

Loading dose on day1: 200 mg diluted in 500 mL 0.9% sodium chloride solution by I.V Infusion.

Maintenance dose on days 2-5 or days 2-10: 100 mg in over 30 min by I.V infusion.

FAV group patients had been administered Favipiravir

Loading dose on day 1: 1600 mg or 1800 mg in Ryle tube or orally/12 hr Maintenance dose on days 2-5 or days 2-10: 600 mg or 800 mg in Ryle tube or orally/12 hr REG group patients had been administered (casirivimab and imdevimab): in a dose of 1.2 g as I.V infusion (single dose) over 30-60 min. The research duration was six months. Outcomes Clinical outcomes that were measured in this part of the research were the duration of hospitalization, and duration of ICU stay.

Sample Size

Using ANOVA or Kruskal-Wallis test in the G*Power program, 246 patients as a sample size would yield not less than 80% power in the need for invasive mechanical breathing with a 95% confidence level and significance level of 0.05. We expanded the sample size to 106 patients in both the remdesivir and Favipiravir groups as opposed to 53 patients in the antibodies cocktail REG group to make up for the projected loss-to-follow-up and to boost the study power. A ratio of (2:2:1) was used because the antibodies cocktail product was only available for roughly 50 COVID-19 patients. Regarding the number of patients who received each medicine, the ratio (2:2:1) was also the most accurate according to number of patients using these medications (Hegazy *et al*., 2023a). The death rate for these three months was obtained using an online system. The typical monthly admission rate at the Isolation Hospital-Mansoura University was 250 cases, so 250 cases would make up our needed sample.

Statistical analysis

A proportion was used to represent categorical variables. The continuous variables were displayed by the mean and standard deviation. In this investigation, the intention-to-treat approach was employed. SPSS version 26 was used to conduct the statistical analysis. As there were three groups to compare, Kruskal-Wallis test or ANOVA was employed to compare the groups. We stated that the level of statistical significance for our tests had a *p*-value of less than 0.05 (Hegazy *et al*., 2023a).

To compare baseline characteristics between the study groups, the ANOVA or Kruskal-Wallis test was performed, depending on the data type (parametric or non-parametric) and the distribution of parametric data (normal or not). The *p*-value for our statistical tests was revealed. *p*- value 0.05 was the threshold for statistical significance (Hegazy *et al*., 2023b).

Logistic regression was used when there were disparities in some baseline characteristics. This made it possible to determine whether the impact of these variables on the study's major outcomes was caused by antiviral medications by excluding the influence of these confounding variables (Hegazy *et al*., 2023c). Regarding the results, we examined the PCR test outcome after hospital discharge and reporting the *p*-value using the Kruskal-Wallis test.

RESULTS

From November 2021 to April 2022, 698 PCR-confirmed COVID-19 patients were assessed for eligibility, were excluded, and 265 patients are included and allocated to three groups (Regn-cov, remdesivir, and favipiravir) in a ratio 1:2:2. There is no loss to follow up and all patients allocated in the study are analyzed for outcomes (intention-to-treat analysis) as shown in flow-chart (Figure 4).

Baseline variables

Table 1 shows the differences between the groups and compares each group's baseline characteristics with the other two groups in case of statistically significant differences between the three groups. Supplementary Figures (S1-S15) show the baseline characteristics between the three groups.

Gender

There was statistically significantly more female in Rem group than Fav group (Hegazy *et al*., 2023b).

Age

Between REG and FAV groups and REM and FAV groups, there is a statistically significant difference, however between REG and REM groups, there is no statistically significant difference Number of comorbidities The difference between REM and FAV groups is statistically significant, however the differences between REG and REM groups and REG and FAV groups are statistically non-significant.

Method of diagnosis

There is a statistically insignificant difference between the three groups Severity of COVID-19 There are statistically significant differences between REG and REM groups and REG and FAV groups are statistically significant, however, the difference between REM and FAV groups is not statistically significant. REG group has less severe cases than REM and FAV groups.

Symptoms number

There are statistically significant differences between REG and REM groups and REG and FAV groups, while there is a statistically non-significant difference between REM and FAV groups (Hegazy *et al*., 2023c).

Table 1: Comparison of baseline characteristics between groups.

		Casirivimab/Imedvimab (A)	Remdesivir (B)	Favipiravir (C)
Age		5 ±16	59±16	6±14
*p*1= 0.006		*p*2= 0.63	*p*3= 0.07	p4=0.07
Gender	Male	24/53	42/106	61/106
	Female	29/53	64/106	45/106
p1 = 0.03		*p*2= 0.501	*p*3= 0.09	p4=0.145
Number of co-morbidities	0	10/53	32/106	22/106
	1	16/53	27/106	19/106
	2	14/53	28/106	33/106
	3	11/53	16/106	18/106
	4	2/53	2/106	10/106
	5	0/53	1/106	3/106
	6	0/53	0/106	1/106
p= 1 0.022		*p* 2=0.207	*p*= 3 0.06	*p* 4 = 0.32
Method of diagnosis	Symptoms	0/53	0/106	0/106
	Labs and Radiology	0/53	0/106	0/106
	PCR confirmed	53/53	106/106	106/106
p 1> 0.9		*p*2 = NA	= *p* 3 NA	*p* 4 = NA
Severity of COVID-19	Moderate	18/53	20/106	20/106
	Severe	27/53	60/106	53/106
	Critical	8/53	26/106	33/106
p= 1 0.024		*p*2= 0.035	*p*= 3 0.475	*p* 4= 0.07
Number of symptoms	2	4/53	2/106	2/106
	3	13/53	6/106	4/106
	4	32/53	97/106	97/106
	5	4/53	1/106	3/106
p= 1 0.001		*p*2= 0.003	*p*3= 0.482	*p*4< 0.01
Heart rate		82±12	85±16	87±17
*P*1= 0.345		*P*2= NA	*p*3= NA	*p*4= NA
Respiratory rate		24±3	25±6	24±5
*p*1= 0.652		p2=NA	*p*3= NA	p4=NA
Body temperature		37±0.49	37±0.45	37±1
p 1=0.288		p2=NA	*p* 3=NA	*p*4= NA
O_2 saturation on O_2 therapy		96±2.4	95±3.8	96±3.3
p1=0.942		*p* 2=NA	*p*=3 NA	p4=NA
O_2 saturation on room air		92±5	87±7	88±7
p1<0.01		*p* 2< 0.01	*p*3= 0.448	*p*4< 0.01
Sodium level		146±30	145 ±20	144±18.5
p1=0.227		p2=NA	*p*3 =NA	p4=NA
Potassium level		3.6±0.5	3.47±0.43	3.7±0.8
p1=0.009		*p*2= 0.52	p3=0.003	*p*4= 0.648

		Casirivimab/Imedvimab (A)	Remdesivir (B)	Favipiravir (C)
Platelets		234±91	211±92	217±102
p 1=0.23		*p* 2=NA	*p* 3=NA	*p* 4=NA
PaO_2 (1)		78±42	56±35	63±39
p1=0.005		*p* 2= 0.001	*p*3= 0.252	*p* 4= 0.2
$PaCO_2$ (2)		37±12	37±14	34.6±12
p1=0.891		*p* 2= NA	*p* 3= NA	*p* 4=NA
PaO_2/FiO_2 (3)		456±27	215±40	290±140
p1=0.01		*p* 2= 0.002	p3=0.136	*p*4= 0.69
GCS (4)	4	0	2	0
	6	0	1	0
	8	0	0	1
	9	0	0	1
	10	0	2	8
	13	0	0	3
	14	1	4	7
	15	52	97	86
p1=0.003		p2=0.202	*p*3= 0.019	p4=0.001

A: Positive PCR-confirmed COVID-19 patients who received casirivimab/Imdevimab, B: Positive PCR-confirmed COVID-19 patients who received remdesivir for 5-10 days, C: Positive PCR-confirmed COVID-19 patients who administered favipiravir for 5- 10 days.p1: *p*-value between A, B, C,p2: *p*-value between A, B,p3: *p*-value between B, C,p4: *p*-value between A, C.**p*-value less than 0.05 is considered a statistically significant difference Arterial Saturation pressure of Oxygen, (2) Arterial pressure of carbon dioxide, (3) a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen, (4) Glasgow coma scale.

Vital signs

There is no statistically significant difference between the three groups in temperature, respiratory rate, and heart rate. Coagulation profile Statistically significant differences exist between REG and REM groups and REG and FAV groups in PT and INR. Blood picture A statistically significant difference between REM and FAV groups in Total Leukocytic Count (TLC) and REG and REM groups and REG and FAV groups in hematocrit. non statistically significant difference exists between the three groups in platelets, lymphocytic counts, and hemoglobin.

Electrolytes Potassium level was statistically significantly higher in FAV group than REM group.

Blood gases

PaO_2 and PaO_2/FiO_2 values were statistically significant higher in REG group than in REM group, and PaO_2 values were statistically significantly higher in REG group than in FAV group.

Regression analysis

As indicated in Table 2, regression analysis was conducted to investigate the impact of baseline characteristics (which demonstrate difference between the three groups) on the study's findings and the potential existence of confounding variables (Hegazy *et al.*, 2023c). After regression analysis, all baseline characteristics, that showed statistically significant difference between the three groups, had no effect on the study outcomes with exception of PaO_2 and PaO_2/FiO_2.

The effect of interventions on outcomes of the study

If there are statistically significant differences in the clinical outcomes between the three groups, it is shown in Table 3 along with a pairwise comparison of the clinical outcomes between each pair of groups.

Supplementary Figures (S16-S26) show these outcomes across the three groups.

The effect on platelet counts

Statistically significant differences existed between REG and FAV groups and REM and FAV groups in platelet count on days 3, 7.

The effect on oxygen pressure in blood

There were statistically significant differences existed in PaO_2/FiO_2 on day 3, 7, 14 between REG and REM groups and REG and FAV groups

The effect on consciousness level

A statistically significant difference in GCS on day 3 existed between REG and FAV groups and REM and FAV groups and on day 7 between the three groups. The effect on duration of

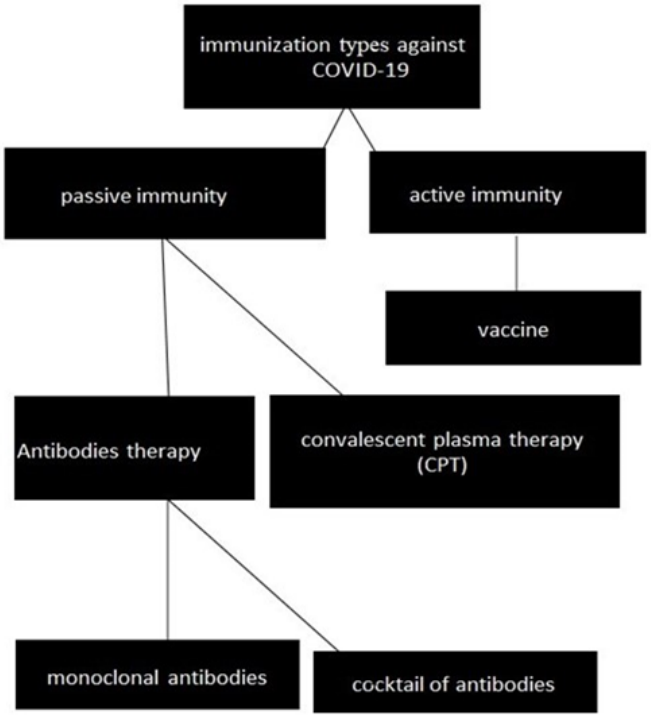

Figure 1: Types of immunization against COVID-19.

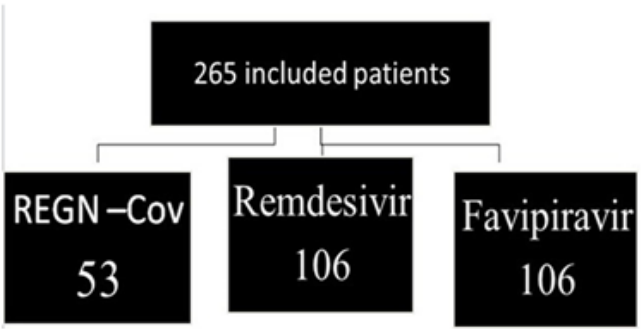

Figure 2: Number of the included patients in the three groups.

hospitalization A statistically significant difference in duration of hospitalization exists between REG and REM groups.

The effect on duration of ICU stay

There were statistically significant differences in duration of ICU stay between REG and REM groups and REG and FAV groups.

DISCUSSION

This study compared the efficacy of Reg-Cov (antibody cocktail) with favipiravir and remdesivir in COVID-19 hospitalized patients. There are no similar or related studies to be compared to this study. The gap of knowledge in antiviral treatment of COVID-19 is lacking a comparative study to compare the `safety and efficacy of antiviral agents. So, this research aimed to compare the safety and efficacy between the recent immunotherapy against

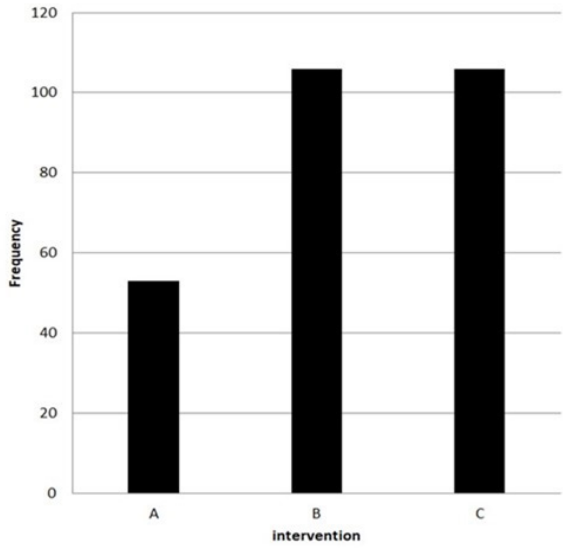

Figure 3: Interventions in each group. A= Casirivimab/ Imdevimab B= Remdesivir C= Favipiravir.

COVID-19 (monoclonal antibodies), and conventional antiviral agents. Although casirivimab and imdevimab lack inhibitory effect against omicron variant.[10] They achieved better clinical outcomes than other antiviral agents.

The effect on platelet counts

In the present study, platelets count on days 3, 7 is statistically significantly lower in Fav group than in Reg and Rem groups. So, it is concluded that favipiravir decreases platelet count and is associated with thrombocytopenia, while remdesivir and regn-cov do not significantly decrease platelet count. No other studies have investigated the effect of regn-cov, remdesivir on platelet count up to now. In contrast to our study, another study had shown that favipiravir had not significantly decrease platelet count (Yaylaci *et al*., 1992).

The effect of interventions on oxygen pressure in blood

PaO_2/FiO_2 value on days 3, 7, 14 is statistically significantly higher in Reg group than in Rem and Fav groups. From these results, it is concluded that Reg group has a more favorable oxygen level in blood than Rem and Fav groups. However, there are no other studies up to now that prove the effect of regn-cov in decreasing oxygen pressure.

The effect of interventions on consciousness level

Our research showed that GCS on day 3 was statistically significantly lower in Fav than in Reg and Rem groups, while GCS on day 7 was statistically significantly higher in Reg group than Rem and Fav groups and in Rem group than Fav group (A>B>C). There are no other studies up to now investigating the effect of all three antiviral agents on GCS.

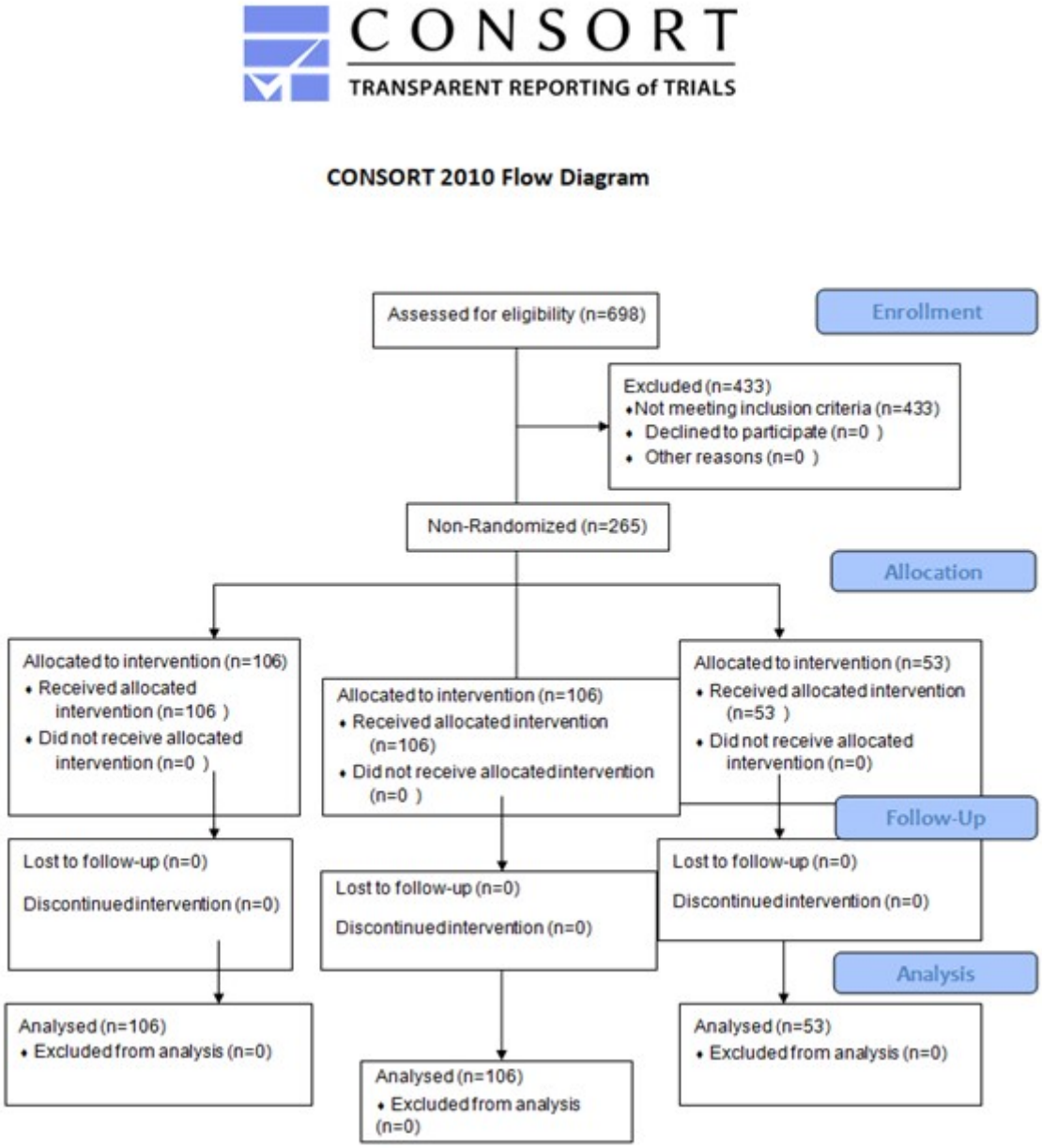

Figure 4: Flow Chart of participants in the research.

The effect of interventions on duration of hospitalization in our study Reg group had statistically significantly less duration of hospitalization than Rem group. These results come in consonance with the findings of Junpei Komagamine *et al.*, who concluded that regn-cov decreased duration of hospital stay (Komagamine *et al.*, 2021). Quratulain Shaikh *et al.*, had shown that remdesivir increased the length of hospital stay (Shaikh *et al.*, 2022), like what proved in our study. Also, favipiravir was associated with an increase in hospital stays as studied by Saleh Al-Muhsen *et al.*, (Al-Muhsen *et al.*, 2022) However, another study, conducted by Abdulrahman Tawfik *et al.*, showed that early use of favipiravir decreased the duration of hospitalization and improved clinical outcomes (Tawfik *et al.*, 2022).

Limitations of this study

The differences in some baseline characteristics between the three groups, single blinding research (non-blinding of interventions to investigators), not applicable to non-hospitalized COVID-19 patients (not including outpatients), and non-randomization of interventions.

Strengths of this study

It is an interventional clinical study (clinical trial), it is the only research to study the differences between these investigational antiviral agents (Regn-cov, Remdesivir, and Favipiravir) up to now and Comprehensive investigation of both the safety and efficacy of COVID-19 antiviral agents.

Table 2: The Effect of confounding variables on duration of hospitalization.

	Unstandardized Coefficients		Standardized Coefficients		t	*p*-value
	B	Std. Error	Beta	Std. Error		
(Constant)	0.80	1.297			0.621	0.535
Age	0.003	0.001	0.098	0.053	1.835	0.098
Gender	0.029	0.044	0.038	0.058	0.652	0.41
Number of co-morbidities	-0.002	0.015	-0.007	0.048	-0.144	0.54
Severity of COVID	-.004	0.036	-0.007	0.059	-0.12	0.82
Heart rate	.001	0.001	-0.008	0.049	-0.16	0.078
Respiratory rate	0.006	0.004	0.066	0.049	1.328	0.09
Temperature	-0.042	0.024	-0.073	0.042	-1.744	0.078
Sodium	-0.001	0.001	-.059	0.057	-1.044	0.87
Potassium	0.004	0.032	0.007	0.053	0.133	0.71
Platelets	0.001	0.001	0.04	0.05	0.086	0.039
PaO_2 (1)	-.002	0.001	-0.191	0.067	-2.841	0.009
$PaCO_2$ (2)	-.005	.002	-0.149	0.052	-2.852	0.007
PaO_2/Fio_2 (3)	0.001	.000	0.175	0.065	2.695	0.005
GCS(4)	0.022	.015	0.073	0.048	1.505	0.2

*p-value less than 0.05 is considered a statistically significant difference (1) Arterial Saturation pressure of Oxygen, (2) Arterial pressure of carbon dioxide, (3) a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen, (4) Glasgow coma scale.

Table 3: The Differences in outcomes between the groups.

		Casirivimab Imdevimab (A)	Remdesivir (B)	Favipiravir (C)
Platelets on day 3		271±97	253±105	226±116
p1=0.047		p2=0.67	p3=0.04	p4=0.036
Platelets on day 7		268±101	243±116	212±123
*p*1= 0.015		p2=0.038	p3=0.027	p4=0.008
Platelets on day14		248±136	216±126	215±126
p1= 0.814		p2=NA	p3=NA	*p*4 =NA
Platelets on day 28		NA	246±113	250±101
B and C		NA	*p*3= 0.157	NA
GCS on day 3	3	0	3	6
	4	0	1	0
	6	0	1	0
	7	0	0	1
	8	0	0	1
	9	0	0	1
	10	0	2	10
	12	0	0	1
	13	1	0	3
	14	1	5	6
	15	51	94	77

		Casirivimab Imdevimab (A)	Remdesivir (B)	Favipiravir (C)
p1<0.01		p2=0.002	p3=0.213	p4<0.01
GCS on day 7	3	0	10	13
	6	0	1	1
	7	0	0	1
	9	0	0	1
	10	0	3	11
	12	0	0	1
	13	0	1	1
	14	0	3	3
	15	39	66	42
p1<0.01		p2= 0.003	p3= 0.011	p4 < 0.01
GCS on day14	3	0	6	4
	10	0	0	3
	13	0	1	0
	14	0	1	2
	15	4	11	7
p1 =0.0189		p2= NA	p3 = NA	p4 = NA
GCS on day28	3	0	2	1
	15	0	2	0
NA		NA	p3= 0.414	NA
PaO_2/FiO_2 on day 3		298 ±211	154 ±139	166±130
p1 < 0.01		p2= 0.478	p3<0.01	p4<0.01
PaO_2/FiO_2 on day 7		320±94	163.55±172.6	178±128
p1<0.01		p2=0.413	p3<0.01	P4<0.01
PaO2/FiO_2 on day 14		398±52	154.7±174	165±98
p1=0.005		p2=0.155	p3=0.001	p4=0.004
PaO_2/FiO_2 on day 28		NA	172±181	53±0
NA		NA	p3=0.48	NA
Duration of hospital stay		8.9±3.5	11.8±6	10.59±5
p1=0.011		p2= 0.054	p3=0.004	p4=0.185
Duration of ICU stay		1.45±1.835	7.6±7.614	7±6
p1<0.01		p2= 0.51	p3<0.01	p4<0.01

Unit of duration: days, **p1:** *p*-value between A, B, C, **p2:** *p*-value between A, B, **p3:** *p*-value between B, C, **p4:** *p*-value between A, C. **p*-value less than 0.05 is considered a statistically significant difference, **A:** Positive PCR-confirmed COVID-19 patients who received casirivimab /Imdevimab as a single dose, **B:** Positive PCR-confirmed COVID-19 patients who received remdesivir for 5-10 days, **C:** Positive PCR-confirmed COVID-19 patients who administered favipiravir for 5- 10 days.

Generalizations of this study

The results of the study are only applicable to COVID-19 hospitalized patients and not applied to outpatients.

CONCLUSION

From the results, although Casirivimab and imdevimab lack antiviral activity against omicron variant of COVID-19, Casirivimab and imdevimab (REG group) achieve less duration of hospital and ICU stay than Remdesivir and Favipiravir groups.

ACKNOWLEDGEMENT

This research is a large clinical trial because it contains several aims, data, and outcomes to investigate the efficacy and safety of Casirivimab and imdevimab and the other two antiviral agents, so this research is divided into five parts (of the same interventions and demographic data) and is published in five stages as described in study protocol due to size limitation in journal publishing.

ETHICS APPROVAL

The protocol of the study was approved by Research Ethics Committee, Ministry of Health, Egypt, 10-2022/18, Research Ethics Committee, Tanta University-Faculty of Medicine, 35039/11/21, and IRB, Mansoura University-Faculty of Medicine. Registration: NCT05502081 at Clinicaltrials.gov.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

COVID-19: Corona Virus induced disease-2019; **PCR:** Polymerase Chain Reaction; **Non-RCT:** Non-Randomized Controlled Trial; **MUH:** Mansoura University Hospital; **WHO:** World Health Organization; **SARS-CoV-2:** Severe Acute Respiratory Syndrome-Corona Virus 2; **SpO_2:** Arterial Saturation pressure of Oxygen; **PaO_2/FiO_2:** A ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; **FDA:** Food and Drug Administration; **ACE2:** Angiotensin-Converting Enzyme 2; **REGN-COV2:** Trade name for Casirivimab AND Imdevimab antibodies combination; **EUA:** Emergency Use Authorization; **I.V:** Intravenous; **S.C:** Subcutaneous; **ICU:** Intensive Care Unit; **GCS:** Glasgow Coma Score; **PT:** Prothrombin Time; **ANOVA:** Analysis of variance.

SUMMARY

Casirivimab and imdevimab (REG group) achieve less duration of hospital and ICU stay than Remdesivir and Favipiravir groups.

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