ORIGINAL ARTICLE

Clinical Trials Study

Comparing the efficacy of regen-cov, remdesivir, and favipiravir in reducing invasive mechanical ventilation need in hospitalized COVID-19 patients

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) pandemic stimulates research works to find a solution to this crisis from starting 2020 year up to now. With ending of the 2021-year, various advances in pharmacotherapy against COVID-19 have emerged. Regarding antiviral therapy, casirivimab and imdevimab antibody combination is a type of new immunotherapy against COVID-19. Standard antiviral therapy against COVID-19 includes Remdesivir and Favipiravir.

AIM

To evaluate the efficacy of antibodies cocktail (casirivimab and imdevimab) compared to standard antiviral therapy in reducing the need for invasive mechanical ventilation (IMV).

METHODS

265 COVID-19 polymerase chain reaction confirmed patients with indication for antiviral therapy were included in this study and were divided into 3 groups (1: 2: 2): Group A: REGN3048-3051 antibodies cocktail (casirivimab and imdevimab), group B: Remdesivir, group C: Favipiravir. The study design is a single-blind non-randomized controlled trial Mansoura University Hospital owns the study's drugs. The duration of the study was about 6 mo after ethical approval.

RESULTS

Casirivimab and imdevimab achieve less need for O_2 therapy and IMV, with less duration of this need than remdesivir and favipiravir.

CONCLUSION
Group A (casirivimab and imdevimab) achieve better clinical outcomes than groups B (remdesivir) and C (favipiravir) intervention groups.

Key Words: Antivirals; Casirivimab and imdevimab; Coronavirus disease 2019; Favipiravir; Remdesivir

Core Tip: This research can benefit the coronavirus disease 2019 (COVID-19) patients by determining the most appropriate antiviral drug according to the case. This study may change the protocol of treatment of COVID-19 patients. Casirivimab and imdevimab achieve better clinical outcomes than remdesivir and favipiravir.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral disease triggered coronavirus 2 that killed a considerable number of individuals worldwide[1]. COVID-19 infection is graded as mild, moderate, severe, or critical[2]. From the beginning of the 2020 year until the present, the COVID-19 pandemic pushes research efforts to discover a solution to this catastrophe. Various improvements in pharmacotherapy against COVID-19 have surfaced as the year 2021 draws to a close[3].

Standard and controversial antivirals used in COVID-19 treatment (remdesivir and favipiravir)

Remdesivir is a conventional antiviral against COVID-19 that has been licensed by the Food and Drug Administration (FDA) for the treatment of mild, moderate, severe, and critical hospitalized COVID-19 patients[4]. Favipiravir, ivermectin, nitazoxanide, hydroxychloroquine, and ribavirin are among other medicines that have exhibited controversial antiviral activity. Favipiravir has become a routine antiviral treatment for mild and moderate COVID-19 outpatients[5].

Immunotherapy advances for COVID-19 treatment

Immunotherapy to target virus antigens has just emerged, with a goal date of the end of 2020[6]. Figure 1 depicts two types of immunotherapies: Passive immunotherapy and active immunotherapy. Passive immunotherapy involves either the direct infusion of produced antibodies directed specifically at viruses or the administration of products containing antibodies, such as plasma. Active immunotherapy, like vaccination, helps the body generate antibodies against viruses [6].

These antibodies have three antiviral targets: antibodies that block virus attachment and entrance, antibodies that inhibit various aspects of the immune system response, and antibodies that limit virus multiplication and transcription. Table 1 lists many groups of antibodies under research for COVID-19 therapy, as well as their targets[6].

Antibodies cocktail (casirivimab and imdevimab) against COVID-19

This study focuses on an antibody cocktail that includes casirivimab and imdevimab (REGN3048-3051). REGN3048 and REGN3051 are monoclonal antibodies that target the spike glycoprotein on the surface of viral particles, blocking viral entry into human cells *via* the angiotensin-converting enzyme 2 receptor[7,8]. They show promising antiviral activity, but more research is needed to investigate their benefit in COVID patients[9].

Previous research[9] on casirivimab and imdevimab had shown that the efficacy of this antibody cocktail is proven in treatment of outpatients with COVID-19 in both high (8.0 g of REGN3048-3051), and low (2.4 g of REGN3048-3051) doses when compared to placebo. Time-weighted average change in viral load from baseline to day 7 (log10 scale) in patient, and clinical efficacy: Percentage of patients with symptoms offset on day 7, and one or more medically related visits.

According to a recent study[9], effectiveness is higher in outpatients whose immune response has not yet matured to make antibodies against virus (seronegative outpatients) and in outpatients with a high baseline viral load.

Data for REGN3048-3051 are now available. The FDA has allowed an Emergency Use Authorization (EUA) for REGN3048-3051 in the post-exposure prophylaxis and treatment of moderate and mild COVID-19 in pediatric and adults outpatients (weighing < 40 kg, and >12 years of age) who have positive polymerase chain reaction (PCR) results of COVID-19 and are at high risk of progressing to severe COVID-19 that needs hospital admission or leads to death[10].

Table 1 Antibodies candidate against severe acute respiratory syndrome coronavirus 2 under investigation by pharmaceutical companies

Antibody	Mechanism	Company	Stage of study/identification method
Canakinumab (ilaris®)	IL-1β inhibitor	Novartis	In clinical stage for several inflammatory diseases including arthritis, periodic fever and lung cancer; repurposed by novartis for COVID-19
Secukinumab (cosentyx®)	IL-17 inhibitor	Novartis	In clinical stage for several autoimmune diseases including psoriasis; repurpose by novartis for COVID-19
TZLS-501	Fully human monoclonal antibody targeting the receptor of IL-6, it binds to both membrane-bound and soluble forms of IL-6R, and rapidly depletes the circulating levels of IL-6 in blood	Tiziana Life Sciences and Novimmune	Preclinical stage
Pritumumab	Fully human IgG antibody targeting vimentin	Nascent Biotech Inc.	Received FDA approve for several carcinoma; Research began for COVID-19
COVID-HIG and COVID-EIG	Hyperimmune polyclonal antibody derived from human plasma or immunized horse	Emergent BioSolutions	Enter clinical trial within 4-5mo
Rcig	Recombinant anti SARS-CoV-2 hyperimmune gamma globulin, polyclonal antibodies	GigaGen	Preclinical stage-Aimed for COVID19 hospitalized patients and prophylaxis in high-risk individuals
Antibody cocktail including REGN3048-3051	Fully human multivalent antibodies against the spike protein isolated from genetically modified mice or recovered COVID-19 patients	Regeneron	Phase 1 clinical trial for Middle East Respiratory Syndrome completed last year; clinical trial for SARS-CoV-2 starts by early summer

IL: Interleukin; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; IgG: Immunoglobulin G; FDA: Food and Drug Administration.
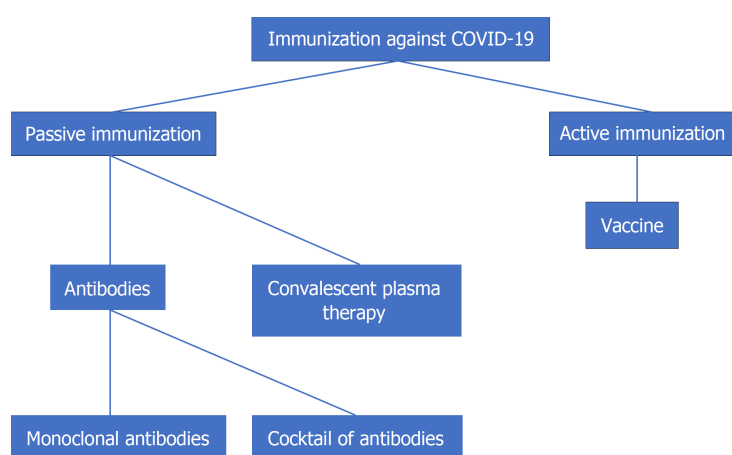
DOI: 10.12998/wjcc.v11.i26.6105 **Copyright** ©The Author(s) 2023.

Figure 1 Immunization approaches against coronavirus disease 2019. COVID: Coronavirus disease 2019.

Casirivimab and imdevimab, on the other hand, are still not approved for use in patients[10] who require an increase in baseline flow rate of oxygen due to COVID-19 in those on chronic oxygen therapy due to non-COVID-19 related comorbidity, require oxygen therapy due to COVID-19, or hospitalized due to COVID-19.

Casirivimab and imdevimab are now licensed experimental antibodies; however, unexpected and serious side events have been recorded with their use[10]. After a single intravenous injection, this antibody combination exhibits linear pharmacokinetics, with half-lives ranging from 25 to 37 d. Casirivimab and imdevimab are not metabolized by liver cytochrome enzymes and are not eliminated by the kidneys[10]. The importance of this study came from that it is the only study that has discussed the use of casirivimab and imdevimab in COVID-19 patients.

The gap of knowledge comes from the limitations of the previous studies including short duration of follow up, non-using much clinically focused outcomes, non-studying antiviral efficacy on long-term in lowering the level of inflammatory markers, and these studies had been conducted on outpatients only and not included inpatients. This research is an extension of published paper that has written by the same authors[11].

Aim of the study

The purpose of this study is to compare the efficacy of a cocktail of antibodies (casirivimab and imdevimab) to standard antiviral medication (remdesivir and Favipiravir) in minimizing the requirement for invasive mechanical ventilation

(IMV) in hospitalized patients with moderate, severe, or critical COVID19.

Patients and population
265 COVID-19 PCR confirmed patients with indication for antiviral therapy were included in this study and were randomized (1: 2: 2) into 3 groups: Group A: Antibodies cocktail (casirivimab and imdevimab), group B: Remdesivir, group C: Favipiravir[11]. A ratio of (1: 2: 2) was chosen as this ratio is the closest to reality according to number of patients who received each drug, and also antibodies cocktail product was available for only about 50 COVID-19 patients. Population in this study was COVID-19 patients hospitalized in isolation hospital-Mansoura university[11]. A computer file containing a written informed consent from included patients was provided[11].

Inclusion criteria
Patient should fulfill all these characteristics to be included: weight not less than 40 kg, age more than 12 years old, PCR-confirmed patients to be positive before inclusion, and moderate, severe or critical COVID-19 disease as defined by WHO [11].

Exclusion criteria
Patient should not have any of the following to be included: Prior use of standard antiviral therapy (remdesivir or favipiravir), history of infusion related reactions or hypersensitivity due to monoclonal antibodies administration, patients expected to die within 48 h, and current use of non-standard antiviral therapy (oseltamivir, hydroxychloroquine, azithromycin, ivermectin, nitazoxanide, acyclovir, ribavirin, semipirvir, lopinavir/ritonavir, sofosbuvir, daclatasvir)[11].

Interventions
Population included in this study was assigned into 3 groups with 1: 2: 2 ratios to receive either casirivimab and imdevimab or standard antiviral therapy (remdesivir or favipiravir) as shown Figures 2 and 3[11].

Group A patients received casirivimab and imdevimab in low-dose 1.2 gm dissolved in 250 mL normal saline administered as single I.V infusion dose within 30-60 min. Group B patients received remdesivir : Loading dose (day 1): 200 mg dissolved in 500 mL normal saline administered by I.V infusion over 60 min. Maintenance dose (day 2-5 or day 2-10): 100 mg dissolved in 250 mL normal saline administered by I.V infusion over 30 min. Group C patients received Favipiravir : Loading dose (day 1): 1800 or 1600 mg administered enterally every12 h. Maintenance dose (day 2-5 or day 2-10): 800 or 600 mg administered enterally every 12 h. standard of care had been given to all patients as guided by Egyptian COVID-19 treatment protocol[11].

MATERIALS AND METHODS

The type of this study is single blind non-randomized controlled trial (non-RCT) and is considered a phase IV clinical trial (post-marketing study) to report efficacy of new medicine[11]. Another resource used to obtain information about casirivimab and imdevimab is fact sheet for health care providers-EUA of casirivimab and imdevimab which provides clinical data about the use of this antibodies cocktail. Endnote citation software was used for references citation[11].

The research protocol was approved by Institutional review board, faculty of medicine, Mansoura University, MS21.11.1737, research ethics committee, faculty of medicine, Tanta University, 35039/11/21, and research ethics committee, ministry of health, Egypt, 10-2022/18. Registry name and registration number: Clinicaltrials.gov, NCT-05502081.

Outcomes
Outcomes include need for IMV, and IMV and oxygen support duration (days). In addition to clinical outcomes measured before and during intervention, patients' characteristics (age, gender) and relevant medical and medication history and current COVID-19 treatment drugs were recorded on admission. Duration of research was about 6 mo from November 2021 to April 2022.

Statistical analysis and sample size
Statistical analysis: Categorical variables were presented as proportion. Continuous variables were presented as mean ± SD. Intention-to-treat strategy was used in this study. Statistical analysis was achieved with SPSS, version 26. ANOVA or Kruskal-Walli's test was used for comparison between groups, as comparison was performed between three groups. We reported the *P*-value for our statistical tests with level of statistical significance is *P* value ≤ 0.05[11].

Regarding baseline characteristics, Kruskal-Wallis or ANOVA test (depending on type of data and the continuous data distribution (normal or not)) was used to compare these characteristics between the study groups. We reported the *P* value for our statistical tests. The level of statistical significance was *P* value ≤ 0.05[11]. In case of existing differences in some baseline characteristics, logistic regression was performed. This allowed studying the effect of these variables on the primary outcomes of the study to exclude the effect of these confounding variables and to ensure the effect on the outcomes is due to antiviral drugs[11]. Regarding the outcomes, we compared the need for IMV and duration of this need using the Kruskal-Walli's test with reporting the *P* value.

Sample size: A total sample sizes of 246 patients would achieve at least 80 % power to detect a risk difference of 0.2 (20%) in the need for IMV with a significance level (α) of 0.05 and 95% confidence level using the ANOVA or Kruskal-Walli's
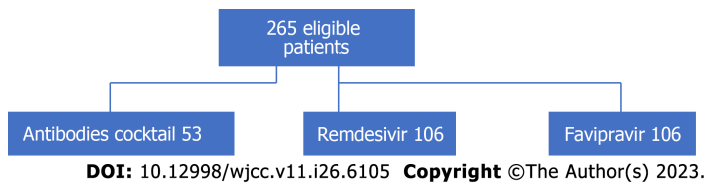
Figure 2 Assignment of the included coronavirus-infected cases at their groups.
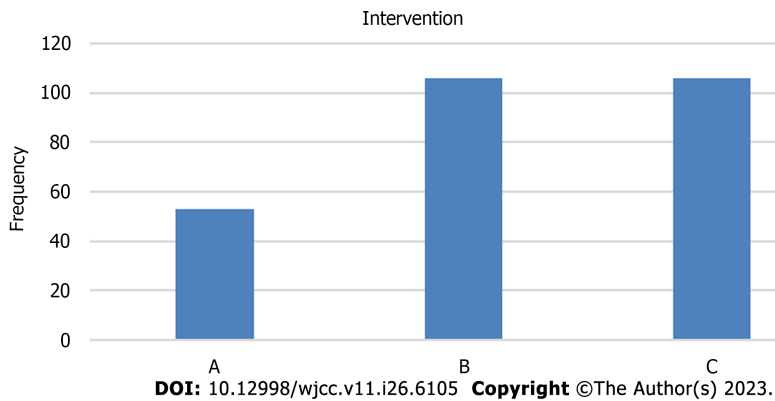
Figure 3 Frequency of interventions in included patients.

test of independent proportion in G∗Power software. To compensate for the estimated loss-to-follow-up and to increase the study power, we increased the sample size to 53 patients in Antibodies cocktail group compared to 106 patients in both remdesivir and favipiravir groups. As antibodies cocktail product was available for only about 50 COVID-19 patients, a ratio of (1: 2: 2) was used. In addition, the ratio (1: 2: 2) is the closest to reality according to number of patients who received each drug[11]. The online system had been used to obtain mortality rate in these three months[11]. The admission rate at Isolation Hospital-Mansoura University was 250 cases per month on average; our needed sample was about 250 cases[11].

RESULTS

All continuous data revealed no normal distribution after statistical analysis with SPSS software. As a result, the Kruskal-Wallis test was used to compare categorical, nominal, and non-normally distributed continuous data between the three groups. Figure 4 represent a flow chart showing the flow of patients in the trial.

Baseline characteristics

Table 2 shows the statistical significance of the differences between the three groups (the first *P* value) in baseline characteristics, as well as a comparison of each two groups (the following three *P* values) in baseline characteristics if there is a statistically significant difference between the three groups. Supplementary Figures 1-9 show the frequencies and distributions of baseline characteristics in the three groups[11].

Age: A-C and B-C have a statistically significant difference, but A-B has a statistically non-significant difference[12].

Gender: There is a statistically significant difference between B and C, but not between A and B or A and C[11].

The total number of comorbidities: There is a statistically significant difference between B and C, but not between A and B or A and C[12].

Diagnosis method: The three groups differ in a statistically insignificant way[12].

COVID-19 severity: There are statistically significant differences between A-B and A-C, but no difference exists between C-B. Group A has statistically considerably fewer severe cases than groups B and C[12].

Number of symptoms: There is a statistically significant difference between A-B and A-C and a statistically non-significant difference between C-B[12].

Antibiotics use: In general, there is no statistically significant difference in antibiotic use across the three groups. In the case of macrolides (azithromycin and clarithromycin), there is only a statistically significant difference between A and C.

Variables	Intervention			
	Casirivimab/Imdevimab (A)	Remdesivir (B)	Favipiravir (C)	*P* value[a]
Age	58.34 ± 16.096	59.30 ± 15.985	65.02 ± 14.261	0.006
B and C				0.07
A and C				0.07
A and B				0.63
Gender				0.03
Male	24/53	42/106	61/106	
Female	29/53	64/106	45/106	
B and C				0.09
A and C				0.145
A and B				0.501
Number of co-morbidities				0.022
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	
B and C				0.06
A and C				0.32
A and B				0.207
Method of diagnosis				1
Symptoms only	0/53	0/106	0/106	
Labs and radiology	0/53	0/106	0/106	
PCR confirmed	53/53	106/106	106/106	
B and C				NA
A and C				NA
A and B				NA
Severity of COVID				0.024
Moderate	18/53	20/106	20/106	
Sever	27/53	60/106	53/106	
Critical	8/53	26/106	33/106	
B and C				0.475
A and C				0.07
A and B				0.035
Number of symptoms				0.001
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	

Table 2 The Significance of differences in baseline characteristics between the three groups

B and C				0.482
A and C				0
A and B				0.003
Antibiotics use				1
Yes	53/53	106/106	106/106	
No	0/53	0/106	0/106	
B and C				0.102
A and C				0.002
A and B				0.075
Macrolide use				0.007
Yes	8/53	8/106	2/106	
No	45/53	98/106	104/106	
B and C				0.102
A and C				0.002
A and B				0.075
Fluroquinolones use				0.106
Yes	41/53	92/106	95/106	
No	12/53	14/106	11/106	
B and C				NA
A and C				NA
A and B				NA
3rd and 4th generation cephalosporin use				0.551
Yes	39/53	86/106	83/106	
No	14/53	20/106	23/106	
B and C				NA
A and C				NA
A and B				NA
Carbapenems use				0.168
Yes	10/53	32/106	22/106	
No	43/53	74/106	84/106	
B and C				NA
A and C				NA
A and B				NA
Piperacillin/tazobactam use				1
Yes	0/53	0/106	0/106	
No	53/53	106/106	106/106	
B and C				NA
A and C				NA
A and B				NA
Amoxicillin/clavulanate use				0.472
Yes	0/53	0/106	0/106	
No	53/53	106/106	106/106	

B and C				NA
A and C				NA
A and B				NA
Cotrimoxazole use				1
Yes	0/53	0/106	0/106	
No	53/53	106/106	106/106	
B and C				NA
A and C				NA
A and B				NA
Linezolid use				0.115
Yes	5/53	12/106	4/106	
No	48/53	94/106	102/106	
B and C				NA
A and C				NA
A and B				NA
Teicoplanin use				0.365
Yes	1/53	0/106	2/106	
No	52/53	106/106	104/106	
B and C				NA
A and C				NA
A and B				NA
Anticoagulant use				0.411
Yes	49/53	101/106	96/106	
No	4/53	5/106	10/106	
B and C				NA
A and C				NA
A and B				NA
Dose of anticoagulant				0.088
Prophylactic	39/53	80/106	81/106	
Therapeutic	14/53	26/106	25/106	
B and C				NA
A and C				NA
A and B				NA
Antiplatelet use				0.012
Yes	5/53	6/106	0	
No	48/53	100/106	106/106	
B and C				0.039
A and C				0.005
A and B				0.262
Steroids use				0.002
Yes	45/53	105/106	98/106	
No	8/53	1/106	8/106	
B and C				0.5

A and C				0.068
A and B				0.001
Additive-therapy use				0.104
Yes	51/53	106/106	105/106	
No	2/53	0/106	1/106	
B and C				NA
A and C				NA
A and B				NA
Paracetamol use				0.019
Yes	50/53	105/106	106/106	
No	3/53	1/106	0/106	
B and C				0.574
A and C				0.006
A and B				0.022
Zinc use				0.003
Yes	4/53	0/106	1/106	
No	49/53	106/106	105/106	
B and C				0.614
A and C				0.004
A and B				0.001
Acetyl cysteine use				0.135
Yes	52/53	106/106	106/106	
No	1/53	0/106	0/106	
B and C				NA
A and C				NA
A and B				NA
Lactoferrin use				0.135
Yes	1/53	0/106	0/106	
No	52/53	106/106	106/106	
B and C				NA
A and C				NA
A and B				NA
Vitamin C use				0.07
Yes	4/53	7/106	1/106	
No	49/53	99/106	105/106	
B and C				NA
A and C				NA
A and B				NA
O_2 therapy use				0
Yes	37/53	99/106	102/106	
No	16/53	7/106	4/106	
B and C				0.497
A and C				0

A and B				0
NP use				0.84
Yes	18/53	35/106	39/106	
No	35/53	71/106	67/106	
B and C				NA
A and C				NA
A and B				NA
SFM use				0.002
Yes	30/53	82/106	87/106	
No	23/53	24/106	19/106	
B and C				0.428
A and C				0
A and B				0.004
MR use				0.003
Yes	8/53	33/106	14/106	
No	45/53	73/106	92/106	
B and C				0.001
A and C				0.783
A and B				0.019
HFNC use				0.202
Yes	5/53	22/106	18/106	
No	48/53	84/106	88/106	
B and C				NA
A and C				NA
A and B				NA
CPAP use				0
Yes	4/53	39/106	36/106	
No	49/53	67/106	70/106	
B and C				0.635
A and C				0.001
A and B				0
IMV use				0
Yes	1/53	29/106	29/106	
No	52/53	77/106	77/106	
B and C				1
A and C				0
A and B				0
Vasopressor use				0.002
Yes	0/53	23/106	18/106	
No	53/53	83/106	88/106	
B and C				1
A and C				0.016
A and B				0.001

Prone positioning				0.75
Yes	0/53	5/106	9/106	
No	53/53	101/106	97/106	
B and C				NA
A and C				NA
A and B				NA
O_2 saturation on O_2 therapy	96.26 ± 2.391	95.86 ± 3.795	96.01 ± 3.130	0.942
B and C				NA
A and C				NA
A and B				NA
O_2 saturation on RA	92.36 ± 4.816	87.62 ± 7.171	88.35 ± 7.006	0
B and C				0.448
A and C				0
A and B				0
PaO_2	77.868 ± 41.79	56.432 ± 35.30	63.294 ± 39.45	0.005
B and C				0.252
A and C				0.2
A and B				0.001
$PaCO_2$	36.689 ± 12.59	37.325 ± 14.60	37.603 ± 12.08	0.891
B and C				NA
A and C				NA
A and B				NA
PaO_2/FiO_2	233.5057 ± 207	156.7358 ± 171	164.142 ± 138	0.01
B and C				0.136
A and C				0.69
A and B				0.002

[a]$P < 0.05$ is considered a statistically significant difference between the compared groups. (1) Comparing between the three groups (A, B, C); (2) A pairwise comparison between every 2 groups (A-B, B-C, A-C), if there is a statistically significant difference between the three groups as presented by the comparing between the three groups (A, B, C). NA: Not available; NP: Nasal prongs; SPM: Simple face mask; MR: Mask reservoir; RA: Room air; PCR: Polymerase chain reaction; HFNC: High-flow nasal cannula; COVID: Coronavirus disease; CPAP: Continuous airway positive pressure; IMV: Invasive mechanical ventilation.
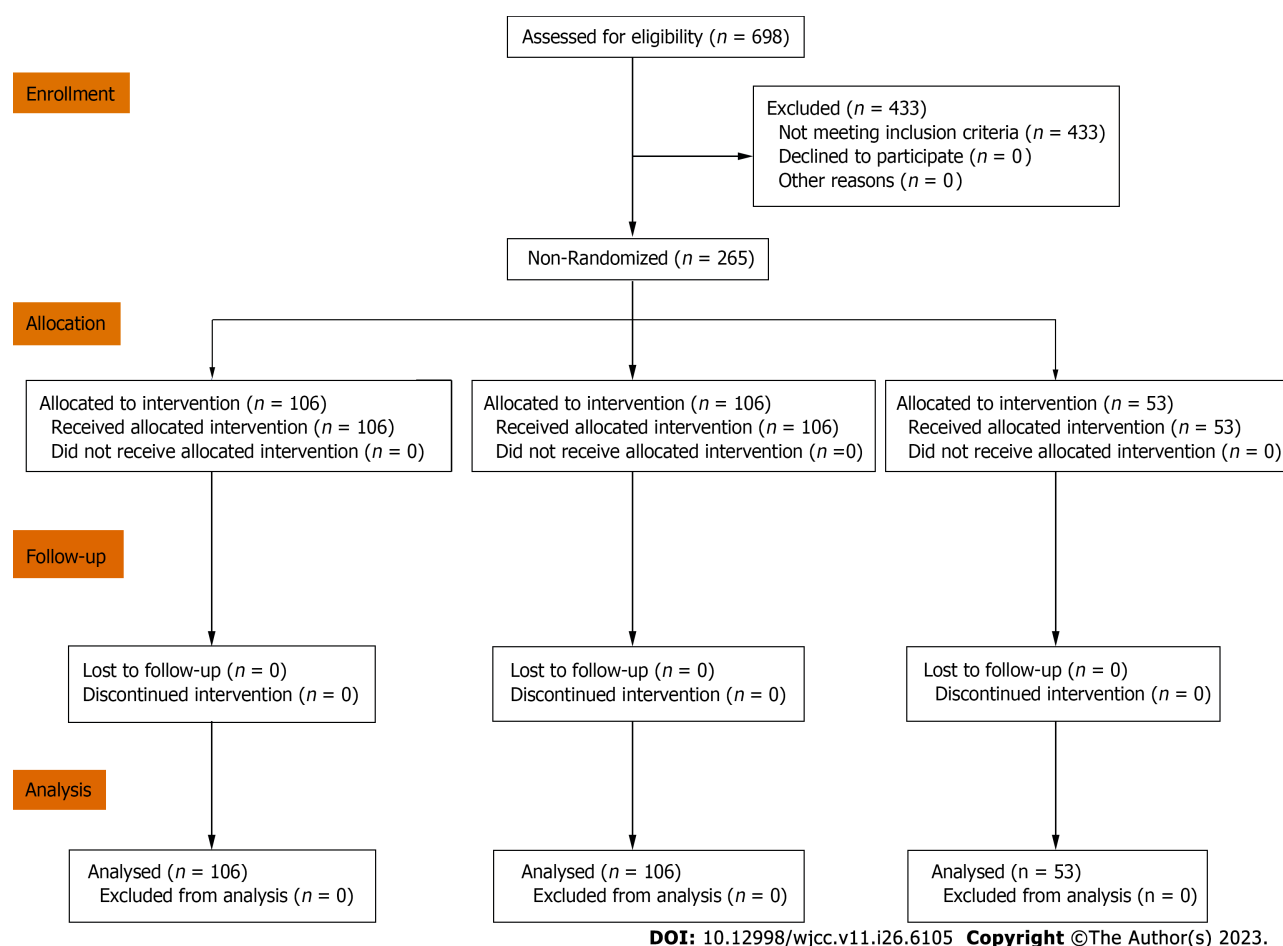
Use of anticoagulants (enoxaparin, heparin, rivaroxaban): In terms of anticoagulant use, whether preventive or therapeutic dose, there is a statistically insignificant difference between the three groups.

Antiplatelet therapy (aspirin, clopidogrel): There is a statistically significant difference between A and C, but not between A and B and C and B.

Steroids (dexamethasone, prednisolone, and methylprednisolone) usage: A statistically significant difference exists between A and B, but no differences exist between A and C and C and B.

Uses of adjunct therapy (paracetamol, vitamin C, zinc, acetyl cysteine, lactoferrin): Among the three groups, there is a statistically insignificant difference in additive treatment use. Regarding paracetamol and zinc consumption, there is only a statistically significant difference between A-C and A-B.

Use of oxygen therapy: In general, the differences between A-B and A-C are statistically significant, while the difference between C-B is statistically non-significant. In terms of nasal prongs and high-flow nasal cannula use, there is a statistically insignificant difference between the three groups. Regarding the use of a simple face mask (SFM), continuous positive airway pressure, or non-invasive ventilation (NIV), and IMV, there is a statistically significant difference between A-B and A-C. In the use of mask reservoirs (MR), there is a statistically significant difference between B and C.

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                              │ Assessed for eligibility (n = 698) │
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Figure 4 Flow chart of patients in the study. A = casirivimab/imdevimab; B = remdesivir; C = favipiravir.

Use of vasopressors: In terms of vasopressor use, A-B and A-C comparisons show statistically significant differences and C-B comparison shows a statistically non-significant difference. The use of vasopressors is statistically significantly lower in group A than in groups B and C.

Prone positioning: The three groups have a statistically insignificant difference in prone positioning.

Blood gases: There is a statistically significant difference in PaO_2 between A-B and A-C, as well as A-B in PaO_2/FiO_2. In $PaCO_2$, there is a statistically insignificant difference between the three groups.

Regression analysis

Table 3[11] shows how regression analysis was used to investigate the effect of baseline parameters-which reveal a statistically significant difference between groups-on the study outcomes and the likelihood of confounding variables.

Outcomes following intervention in the three groups

Table 4 displays the significance of differences in clinical outcomes between the three groups and also includes a pairwise comparison of clinical outcomes between each two groups if there is a statistically significant difference between the three groups[11]. The distributions and frequency of these outcomes across the three groups are depicted in Supplementary Figures 10-16 in the supporting information.

Influence on blood oxygen pressure: On days 3, 7, and 14, statistically significant differences in PaO_2/FiO_2 exist between A-B and A-C.

IMV need during hospitalization: There is a statistically significant difference in IMV need between A-B and A-C.

Influence on the number of days requiring IMV or O_2 therapy: There is a statistically significant difference in number of days with need for IMV or oxygen therapy between A-B and A-C.

Table 3 The best regression model for studying effects of confounding variables on need for invasive mechanical ventilation

	Unstandardized coefficients		Standardized coefficients		*t*-value	*P* value
	B	Std. Error	Beta	Std. Error		
(Constant)	0.806	1.297			0.621	0.535
Age	0.003	0.001	0.098	0.053	1.835	0.068
Gender	0.029	0.044	0.038	0.058	0.652	0.515
No of co-morbidities	-0	0.015	-0.01	0.048	-0.144	0.885
Severity of COVID	-0	0.036	-0.01	0.059	-0.123	0.903
No of symptoms	0.029	0.033	0.049	0.057	0.854	0.394
Macrolide	-0.03	0.083	-0.03	0.074	-0.362	0.718
Fluroquinolones	0.001	0.068	0.001	0.073	0.02	0.984
Cephalosporin	0.046	0.071	0.052	0.081	0.646	0.519
Carbapenems	0.057	0.07	0.065	0.08	0.818	0.415
Amox/calv	-0.19	0.398	-0.02	0.039	-0.479	0.632
Linezolid	-0.01	0.072	-0.01	0.058	-0.097	0.923
Teicoplanin	-0.2	0.316	-0.03	0.044	-0.636	0.526
Other Antibiotics	-0.03	0.105	-0.01	0.043	-0.274	0.784
Anticoagulant	-0.1	0.099	-0.07	0.067	-1.033	0.303
Prophylaxis/therapeutic	-0.01	0.048	-0.02	0.063	-0.298	0.766
Antiplatelet	-0.03	0.083	-0.02	0.06	-0.34	0.734
Steroids	-0.04	0.078	-0.04	0.065	-0.561	0.576
Additive therapy	0.096	0.12	0.041	0.051	0.803	0.423
Paracetamol	-0.05	0.095	-0.02	0.05	-0.475	0.635
Zinc	-0.1	0.084	-0.06	0.049	-1.21	0.228
Acetylcysteine	-0.03	0.176	-0.01	0.052	-0.151	0.88
Lactoferrin	0.312	0.237	0.092	0.07	1.315	0.19
Vitamin C	0.044	0.072	0.031	0.05	0.615	0.539
Nasal prongs use	-0	0.043	-0.01	0.055	-0.083	0.934
FM use	0.04	0.053	0.046	0.06	0.764	0.446
MR use	-0.03	0.05	-0.03	0.054	-0.538	0.591
HFNC use	0.004	0.05	0.003	0.048	0.071	0.944
CPAP	0.003	0.092	0.004	0.101	0.035	0.972
vasopressor	0.054	0.093	0.042	0.072	0.579	0.563
Prone position	-0.18	0.105	-0.08	0.046	-1.74	0.084
PaO_2	-0	0.001	-0.19	0.067	-2.841	0.005
$PaCO_2$	-0.01	0.002	-0.15	0.052	-2.852	0.005
PaO_2/Fio_2	0.001	0	0.175	0.065	2.695	0.008

$P < 0.05$ mean the baseline characteristic does not affect the study outcomes; $P \geq 0.05$ mean the baseline characteristic can affect the study outcomes.
COVID: Coronavirus disease; FM: Face mask; MR: Mask reservoirs; HFNC: High-flow nasal cannula; CPAP: Continuous airway positive pressure.

DISCUSSION

In this study, casirivimab and imdevimab were compared to remdesivir and favipiravir for treatment in COVID-19 hospitalized patients. There are no comparable treatment comparisons or relevant studies to compare this research to for similarities and differences[11].

Regarding bassline characteristics

The age difference between groups A and B is statistically significant. Group B has statistically considerably more females than group C. The co-morbidities number in group C is statistically considerably higher than in group B. A statistically significant less severe cases exist in group A than groups B and C. Group A has a statistically significantly lower number of symptoms than groups B and C. PaO_2 and PaO_2/FiO_2 values are statistically considerably higher in group A than in group B, and PaO_2 values are statistically significantly higher in group A than in group C. In terms of antibiotic use, there is a statistically insignificant difference between the three groups. Antiplatelet (aspirin) use is statistically significant higher in group A than in group C, while steroid use is statistically significant higher in group B than in group A. The use of O_2 therapy in group A is statistically significant less than groups B and C and O_2 therapy using SFM, NIV, IMV in group A is statistically significant less than groups B and C, while the use of MR as O_2 source is more in group B than group C. the use of vasopressors in group A is statistically significant less than groups B and C. Finally, there is statistically significant more cases in group A who not need O_2 therapy with statistically significant higher O_2 saturation on room air than groups B and C.

Regression analysis

Following a statistical analysis of the baseline characteristics of the three groups' cases, some baseline parameters show statistically significant differences between the three groups. Gender, age, severity of COVID, number of co-morbidities, number of symptoms, usage of antiplatelets, steroids, and zinc upon admission differ between the three groups[11].

As a result, it is vital to rule out the effect of these variables on the study's outcomes, which are indicated by the necessity for invasive mechanical breathing. As a result, regression analysis was used to investigate the influence of these variables on the study's outcome (need for IMV). Regression analysis showed that all baseline differences between the three groups did not affect the research outcome (IMV need).

Regarding the outcomes after intervention in the three groups

Effect on oxygen pressure in blood: PaO_2/FiO_2 values on day 3, 7, 14 are statistically significant lower in groups B and C than group A. From these results, it is concluded that group A has more favorable oxygen level in blood than groups B and C.

Need for IMV during hospitalization: Group A has statistically significant lower need for IMV than groups B and C.

Effect on number of days in which there is need for IMV or oxygen therapy: Group A has statistically significant less duration with need for O_2 therapy or IMV than groups B and C.

The study's limitations include non-blinding of drugs, non-randomization of antiviral agents between included patients, applicable only on hospitalized COVID-19 patients (not outpatients), and baseline characteristics differences across the groups. This study's generalizability is limited to COVID-19 hospitalized patients and does not include COVID-19 outpatients.

CONCLUSION

Casirivimab and imdevimab achieve less need for O_2 therapy and IMV, less duration of this need than remdesivir and favipiravir. So, Casirivimab and imdevimab achieve better outcomes than remdesivir and favipiravir.

Table 4 The Significance of differences in baseline characteristics between the three groups

Variables	Intervention			P value[a]
	Casirivimab/Imdevimab(A)	Remdesivir (B)	Favipiravir (C)	
PaO_2/FiO_2 on day 3	298.57 ± 211.3	154.14 ± 138.9	166.96 ± 130	0
B and C				0.478
A and C				0
A and B				0
PaO_2/FiO_2 on day 7	320.62 ± 93.64	163.55 ± 172.6	178.59 ± 138	0
B and C				0.413
A and C				0
A and B				0
PaO_2/FiO_2 on day 14	389.75 ± 51.93	154.67 ± 174	165.2 ± 98.87	0.005
B and C				0.155
A and C				0.022
A and B				0.001
PaO_2/FiO_2 on day 28		172.75 ± 181	53 ± 0	0.48
B and C				NA
Need for IMV				0.005
Yes	1/53	22/106	22/106	
No	52/53	84/106	84/106	
B and C				1
A and C				0.003
A and B				0.003
Duration of need for O_2 therapy and IMV	3.72 ± 3.527	9.2 ± 7.107	7.46 ± 5.077	0
B and C				0.119
A and C				0
A and B				0

[a]$P < 0.05$ is considered a statistically significant difference between the compared groups. (1) Comparing between the three groups (A, B, C); (2) A pairwise comparison between every 2 groups (A-B, B-C, A-C), if there is a statistically significant difference between the three groups as presented by the comparing between the three groups (A, B, C); NA: Not available. IMV: Invasive mechanical ventilation.

ARTICLE HIGHLIGHTS

Research background

Various advances in immunotherapy against coronavirus disease 2019 (COVID-19) have emerged. Casirivimab and imdevimab antibody combination is a type of new immunotherapy against COVID-19. Other antiviral therapy against COVID-19 includes remdesivir and favipiravir.

Research motivation

This study may change the protocol of treatment of COVID-19 patients.

Research objectives

The objectives are to compare the efficacy of antibodies cocktail (casirivimab and imdevimab), remdesivir, and favipravir in reducing the need for invasive mechanical ventilation.

Research methods

The study design is a single-blind non-randomized controlled trial Mansoura University Hospital owns the study's drugs. The duration of the study was about 6 mo after ethical approval.

Research results

Casirivimab and imdevimab cause less need for O_2 therapy, and invasive mechanical ventilation, also they achieve less duration of this need than remdesivir and favipiravir.

Research conclusions

Casirivimab and imdevimab achieve better clinical outcomes than remdesivir, and favipravir.

Research perspectives

COVID-19 catastrophe causes progress in research works to find an end to this crisis. With ending of 2021 year.

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This study is a part of big research that was divided into five parts to enable their publication as it discusses several outcomes (size limitations in journal publication)and one part of this research has been published which is clinical study to compare the efficacy and safety of casirivimab and imdevimab, remdesivir, and favipiravir in hospitalized COVID-19 patients.

FOOTNOTES

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