Faculty of Pharmacy, Tanta University

A Research proposal submitted for partial fulfillment of Master's Degree in Pharmacy

(Clinical Pharmacy)

Study Protocol title

Clinical Study to Evaluate the Possible Efficacy and Safety of Antibodies Combination (Casirivimab and Imdevimab) Versus Standard Antiviral Therapy (Remdesivir and Favipravir) as Antiviral Agent against Corona Virus 2 Infection in Hospitalized COVID-19 Patients

Date: 24/01/2023

Protocol ID: MS.21.11.1737

Introduction:

COVID-19 is an infectious viral disease caused by SARS CoV-2 (sever acute respiratory syndrome-corona virus 2) that has affected large number of people all over the world with high mortality rate (1). COVID-19 infection has been classified(2) as

1- Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.

2-Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level.

3-Severe Illness: Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.

4-Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunctions.

Covid-19 pandemic stimulates research works to find a solution to this crisis from starting 2020 year up to now. With ending of 2021 year, various advances in pharmacotherapy against COVID-19 have emerged (3).

Regarding antiviral drugs used in treatment of COVID-19, remdesivir has approved by Food and drug administration (FDA)(4). Other drugs have shown controversial antiviral activity include: favipravir, ivermectin, nitazoxanide, hydroxychloroquine, ribavirin (5).

Recently, with the end of 2020, immunotherapy to target virus antigen has developed (6).Figure 1 shows two types of immunotherapy include active and passive immunotherapy. Active immunotherapy is to enhance body to produce antibodies against virus as by vaccination. Passive immunotherapy involves direct administration of prepared antibodies acting specifically against virus or administration of product containing antibodies like plasma (6).

In this study, the point of research is antibodies cocktail including REGN3048-3051(**casirivimab and imdevimab)**. There are three targets for these antibodies to work as antiviral including:

1) antibodies that prevent the virus attachment and entry
2) antibodies that inhibit the virus replication and transcription
3) antibodies that hinder various steps of the immune system response

Table 1 includes various types of antibodies under investigation for treatment of COVID-19 and their targets(6).

REGN3048 and REGN3051 are human monoclonal antibodies (mAb) targeting the spike glycoprotein on surface of viral particles thereby preventing viral entry into human cells through the angiotensin-converting 2(ACE2) enzyme receptor (7, 8), and have shown promising antiviral activity and need for further investigation to prove their benefit in COVID patients(9).

Previous study(9) on REGN3048-3051 has mentioned that both efficacy and safety of this antibodies cocktail are proved in COVID-19 outpatients treatment in both low (2.4 g of REGN-COV2), or high (8.0 g of REGN-COV2) dose when compared to placebo, Efficacy is measured as

1-Virologic Efficacy
Time-weighted average change from baseline in viral load through day 7 (log10 scale) in patient.

2-Clinical Efficacy
Percentage of patients with one or more medically attended visits
- Symptoms offset at day 7

Safety is measured as

Percentage of treated patients who experience infusion related and hypersensitivity reactions and incidence of any serious and unexpected adverse effect.

This previous study(9) concluded that efficacy is greater and more obvious in seronegative outpatients (whose immune response is not developed yet to produce antibodies against virus) and with high baseline viral load outpatients.

Now, data(10) is available for these new antibodies cocktails. The U.S. Food and Drug Administration (FDA) has allowed an Emergency Use Authorization (EUA) for casirivimab and imdevimab combination in the treatment and post-exposure prophylaxis of mild to moderate COVID-19 in adults and pediatric outpatients (more than12 years of age and not less than 40 kg) with positive Polymerase Chain Reaction (PCR) results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19 requiring hospitalization or causing death.

In contrast, REGN3048 and REGN3051 are still not authorized for use in patients(10):

-who are hospitalized due to COVID-19, OR

-who require oxygen therapy due to COVID-19, OR

-who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity(10).

Now, casirivimab and imdevimab are approved investigational antibodies, Serious and unexpected adverse effects can occur that not previously reported with their use(10).

Confirmed adverse effects include hypersensitivity and infusion related reactions and the study have showed that there is no difference in safety profile between intravenous (I.V) infusion and subcutaneous (S.C) injection. Data about use during pregnancy and breastfeeding mother is insufficient yet. Also, Data not support any dosage adjustment in hepatic and renal patients (10).

This antibody combination follows linear pharmacokinetics after its single intravenous doses with half-life of about 25 to 37 days for both antibodies. Regarding elimination, this combination is not metabolized by liver cytochrome enzymes ,and not excreted by kidneys (10).

Limitations of previous study include

1-short duration of follow up

2-not used much clinical relevant outcomes like mortality rate

3- Not studied the long term effect of antiviral efficacy in lowering viral load on inflammatory markers.

4- Study performed on non-hospitalized patients and not included hospitalized patients (trial is done only on outpatients and not inpatients)

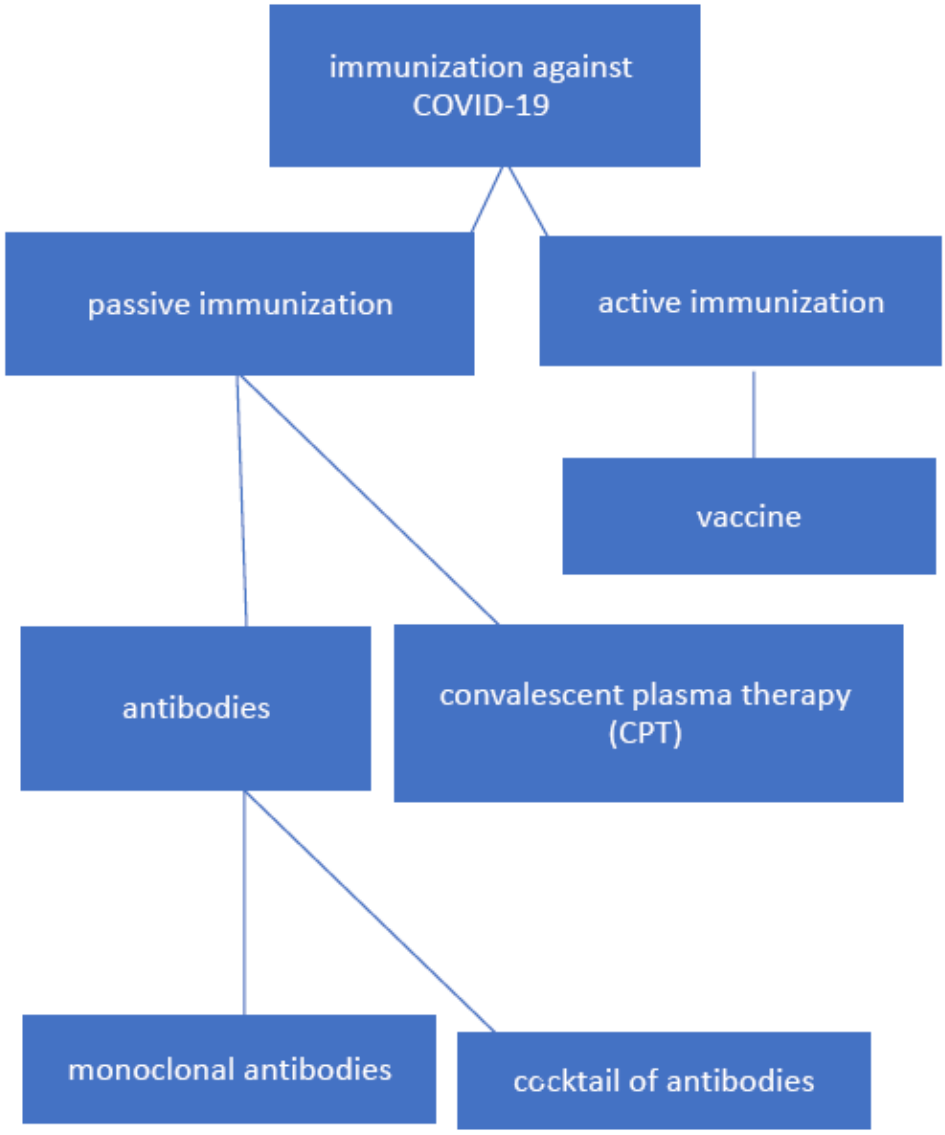

Fig.1: Immunization approaches against COVID-19(6)

Table 1 shows antibodies candidate against SARS-CoV-2 under investigation by pharmaceutical companies(6).

Antibody	**Mechanism**	**Company**	**Stage of study/identification method**
VIR-7831/VIR-7832	-Neutralize highly conserved epitope in s protein -Induce NK-mediated antibody-dependent cell cytotoxicity	VIR biotechnology and GSK	Designed based on S309 (isolated from SARS-Cov patients)
SAB	Anti SARS-CoV-2 fully human poly clonal antibodies	SAB Biotherapeutics	-Antibodies produced in genetically engineered cattle will enter clinical trial by early summer -SAB-301 against MERS passes phase 1 of clinical trial and entered phase II/III
–	Target multiple viral S epitope	ImmunoPrecise	Using B cell Select® and Deep Display® technology
COVID-HIG and COVID-	Hyperimmune polyclonal antibody derived from	Emergent BioSolutions	Enter clinical trial within 4–5 months

EIG	human plasma or immunized horse		
Rcig	Recombinant anti SARS-CoV-2 hyperimmune gammaglobulin, 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 (MERS) completed last year -Clinical trial for SARS-CoV-2 starts by early summer

Aim of the study:

1-To evaluate the efficacy of antibodies cocktail (casirivimab and imdevimab) compared to standard antiviral therapy in reducing 28-day mortality in hospitalized patients with moderate, severe or critical COVID19

2-To evaluate safety of antibodies cocktail (casirivimab and imdevimab) compared to standard antiviral therapy by monitoring of hypersensitivity and infusion related reactions or other significant adverse effects

Population:

265 COVID-19 PCR confirmed patients with indication for antiviral therapy is included in this study and will be randomized (2:1:1) into 3 groups

1- Group A: REGN3048-3051(Antibodies cocktail (casirivimab and imdevimab))
2-group B: Remdesivir
3-group C: Favipravir

Population in this study are patients hospitalized in isolation hospital-Mansoura university.

A computer file containing a written informed consent from included patients will be provided. Paper will not be a tool for providing agreement by patients or their relatives to avoid transmission of infection.

Inclusion criteria

Patient should fulfill all this characteristics to be included:

1-age more than 12 years old.
2-weight not less than 40 kg.
3-Moderate, sever or critical COVID-19 disease as defined by WHO.
4-PCR- confirmed patients to be Positive before inclusion.

Exclusion criteria

Patient should not have any of the following to be included:

1-history of hypersensitivity or infusion related reactions after administration of monoclonal antibodies.
2-prior use of standard antiviral therapy (remedsvir or favipravir).
3-Current use of controversial antiviral therapy (hydroxychloroquine, ivermectin, nitazoxanide, oseltemavir, acyclovir, ribavirine, lopinvir/rotinvir, sofosfbuvir, decltasevir, semipirvir, azithromycin).
4-patients expected to die within 48 hours.

Interventions:

Population included in this study will be assigned into 3 groups with 1:2:2 ratios to receive either antibodies cocktail or standard antiviral therapy (remdesvir, favipravir) as shown in table2 and figures 2 & 3.

Group A patients will receive REGN3048-3051(Antibodies cocktail (casirivimab and imdevimab)) in low-dose regimen 1.2 gm (1200 mg of combined antibodies) diluted in 250 ml 0.9% sodium chloride solution as single I.V infusion over 30-60 minutes.

Group B patients will receive Remdesivir :
Day1 (loading dose): 200 mg (two 100mg vials) diluted in 500ml 0.9% sodium chloride solution infused I.V over 60 minutes
Day 2-5 or Day 2-10 (maintenance dose): 100 mg (one 100mg vial) in 250 ml 0.9% sodium chloride solution infused I.V over 30 minutes

Group C patients will receive Favipravir :
Day 1 (loading dose): 1600 mg (8 tablets) or 1800 mg (9 tablets) orally or in Ryle tube / 12 hours
Day 2-5 or day 2-10 (maintenance dose): 600 mg (3 tablets) or 800 mg (4 tablets) orally or in Ryle tube / 12 hours

Patients will be received standard of care by Physicians, Clinical pharmacist , Nurses and as guided by Egyptian COVID-19 treatment protocol.

Table 2 : The three intervention groups of the study

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	A	53	20.0	20.0	20.0
	B	106	40.0	40.0	60.0
	C	106	40.0	40.0	100.0
	Total	265	100.0	100.0	

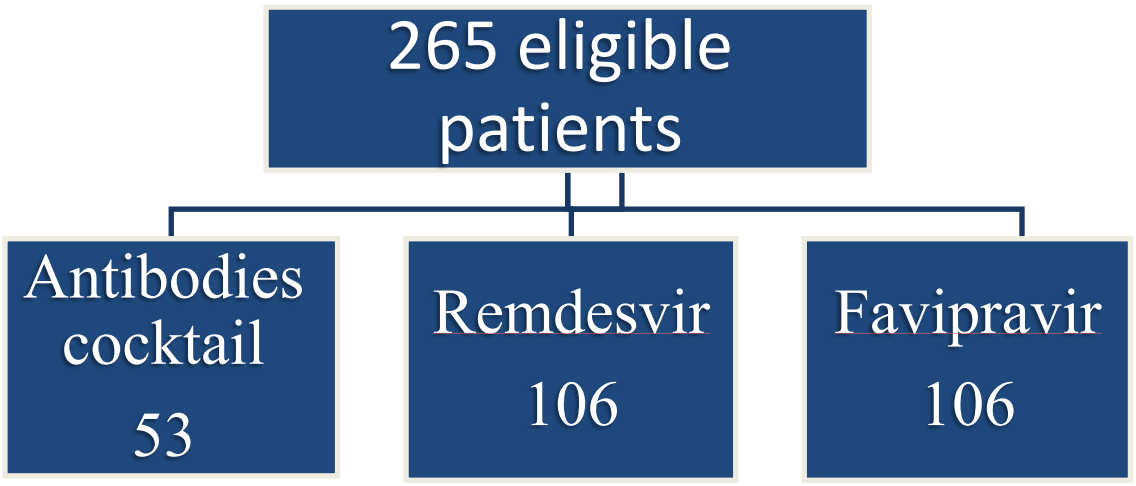

Figure 2: Assignment of the included COVID cases at their groups.

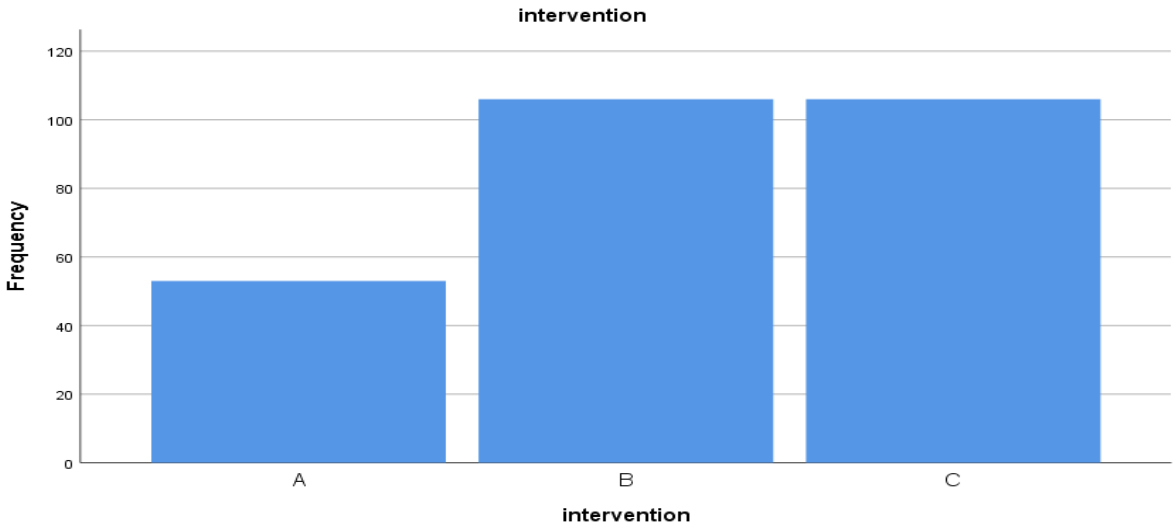

Figure 3: Frequency of interventions in included patients

Method:

The type of this study is single blind non-RCT and is considered a Phase IV Clinical trial (post-marketing study) to report efficacy and safety of new medicine.

We use PubMed search tool to find clinical studies that performed to test efficacy and safety of developed immunotherapy in treatment of COVID-19 with about 4,000 results with focusing on antibodies developed as antiviral against COVID-19 obtaining only 70 results from which REGN-COV2, a Neutralizing Antibody Cocktail is selected with its only one clinical study up to now (REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19) which is published in New England Journal of Medicine on January 21, 2021.

Another resource used to obtain data 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 is used for citation of references.

Outcomes:

Parameters that will be assessed during hospitalization at day 0(baseline), day 3, 7, 14, 28 include:
- C-reactive protein (CRP)
- ferritin
- lactate dehydrogenase (LDH)
- D-dimer
- serum creatinine(S.Cr) and estimated creatinine clearance(CrCl)
- alanine aminotransferase) (ALT), aspartate aminotransferase (AST), albumin, bilirubin

Clinical outcomes measured before & during intervention
1) Primary outcomes
1- 28-days mortality rate (efficacy).
2-PCR test results at end of hospital visit (efficacy).
3-precentage of patients who developed infusion related or hypersensitivity reactions during and after the end of drug infusion and reporting of any Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use that may cause drug discontinuation (Safety).

2) Secondary outcomes
1-Need for invasive mechanical ventilation.
2- Invasive mechanical ventilation and oxygen support duration (days).
3- Time to clinical improvement (defined as 2 points reduction in the WHO disease ordinal progression scale(11&12) or discharge, whatever happens first)
4- ICU and hospitalization length of stay (days).
5- SOFA score(13) on day 0,3,7,14, and 28.
6- COVID19 WHO disease progression score(11&12) from day 0 to day 28.
7- Inflammatory markers including CRP, ferritin, LDH
8- liver and kidney functions

In addition to clinical outcomes measured before and during intervention, Vital signs, glasgow coma score (GCS),complete blood count (CBC), artieral blood gas (ABG) and prothrombin time (PT) is recorded at day0.

Patients' charactrestics(age,gender) and relevant medical and medication history and current COVID-19 treatment drugs will be recorded on admission

Duration of research will be about 6 months from Novmber 2021 to March 2022

Statistical Analysis Plan (SAP):

Intention-to-treat strategy will be used in this study. Intention-to-treat strategy will be used in this study. Statistical analysis will be achieved with SPSS, version 26.

Categorical variables will be presented as proportion and percent. Continuous variables will be presented as mean (standard deviation) for parametric data or as a median (25^{th}-75^{th} percentile) for non-parametric data.

Regarding baseline characteristics, Kruskal-Wallis or ANOVA test (depending on type of data and the continous data distrubation (normal or not)) will be used to compare these characteristics between the study groups. We will report the P-value for our statistical tests with level of statistical significance will be P-value ≤ 0.05.

In case of existiing differences in some basline characteristics, logestic regression will be performed. This allows studying the effect of these variables on the primary outcomes of the study to exclude the effect of these confounding vaiables and to ensure the effect on the outcomes is due to interventions.

Regarding the outcomes, we will compare the 28-day all-cause mortality rate, result of PCR test at hospital discharge and incidence of infusion related or hypersensitivity reactions during and after the end of drug infusion (primary outcome) using the Kruskal-Wallis test with reporting the P-value.

While the secondary outcomes (hospital stay duration, icu stay duration and others) are compared using Kruskal-Wallis or ANOVA test depending on type of data and the distrubation of data (normal or not)

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 28-day all-cause mortality (primary outcome) with a significance level (α) of 0.05 and 95% confidence level using the ANOVA or Kruskal-Wallis test of independent proportion in G*Power software. To compensate for the estimated loss-to-follow-up and increase the study power, we will increase the sample size in both remdesivir and favipravir groups to be 106 patients compared to 53 patients in Antibodies cocktail Group As Antibodies cocktail product is available for only about 50 COVID-19 patients. In addition,the ratio (1:2:2) is the clostest to reality according to number of patients who recieve each drug.

The mortality data was estimated from the average mortality in Augest, Septmper, and Octobar 2021 at the Mansoura University Isolation Hospital among all hospitalized patients. Mortality rate is found to be about 360 cases in these 3 months (120 cases / month). The online system has been used to obtain mortality rate in these three monthes.

The current admission rate at the Mansoura University – Isolation Hospital is 250 cases per month on average; our needed sample is about 250 cases.

Ethical approval:

Ethical approval will be taken from the Research Ethics Committes of Mansoura and Tanta Unversity. Informed consents will be obtained from all participants in this research.Privacy of participants and confidentially of data will be maintined.Benefits of the intervention to the patients outweigh expected risks .Any unexpected risk appered during the course of the research will be cleared to participants and the ethical committee on time.All study procedures will obey the standard of the Declaration of Helsinki (1964) principles.

Data Quality and Safety:

We will collect the data directly into an electronic CRF , no papers are used to collect clinical data to avoid transmission of infection from area of isolation.
Patient confidentiality will be kept before, during and after the study

Publishment of Study results and funding:

We would register protocol and results in Clinicaltrial.gov and aim to publishe this study in peer-review journals.

Funding:
The company of intervention drugs will not support with additional fund or interests.
The investigators declare no relevant conflict of interest

Confilct of interest:
none

IRB, Faculty of medicine, Mansoura university

Informed Consent Form (ICF)

Title of Research	**Clinical Study to Evaluate the Possible Efficacy and Safety of Antibodies Combination (Casirivimab and Imdevimab) Versus Standard Antiviral Therapy (Remdesivir and Favipravir) as Antiviral Agent Against Corona Virus 2 Infection in Hospitalized COVID-19 Patients**
Steps of Research	1. Divide the cases into 3 groups according to antiviral therapy 2 - Follow up cases before, during and after taking doses of medicine while they are in the hospital and after their discharge 3 - Collect clinical data on cases to compare them statistically and obtain results
Duration of Research	6 months after receiving the approval of the scientific committee
Location	Isolation Hospital-Mansoura University
Benefits of Research	1 -to benefit COVID-19 patients by determining the mo appropriate antiviral treatment according to the case 2 - Inform the community of the results of this researc which may change the protocol of treatment of COVID-19 patients
Possible side effects	Some rare allergy symptoms that may have been produced from vein injections. So cases are followed up while taking the meds.

I (who signature below) acknowledge that the researcher has informed me that:

1-Research does not conflict with the values and ethics of society.

2- Emphasizing the confidentiality of the research and my right to leave it unaccountable and without affecting medical care

The name of the participating patient:

Signature of the participating patient:

Signature of the principal researcher:

Date:

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