Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Among close contacts of COVID-19 patients, should casirivimab + imdevimab cocktail be used as post-exposure prophylaxis?

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RECOMMENDATIONS

We suggest the subcutaneous use of casirivimab + imdevimab as day 4 post-exposure prophylaxis for COVID-19 close contacts*, ages 12 years and above weighing at least 40 kilograms, who are at risk for severe disease or hospitalization.** *(Moderate quality of evidence; weak recommendation)*

Consensus Issues:
Despite moderate quality of evidence, the panel decided on a weak recommendation for prophylactic use of casirivimab + imdevimab cocktail given the following factors related to equity: (1) prohibitive cost (PHP 25,000-30,000), (2) potential problems with accessibility, (3) limited supply, (4) EUA mandate last October 2021 specifically allowing its use for treatment only and (5) issues on applicability.

The recommendation is based on a single multi-center, randomized controlled trial that was done in the United States. There is a very limited window to administer the drug therefore, the poor contact tracing and the delayed release of test results are issues in our setting that compromises the applicability of the results of this study. The vaccination status of the participants as well as the prevalent viral strains during the time of the trial were considerations of the panel. While neither of the two were discussed in the study, the study was implemented from June 2020 to March 2021.

*The definition of close contacts is the same as in the Living COVID CPG guidelines.
**This includes the following people: elderly; BMI >25; those with chronic diseases such as hypertension, diabetes, and chronic kidney disease; those who are not expected to mount an adequate immune response to the vaccine due to immunosuppressive therapy or those in an immunocompromised state.

Key Findings

There was 1 randomized controlled trial that investigated casirivimab + imdevimab cocktail as post-exposure prophylaxis for RT-PCR SARS-CoV-2 negative close contacts of COVID-19 patients. The results showed a significant decrease in symptomatic and asymptomatic COVID-19 infection. Among those who developed infection, casirivimab + imdevimab resulted in significant decrease in duration of infection. There was no significant difference in serious adverse events between those given casirivimab + imdevimab and placebo. The overall quality of evidence was rated moderate due to imprecision in 1 critical outcome.

Introduction

COVID-19 hypoxemia has been theorized to be related to an immune hyperresponsiveness to viral infection. With recent studies showing high viral titers among hospitalized patients with hypoxemia, it is hypothesized that treatments that effectively reduce viral load could prevent complications and death resulting from COVID-19 infection.[1,2] One such treatment that has shown favorable effects from in vitro studies is Regeneron or REGEN-COV, an antibody cocktail containing two non-competing SARS-COV-2 neutralizing human IgG1 antibodies (casirivimab [REGN10933], imdevimab [REGN10987]). By targeting the receptor-binding domain of the SARS-CoV-2 spike protein, viral entry into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor is prevented.[3,4]

Review Methods

A systematic search was done from inception until September 1, 2021 using Medline, CENTRAL, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and REGEN-COV or REGN-COV2 or casirivimab. We also looked at the COVID-NMA Living Data registry and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Only randomized controlled trials that compared casirivimab + imdevimab against placebo or standard care for post-exposure prophylaxis were included in this review. No limits were placed on age, COVID-19 severity, and dosing.

Results

A total of 41 related articles were found using MEDLINE but only 1 published article met our inclusion criteria. The same article was found when searching CENTRAL, COVID-NMA initiative, and Google Scholar.

The published study was a multicenter randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of casirivimab + imdevimab in 2 parts and was implemented from June 2020 to March 2021. Part A evaluated the use of casirivimab + imdevimab as post-exposure prophylaxis among healthy, previously uninfected household contacts of patients with RT-PCR confirmed COVID-19 at least 12 years of age. They were tested via SARS-CoV-2 RT-PCR on day post-exposure and if their tests were negative, they were enrolled in the trial. Approximately 30% of the participants had at least 1 risk factor for severe COVID-19 (elderly, BMI ≥ 35, chronic kidney disease, diabetes, immunocompromised disease/treatment). 2.8% of the participants were noted to be of Asian race. The four subcutaneous doses equivalent to 600mg casirivimab and 600mg imdevimab were given to the participants on day 1. Part B included the use of casirivimab + imdevimab as treatment for asymptomatic persons with COVID-19. Only the results of part A (involving 1,505 study participants) were published in this report. The primary outcome was the development of symptomatic, RT-PCR confirmed COVID-19 infection during the 28-day assessment period. The secondary outcomes included the number of patients that developed a high viral load ($\geq 10^4$ copies/mL), duration of symptoms, duration of infection (symptomatic or asymptomatic), development of any RT-PCR confirmed infection (symptomatic or asymptomatic), and adverse events.[5]

The overall quality of evidence was rated moderate due to imprecision in 1 critical outcome (serious adverse events). Appraisal of study quality showed no serious risk of bias in this study. The risk of bias summary is in Appendix 3. The GRADE evidence profile is in Appendix 4.

Contacts of COVID-19 patients given casirivimab + imdevimab as post-exposure prophylaxis had significant decreased risks in the development of symptomatic COVID-19 infection (RR 0.19, 95% CI 0.10-0.35) and in the development of symptomatic/asymptomatic COVID-19 infection (RR 0.34, 95% CI 0.23-0.48) compared to those given placebo. There was also a significant reduction in the number of participants who developed high viral load (≥10^4 copies/mL) in the casirivimab + imdevimab group compared to the placebo group (RR 0.14, 95% CI 0.08-0.26). Among the study participants who developed COVID-19 infection, there was significant decrease in the duration of symptomatic infection (MD -2.0 weeks, 95% CI -2.21 to -1.79) and the duration of infection, whether symptomatic or asymptomatic (MD -1.1 weeks, 95% CI -1.18 to -1.02) in the casirivimab + imdevimab group compared to the placebo group.[5]

Safety

Overall, a significantly lower risk of adverse events was found with casirivimab + imdevimab compared to placebo (RR 0.31, 95% CI 0.24-0.40). The most common adverse effects mentioned were headache and injection-site reactions.

There was no significant difference in serious adverse events in the casirivimab + imdevimab group and the placebo group (RR 0.66, 95% CI 0.30-1.47). The serious adverse events reported were cardiac disorders and other infections. None of these were attributed to the treatment received.[5]

Evidence to Decision

The price for the monoclonal antibody cocktail is said to be about USD 1250 per dose, but can reach up to USD 6000. The cost of casirivimab + imdevimab is currently being subsidized by the US federal government.[6,7] As of October 1, 2021, the Philippine FDA granted Emergency Use Authorization for casirivimab and imdevimab to be used as treatment for mild to moderate COVID-19 in patients aged 12 years and older and weighing at least 40 kg that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe disease.[8]

According to the US FDA EUA Fact Sheet for casirivimab + imdevimab, the drug is best administered via 4 subcutaneous injections in 1 day for post-exposure prophylaxis. The vials should be stored in the refrigerator between 2ºC to 8ºC (36ºF to 46ºF). Once the drug is for use, 4 syringes must be prepared with 25-gauge or 27-gauge needles for subcutaneous injections. The prepared syringes must be administered immediately. If immediate administration is not possible, the prepared syringes must be stored at room temperature up to 25ºC for no more than a total of 4 hours. If refrigerated, the syringes must be allowed to equilibrate to room temperature for approximately 20 minutes prior to administration. The injections must be administered in 4 separate injection sites (thighs, back of the upper arms, abdomen except for 2 inches around the navel and waistline should be avoided). Patients must be monitored clinically for at least 1 hour after administration. There is a black box note indicating that the cocktail must be used with caution for pregnant women.[9]

Recommendations from Other Groups

As of 10 August 2021, the US FDA recently expanded the emergency use authorization for casirivimab + imdevimab to include not only treatment for patients with mild to moderate COVID-19 who are at high risk for progression of the disease, but also for post-exposure prophylaxis among patients at least 12 years old and 40 kg who are considered high-risk for progression to severe COVID-19, not fully vaccinated, or not expected to mount an adequate immune response to the vaccine.[10]

As of 27 October 2021, the IDSA [11] and the Australian guidelines [12] issued a conditional recommendation for the use of casirivimab + imdevimab as post-exposure prophylaxis for those at high risk of progression to severe COVID-19, not fully vaccinated, or those with immunocompromised conditions who may not mount adequate immune responses despite being fully vaccinated. The NIH [13] issued a strong recommendation for the subcutaneous delivery of the cocktail. They also released prioritization guidelines that state that this cocktail should be given to those who will benefit most from it for post-exposure prophylaxis when there are logistical or supply constraints.

There were no recommendations from the WHO guidelines (updated March 2, 2021) on the use of casirivimab + imdevimab as post-exposure prophylaxis for COVID-19.[14]

Ongoing Trials

There are currently 4 ongoing randomized clinical trials on casirivimab + imdevimab, with 3 studies evaluating safety and tolerability of the drug and 1 study evaluating the efficacy and safety of the drug when used post-exposure prophylaxis for COVID-19 (Appendix 5).

References

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[13] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 1 November 2021.

[14] World Health Organization. Drugs to prevent COVID-19. 2 March 2021. Available at file:///Users/Carol/Downloads/WHO-2019-nCoV-prophylaxes-2021.1-eng%20(1).pdf. Accessed 24 September 2021.

Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N=10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (9)					
Benefits	Large (5)	Moderate (4)	Small	Uncertain (1)			• Contacts of COVID-19 patients given casirivimab + imdevimab as post-exposure prophylaxis had significant decrease in the development of symptomatic COVID-19 infection (RR 0.19, 95% CI 0.10-0.35) and in the development of symptomatic/asymptomatic COVID-19 infection (RR 0.34, 95% CI 0.23-0.48) compared to placebo.
Harm	Large	Small (10)	Uncertain				• There were significantly less adverse events in the casirivimab + imdevimab group versus control group (RR 0.31, 95% CI 0.24-0.40). • There was no significant difference in serious adverse events (RR 0.66, 95% CI 0.30-1.47).
Certainty of evidence	High	Moderate (9)	Low (1)	Very Low			• Moderate
Balance of effects	Favors drug (9)	Does not favor drug	Uncertain (1)				• Net potential benefit for prevention of COVID-19 and development of adverse outcomes.

Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (6)	Possibly no important uncertainty or variability (3)	No important uncertainty or variability			
Resources required	Uncertain	Large cost (10)	Moderate cost	Negligible cost or savings	Moderate savings	Large savings	• The price of 1 course of subcutaneous casirivimab + imdevimab is estimated to be $1,250-$6,000. • According to the US FDA EUA Fact Sheet for casirivimab + imdevimab, the vials should be stored in the refrigerator between 2ºC to 8ºC. • Using 25-gauge or 27-gauge needles, subcutaneous injections must be administered in 4 separate injection sites.
Certainty of evidence of resources required	No included studies (4)	Very low (2)	Low	Moderate (3)	High (1)		• Cost is based on news websites (Forbes, PMLive)
Cost effectiveness	No included studies (9)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (4)	Reduced (2)	Probably no impact	Increased (4)			• The US FDA, NIH and IDSA (conditional recommendation) recommend the use of casirivimab + imdevimab as post-exposure prophylaxis for selected populations.
Acceptability	Uncertain (9)	No	Yes (1)				
Feasibility	Uncertain (7)	No (3)	Yes				

Appendix 2a. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (REGEN-COV) OR (REGN-COV2) OR (Casirivimab)	Sep 1, 2021 9:00 AM	41	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 AND (REGEN-COV) OR (REGN-COV2) OR (Casirivimab)	Sep 1, 2021 9:30 AM	11	1
Google Scholar	REGEN-COV AND COVID AND randomized trial	Sep 1, 2021 10:00 AM	74	1
COVID-NMA initiative	REGEN-COV REGN-COV2 Casirivimab	Sep 1, 2021 11:30 AM	1	1
ClinicalTrials.gov	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	Sep 1, 2021 1:00 PM	8	0
Chinese Clinical Trial Registry	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 1:30 PM	0	0
EU Clinical Trials Register	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	Sep 1, 2021 3:00 PM	2	0
Republic of Korea - Clinical Research	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 3:30 PM	0	0

Information Service				
Japan Primary Registries Network/ NIPH Clinical Trials Search	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 4:00 PM	2	0
CenterWatch	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 4:30 PM	4	0
chinaxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 8:00 PM	0	0
Medrxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 8:30 PM	2	0
Biorxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2 AND COVID-19	Sep 1, 2021 9:00 PM	48	0

Appendix 2b. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19 *O'Brien et al. (USA, Romania, Moldova)*	RT-PCR negative close contacts of confirmed COVID-19 patients ages 12 and above (n=1505) <u>Duration of follow-up:</u> Approximately 28 days	EXPERIMENTAL: REGEN-COV MAB Cocktail 1200mg SC (600mg Casirivimab + 600mg Imdevimab) CONTROL: Placebo	PRIMARY: Development of symptomatic, RT-PCR confirmed COVID-19 infection within 28 days SECONDARY: Viral load $>10^4$ copies, duration of symptomatic RT-PCR confirmed SARS-CoV-2 infection, duration of any RT-PCR confirmed SARS-CoV-2 infection whether symptomatic or asymptomatic, development of any RT-qPCR confirmed SARS-CoV-2 infection whether symptomatic or asymptomatic	Randomized, double-blind, placebo-controlled

Appendix 3. Study Appraisal

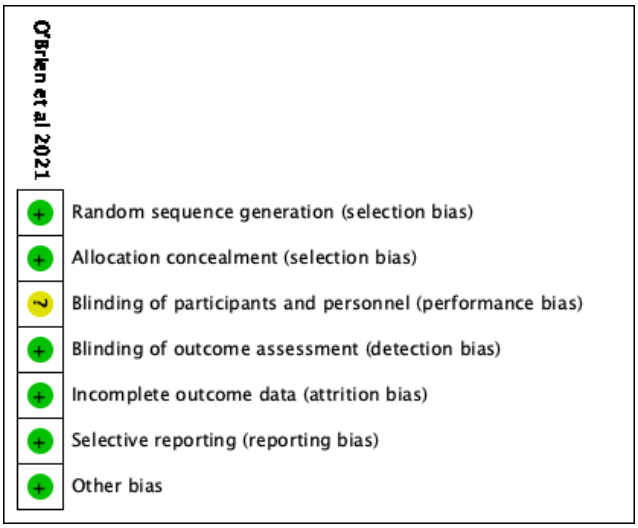

Figure 1. *Risk of bias summary table*

Appendix 4. GRADE Evidence Profile

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 post-exposure prophylaxis
Setting: Outpatient
Bibliography: O'Brien M, Forleo-Neto E, Musser B, et al. Subcutaneous REGEN-COV antibody combination for Covid-19 prevention. NEJM. 2021Aug4. doi:10.1056/NEJMoa2109682

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab + Imdevimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Prevention of symptomatic RT-qPCR SARS-CoV-2 infection (follow up: 28 days)												
1	randomized trial	not serious	not serious	not serious	not serious	none	11/753 (1.5%)	59/752 (7.8%)	**RR 0.19** (0.10 to 0.35)	**64 fewer per 1,000** (from 71 fewer to 51 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Prevention of any RT-PCR confirmed symptomatic or asymptomatic SARS-CoV-2 infection (follow up: 28 days)												
1	randomized trial	not serious	not serious	not serious	not serious	none	36/753 (4.8%)	107/752 (14.2%)	**RR 0.34** (0.23 to 0.48)	**94 fewer per 1,000** (from 110 fewer to 74 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Duration of symptomatic SARS-CoV-2 infection (follow up: 28 days)												
1	randomized trial	not serious	not serious	not serious	not serious	none	753	752	-	MD **2 weeks lower** (2.21 lower to 1.79 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Adverse events (follow up: 28 days)												
1	randomized trial	not serious	not serious	not serious	not serious	none	69/1311 (5.3%)	220/1306 (16.8%)	**RR 0.31** (0.24 to 0.40)	**116 fewer per 1,000** (from 128 fewer to 101 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
Serious adverse events (follow up: 28 days)												
1	randomized trial	not serious	not serious	not serious	serious [a]	none	10/1311 (0.8%)	15/1306 (1.1%)	**RR 0.66** (0.30 to 1.47)	**4 fewer per 1,000** (from 8 fewer to 6 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference
Explanations
a. There is a wide confidence interval.

Appendix 5. Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT04852978 **COVID-19 Study to Assess Immunogenicity Safety and Tolerability of Moderna mRNA-1273 Vaccine Administered with Casirivimab+Imdevimab in Healthy Adult Volunteers**	Randomized controlled trial	USA	Healthy adults or adults with stable, chronic medical conditions with no COVID-19	Casirivimab+imdevimab, Moderna mRNA-1273 vaccine	Extent of effect of casirivimab+imdevimab administration on vaccine-induced neutralizing antibody responses to SARS-CoV-2 Time interval required between casirivimab+imdevimab administration and Moderna mRNA-1273 vaccine to ensure no meaningful impact on vaccine-induced neutralizing antibody responses to SARS-CoV-2	Aug 30, 2022

NCT04519437 **Study Assessing the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of Repeated Subcutaneous Doses of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies (REGN10933+REGN10987) in Adult Volunteers as Related to COVID-19**	Randomized controlled trial	USA	Healthy individuals with no COVID-19	Regeneron vs placebo	Adverse events of special interests	Oct 25, 2021

NCT04452318 **COVID-19 Study Assessing the Efficacy and Safety of Anti-Spike SARS CoV-2 Monoclonal Antibodies for Prevention of SARS CoV-2Infection Asymptomatic in Healthy Adults and Adolescents Who Are Household contacts to an Individual with a Positive SARS-CoV-2 RT-PCR Assay**	Randomized controlled trial	USA	Asymptomatic patients RT PCR negative at baseline with household contact exposure to a known COVID-19 confirmed patients.	Regeneron vs placebo	Proportion of participants who have a positive SARS-CoV-2 RT-qPCR (based on central lab test) and signs and symptoms (strict-term) of SARS-CoV-2 infection during the Efficacy assessment period (EAP) Proportion of participants who have a RT-qPCR confirmed SARS-CoV-2 infection (either symptomatic or asymptomatic) during the EAP Incidence and severity of treatment-emergent	June 15, 2021

					adverse events (TEAEs)	
jRCT2071200117 **A phase I study of casirivimab and imdevimab in Japanese adult volunteers**	Randomized controlled trial	Japan	Healthy individuals ages 20-89 years old	Single dose IV casirivimab+imdevimab vs single dose IV placebo Single dose SC casirivimab+imdesivimab vs single dose SC placebo	Adverse events, pharmacokinetics of casirivimab and imdevimab, incidence of anti-drug antibodies to casirivimab and imdevimab	Not mentioned