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 patients with COVID-19, should leronlimab be used as treatment?

Update by: Carol Stephanie C. Tan-Lim, MD, MSc (Clinical Epidemiology), Natasha Ann R. Esteban-Ipac, MD

Evidence Reviewers: Dan Louie Renz P. Tating, MS (Candidate), RN

RECOMMENDATION

We suggest against the use of leronlimab as treatment for COVID-19 *(Very low certainty of evidence, Weak recommendation)*

Consensus Issue
The evidences of the review are now based on unpublished randomized controlled trials (previously from case series and a case study), however, similar to the previous consensus issue, the panel agreed that further trials are needed to recommend the use of leronlimab for the treatment of COVID-19.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of leronlimab as treatment for COVID-19 *(Very low certainty of evidence)*

Previous Consensus Issue
Further trials are needed to recommend the use of leronlimab for the treatment of COVID-19. The cost and accessibility of this drug must also be considered.

What's new in this version?

This version includes results of two (2) unpublished clinical trials (data obtained based on reports submitted to regulatory agencies).

Key Findings

Two (2) unpublished randomized controlled trial (RCTs) investigated the effect of leronlimab compared to placebo as treatment for patients with COVID-19. There was no significant benefit in the use of leronlimab in reducing mortality, length of hospital stay, resolution of clinical symptoms, and time to symptom resolution. There was no significant difference in serious adverse events and adverse events. The overall quality of evidence was rated very low because of serious risk of bias and very serious imprecision.

Introduction

Several molecules that play a role in determining diffuse tissue damage associated with cytokine release syndrome are upregulated in patients with COVID-19, especially in severe forms. Drugs

inhibiting these molecules could be beneficial in reducing this exaggerated inflammatory response.[1] C-C chemokine receptor type 5 (CCR5) is expressed on the surface of white blood cells, especially T-CD4+ cells and mediates macrophage migration into areas of inflammation, favoring the release of inflammatory cytokines and amplification of the immune response. Leronlimab is a humanized monoclonal antibody inhibiting CCR5.[2]

Review Methods

A systematic search was done from the date of the last search April 5, 2021 until September 20, 2021 using Medline, Cochrane Library, 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 leronlimab. We also looked at the COVID-NMA Living Data 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 leronlimab against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, hospitalization status, and dosing strategy of colchicine. Subgrouping by severity was planned.

Results

Two (2) unpublished RCTs (N = 478) evaluated the use of leronlimab as treatment for patients with COVID-19 and compared it to placebo. One study is a Phase 2 RCT involving 84 patients with mild to moderate COVID-19. The second study is a Phase 2b/3 adaptive RCT involving 394 patients with severe or critical COVID-19. In both studies, leronlimab 700mg was given weekly for a total of 2 doses. Patients were followed up for 14 to 28 days. Outcomes measured included mortality, change in clinical status, duration of hospitalization, need for hospitalization, need for mechanical ventilation, need for oxygen support, and time to clinical resolution. The characteristics of included studies are shown in Appendix 2.

Data from these studies were from statements obtained from the U.S. Food and Drug Administration [3], and pharmaceutical reports. [4,5]. Appraisal of study quality was done based on data found on clinical trial registries. [6-8]

The overall quality of evidence was rated very low because of serious risk of bias and very serious imprecision due to the small number of events and wide confidence intervals. Appraisal of study quality showed serious risk of bias in the included studies due to concerns on reporting bias. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

Mortality

Leronlimab did not show significant benefit in reducing mortality both for mild-moderate and severe-critical COVID-19 patients. Among the severe-critical COVID-19 patients, the relative risk (RR) was 0.96 (95% CI 0.64-1.45). The effect estimate for mild-moderate patients could not be computed due to inadequate data.[3]

Data from the pharmaceutical report on the subgroup of critically-ill COVID-19 (62 patients out of the 394 total patients) reported 78% efficacy of leronlimab compared to placebo on Day 7 mortality, 82% efficacy on Day 14 mortality, 50% on Day 21 mortality, and 31% on Day 28 mortality.[5] However, the US FDA cautions against reliance on this subgroup analysis especially in the context of a clinical trial that failed to show a benefit in the overall population.[3]

Other clinical outcomes
There was no significant difference in the length of hospital stay among the severe-critical COVID-19 patients (21.4 days in both the leronlimab and the placebo treatment groups).[3]

There was no significant benefit in resolution of clinical symptoms at day 3 among mild-moderate COVID-19 patients compared to placebo (RR 1.09, 95% CI 0.75-1.60).[4] Using the total clinical symptom score that ranges from 0 (no symptoms) to 12 (severe symptoms), the mean difference (MD) was -3.5 in the leronlimab group compared to MD -3.4 in the placebo group by Day 14.[3] However, using the National Early Warning Score 2, the pharmaceutical report noted significant benefit among patients given leronlimab compared to placebo in terms of proportion of patients with improved scores by Day 14 (RR 2.23, 95% CI 1.10-4.97).[4]

There was no significant benefit in time to symptom resolution and time to return to normal activity among mild-moderate COVID-19 patients.[3]

Adverse Events
There was no significant difference in adverse events (RR 0.68, 95% CI 0.40-1.14) and serious adverse events (RR 0.42, 95% CI 0.14-1.25) among the mild-moderate COVID-19 patients given leronlimab compared to placebo.[4] Among the severe-critical COVID-19 patients, the pharmaceutical report stated 21% less adverse events in the leronlimab arm compared to the placebo arm, and 3% less serious adverse events in the leronlimab arm compared to the placebo arm.[5]

Recommendations from Other Groups
No recommendations on leronlimab have been released by the US NIH (as of October 7), WHO (as of September 24), Australian Living CPG (as of September 29), and IDSA (as of October 1).[9-12]

Research Gaps
There are three (3) studies that were found in various clinical trial registries, of which 1 was marked completed but no results have been posted yet. This review will be updated as soon as published results from the included studies and results from these registered trials become available.

References

[1] Iannaccone G, Scacciavillani R, Del Buono MG, et al. Weathering the Cytokine Storm in COVID-19: Therapeutic Implications. Cardiorenal Med. 2020;10(5):277-287. doi:10.1159/000509483

[2] Kaplon H, Muralidharan M, Schneider Z, Reichert JM. Antibodies to watch in 2020. MAbs. 2020;12(1):1703531. doi:10.1080/19420862.2019.1703531

[3] U.S. Food & Drug Administration. Statement on Leronlimab. Available from https://www.fda.gov/drugs/drug-safety-and-availability/statement-leronlimab. Accessed September 20, 2021.

[4] CytoDyn. A Phase 2 Study of Leronlimab for Mild to Moderate Coronavirus Disease 2019 (COVID-19). Available from https://mod.isirv.org/repository/avg_2020/Harish_Seetamraju.pdf. Accessed September 20, 2021.

[5] CytoDyn. CytoDyn to Submit Newly Completed Topline Report of CD12 Trial Results to Regulatory Agencies in Multiple Countries including India and Philippines. Available form https://www.cytodyn.com/newsroom/press-releases/detail/533/cytodyn-to-submit-newly-completed-topline-report-of-cd12. Accessed September 20, 2021.

[6] ClinicalTrials.gov. Study to evaluate the efficacy and safety of leronlimab for mild to moderate COVID-19. Available from https://clinicaltrials.gov/ct2/show/NCT04343651. Accessed September 20, 2021.

[7] ClinicalTrials.gov. Study to Evaluate the Efficacy and Safety of Leronlimab for Patients With Severe or Critical Coronavirus Disease 2019 (COVID-19). Available from https://clinicaltrials.gov/ct2/show/NCT04347239. Accessed September 20, 2021.

[8] EU Clinical Trials Register. A Phase 2b/3, Randomized, Double Blind, Placebo Controlled, Adaptive Design Study to Evaluate the Efficacy and Safety of Leronlimab for Patients with Severe or Critical Coronavirus Disease 2019 (COVID-19). Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/chinaxiv.org2020-001996-33/GB. Accessed September 20, 2021.

[9] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 5.1.2. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 20 September 2021.

[10] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 20 September 2021

[11] Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v42.1. Available from https://app.magicapp.org/#/guideline/5596. Accessed 11 September 2021.

[12] World Health Organization. Therapeutics and COVID-19 Living Guidelines. 6 July 2021. Available at https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2. Accessed 11 September 2021.

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 8)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)				
Benefits	Large	Moderate	Small (5)	Uncertain (3)		• Leronlimab did not show significant benefit in reducing mortality both for mild-moderate and severe-critical COVID-19 patients.
Harm	Large	Small (5)	Uncertain (3)			• There was no significant difference in adverse events and serious adverse events • Among the severe-critical COVID-19 patients, there is 21% less adverse events and 3% less serious adverse events in the leronlimab arm
Certainty of Evidence	High	Moderate	Low (2)	Very low (6)		• Rated very low because of serious risk of bias and very serious imprecision due to the small number of events & wide confidence intervals.
Balance of effects	Favors drug	Does not favor drug (6)	Uncertain (2)			• There was no significant benefit in the use of leronlimab in reducing mortality, length of hospital stay, resolution of clinical symptoms, and time to symptom resolution.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability		

Resources Required	Uncertain (8)	Large cost	Moderate Cost	Negligible cost	Moderate savings	Large savings	• No evidence • FDA granted Compassionate Special Permit
Certainty of evidence of required resources	No included studies (8)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (7)	Favors the comparison	Does not favor either the intervention or the comparison (1)	Favors the intervention			
Equity	Uncertain (7)	Reduced (1)	Probably no impact	Increased			
Acceptability	Uncertain (8)	No	Yes				
Feasibility	Uncertain (7)	No (1)	Yes				

Appendix 2. 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 (leronlimab) Filters: April 5, 2021 to September 20, 2021	September 20, 2021 9:00 PM	0	0
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 (leronlimab) Filters: April 5, 2021 to September 20, 2021	September 20, 2021 9:15 PM	4	0
COVID-NMA Initiative	Leronlimab	September 20, 2021 9:30 PM	0	0
Google Scholar	Leronlimab and COVID (search in abstracts)	September 20, 2021 9:32 PM	7	1*
ClinicalTrials.gov	Leronlimab and COVID19	September 20, 2021 9:45 PM	5	5
Chinese Clinical Trial Registry	Leronlimab	September 20, 2021 9:50 PM	0	0
EU Clinical Trials Register	Leronlimab	September 20, 2021 9:51 PM	1	1
Republic of Korea - Clinical Research Information Service	Leronlimab	September 20, 2021 9:52 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Leronlimab	September 20, 2021 9:53 PM	0	0
CenterWatch	Leronlimab	September 20, 2021 9:54 PM	3	0
Cochrane COVID-19 study register	Leronlimab Filters: April 5, 2021 to September 20, 2021	September 20, 2021 9:40 PM	3	2
chinaxiv.org	Leronlimab	September 20, 2021 9:55 PM	0	0
Medrxiv.org	Leronlimab	September 20, 2021 9:56 PM	11	0
Biorxiv.org	Leronlimab	September 20, 2021 9:57 PM	3	0

**Report from pharmaceutical company*

Appendix 3. Characteristics of Included Studies

Study	Study Design	Population	Intervention	Comparison	Outcome
Clinical Trials					
NCT04343651 Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate COVID-19 "CD10"	Phase 2 RCT	84 patients with mild to moderate symptoms of respiratory illness caused by coronavirus 2019 infection	Weekly doses of 700mg leronlimab (PRO 140) SQ	Placebo	Primary outcome: Clinical improvement as assessed by change in total symptom score (for fever, myalgia, dyspnea, and cough) [Time Frame: Day 14] Secondary outcomes: ● Time to clinical resolution ● Change from baseline in National Early Warning Score 2 (NEWS2) ● Change from baseline in pulse oxygen saturation ● Change from baseline in the patient's health status on a 7-category ordinal scale ● Incidence of hospitalization ● Duration (days) of hospitalization ● Incidence of mechanical ventilation supply ● Duration (days) of mechanical ventilation supply ● Incidence of oxygen use ● Duration (days) of oxygen use ● Mortality rate ● Time to return to normal activity
NCT04347239 Study to Evaluate the Efficacy and Safety of Leronlimab for Patients with Severe or Critical Coronavirus Disease 2019 (COVID-19) "CD12"	Phase 2b/3 adaptive RCT	394 patients with severe or critical symptoms of respiratory illness caused by coronavirus 2019 infection	Weekly doses of 700mg leronlimab (PRO 140) SQ	Placebo	Primary outcome: All-cause mortality at Day 28 Secondary outcomes: ● All-cause mortality at Day 14 ● Change in clinical status of subject at Day 14 (on a 7-point ordinal scale) ● Change in clinical status of subject at Day 28 ● Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Day 14

Appendix 4. Study Appraisal

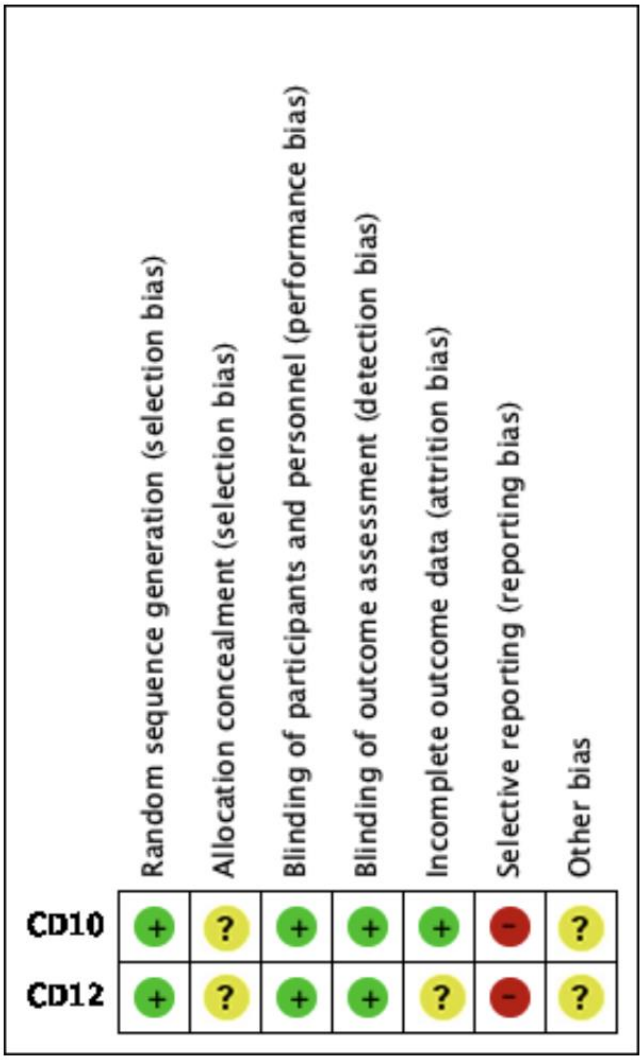

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Leronlimab compared to Placebo for COVID-19
Bibliography: CD10 and CD12 trials

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Leronlimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 14 to 28 days)												
2	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	No significant benefit for mild-moderate patients. No significant benefit for severe-critical patients (RR 0.96, 95% CI 0.64-1.45)				⊕◯◯◯ VERY LOW	CRITICAL
Length of hospital stay												
1	randomised trials	serious [c]	not serious	not serious	very serious [b]	none	263	131	-	MD = 0 days	⊕◯◯◯ VERY LOW	CRITICAL
Resolution of clinical symptoms Day 3												
1	randomised trials	serious [d]	not serious	not serious	very serious [b]	none	35/56 (62.5%)	16/28 (57.1%)	**RR 1.09** (0.75 to 1.60)	**51 more per 1,000** (from 143 fewer to 343 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse events												
2	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	No significant difference among the mild-moderate COVID-19 patients (RR 0.42, 95% CI 0.14-1.25). Among the severe-critical COVID-19 patients, there was 3% less serious adverse events reported in the leronlimab arm compared to the placebo arm.				⊕◯◯◯ VERY LOW	CRITICAL
Adverse events												
2	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	No significant difference among the mild-moderate COVID-19 patients (RR 0.68, 95% CI 0.40-1.14). Among the severe-critical COVID-19 patients, there was 21% less adverse events reported in the leronlimab arm compared to the placebo arm				⊕◯◯◯ VERY LOW	IMPORTANT

a. Issues with reporting bias in 2 studies, attrition bias in 1 study
b. Wide confidence interval, small sample size and number of events
c. Issues with reporting and attrition bias
d. Issues with reporting bias

Appendix 6. Characteristics of Ongoing Studies

Study	Study Design	Population	Intervention	Comparison	Outcome	Estimated Completion Date
NCT04678830 COVID-19 Long-Haulers Study "CD15" Marked complete but no results posted	Phase 2 RCT	50 patients with prolonged symptoms (>6 weeks) caused by COVID-19	Weekly doses of 700mg leronlimab (PRO 140) SQ	Placebo	Primary outcome: Changes from baseline in daily COVID-19-related symptom severity score through Day 56. Secondary outcomes: • Duration of COVID-19 associated symptoms from start of study treatment based on self-assessment using daily symptom diary • Number of symptom-free days of COVID-19 associated symptoms that were present at the start of study treatment (Day 0) based on self-assessment using daily symptom diary • Progression (or worsening) of COVID-19-associated symptoms through Day 56 compared to baseline • Change from baseline in PROMIS® Fatigue Score at Days 28 and 56 • Change from baseline in PROMIS® Cognitive Function Score at Days 28 and 56 • Change from baseline in PROMIS® Sleep Disturbance Score at Days 28 and 56 • Duration (days) of hospitalization during the treatment phase • Incidence of hospitalization during the treatment phase • Change from baseline in pulse oxygen saturation (SpO2) at Day 7, 14, 21, 28, 35, 42, 49, and 56 • Incidence of treatment-related adverse events (TEAEs) • Incidence and severity of treatment-	July 23, 2021

					emergent adverse events (TEAEs) • Incidence of serious adverse events (SAEs) • Incidence of TEAEs and SAEs leading to discontinuation of study medication.	
NCT04901676 Leronlimab in Moderately Ill Patients With COVID-19 Pneumonia	Phase 3, Randomized, Double Blind, Placebo Controlled Trial	612 participants, 18 years and older, moderately ill patients with COVID-19, hospitalized, requiring supplemental oxygen or on non-invasive ventilation or high flow oxygen devices, evidence of pneumonia	Leronlimab subcutaneously once a week (up to 4 doses) until hospital discharge. The first dose will be of 700mg, followed by weekly doses of 350mg	Placebo	<u>Primary outcome:</u> Cumulative incidence of death or respiratory failure until day 28 <u>Secondary outcomes:</u> • Time to clinical recovery • Death or intubation until day 28 • Proportion of patients clinically recovered • All-cause mortality • Proportion of patients discharged alive • Clinical status • Length of hospital stay	February 2022
NCT04901689 Leronlimab in Patients with Coronavirus Disease 2019 (COVID-19) with Need for Mechanical Ventilation or Extracorporeal Membrane Oxygenation	Phase 3, Randomized, Double Blind, Placebo Controlled Trial	316 participants, 18 years and older, critically ill patients with COVID-19, Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) for less than 72 hours. Evidence of pneumonia	Leronlimab 700mg intravenously once a week (up to 4 doses) until hospital discharge	Placebo	<u>Primary outcome:</u> Cumulative proportion of clinical recovery <u>Secondary outcomes:</u> • Proportion of patients clinically recovered • All-cause mortality • Proportion of patients discharged alive • Clinical Status • Duration of invasive mechanical ventilation or ECMO • Length of hospital stay • Length of ICU stay	December 2021