Should Leronlimab (PRO 140) be used in the treatment of COVID-19?

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KEY FINDINGS

- There is still no evidence that Leronlimab is an effective treatment for COVID19 but we await the results of 2 ongoing clinical trials.

- **Leronlimab (PRO 140),[1] a humanized IgG4 monoclonal antibody, is an investigational drug initially indicated for treatment of HIV infection and metastatic triple-negative breast cancer (mTNBC).[1] Leronlimab, a CCR5 receptor antagonist, can potentially offer therapeutic benefit by improving the immune response while abating the "cytokine storm" in COVID-19.[2]**
- **There is no available evidence that leronlimab is an effective treatment for COVID 19.**
- **There is limited evidence for its safety based on trials conducted for HIV.[3] The commonly reported adverse events include headache, lymphadenopathy, diarrhea, fatigue, hypertension, nasal congestion and pruritus.[3]**
- **Currently, it has been granted emergency Interventional New Drug (eIND) status by FDA, targeted to treat patients with respiratory complications associated with COVID-19.[2] There are two ongoing trials involving COVID-19 cases.**
- **Leronlimab is not included in the recommended therapeutic options for COVID19 in the WHO Interim Guidance, and US CDC Clinical Interim Guidelines.**

RESULTS

There are no current available data that support the use of Leronlimab for COVID19. This is based on literature search done using Medline (Pubmed), ClinicalTrials.gov, EU Clinical Trials Register, International Clinical Trials Registry Platform (ICTRP), and National Institutes of Health. Although there are two on-going pharmaceutical-sponsored trials on leronlimab (PRO 140) for COVID19 registered at ClinicalTrials.gov.

Leronlimab (PRO 140) potently inhibits HIV-1 entry and replication at concentrations that do not affect CCR5's chemokine receptor activity in vitro.[4,5] Published preclinical studies also have shown that blocking CCR5 can reduce tumor metastases in laboratory and animal models of aggressive breast and prostate cancer. In a murine xenograft model, leronlimab reduced human breast cancer metastasis by more than 98%.[5]

A systematic review[3] involving three randomized, double-blind, placebo-controlled trials suggests limited indirect, very low quality evidence that leronlimab (PRO 140) is effective in the treatment of HIV infection. Although it may show potent, short-term, dose-dependent, highly significant antiviral activity with tolerable side effects, the number of patients in these three studies was very small. Furthermore, the results of these studies may be influenced by lack of details regarding method of randomization and blinding; as well as if allocation concealment was done. There was also unclear risk for incomplete outcome data and selective reporting. In addition, there is a potential conflict of interest, as the authors of all three trials are connected to the pharmaceutical company that manufactured PRO 140. The most frequent adverse events reported include headache, lymphadenopathy, diarrhea, fatigue, hypertension, nasal congestion and pruritus. However, these adverse events were found to be not adequately reported by the studies for each group. Currently, there is one on-going trial registered at ClinicalTrials.gov on leronlimab for the treatment of HIV that is pharmaceutical-initiated.[4]

For metastatic breast cancer treatment, there are two ongoing non-randomized trials on leronlimab registered at ClinicalTrials.gov.[6] One is a single arm, compassionate use of leronlimab (PRO 140) in combination with treatment of physician's choice in patients with CRR5+ mTNBC until disease progression or intolerable toxicity. Another trial is a phase II single arm study involving the use of leronlimab (PRO 140) combined with carboplatin in cases with mTNBC.[7]

Currently, leronlimab is not part of the recommended treatment options for COVID19 by WHO, and CDC.

CONCLUSION

There is still no evidence that leronlimab is an effective treatment for COVID 19 but we await the results of 2 ongoing trials.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of included studies

No.	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings

Table 2. Characteristics of clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	A Phase 2, Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of **Leronlimab** for Mild to Moderate Coronavirus Disease 2019 (**COVID-**19)	On-going	April 1 to December 4,, 2020	Phase II, randomized double-blind, placebo-controlled multicenter study	US	Mild to moderate COVID - 19 cases male or female adult age ≥ 18 years of age	Leronlimab (700 mg) for 2 weeks	Placebo	PRIMARY Clinical Improvement based on change in total symptom score (for fever, myalgia, dyspnea and cough) SECONDARY Time to clinical resolution (TTCR) [Time Frame: Day 14] Change from baseline in National Early Warning Score 2 (NEWS2) [Time Frame: Days 3, 7, and 14] - based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness). Higher scores

									mean a worse outcome. Change from baseline in pulse oxygen saturation (SpO2) [Time Frame: Days 3, 7, and 14] Change from baseline in the patient's health status on a 7-category ordinal scale [Time Frame: Days 3, 7, and 14] - A 7-category ordinal scale of patient health status ranges from: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities. Lower

									scores mean a worse outcome. Incidence of hospitalization [Time Frame: Day 14] Duration (days) of hospitalization [Time Frame: Day 14] Incidence of mechanical ventilation supply [Time Frame: Day 14] Duration (days) of mechanical ventilation supply [Time Frame: Day 14] Incidence of oxygen use [Time Frame: Day 14] Duration (days) of oxygen use [Time Frame: Day 14] Mortality rate [Time Frame: Day 14] Time to return to normal activity [Time Frame: Day 14] OTHER MEASURES: Change in size of lesion area by chest radiograph or

									CT [Time Frame: Day 14] Change from baseline in serum cytokine and chemokine levels [Time Frame: Days 3, 7, and 14] Change from baseline in CCR5 receptor occupancy levels for Tregs and macrophages [Time Frame: Days 3, 7, and 14] Change from baseline in CD3+, CD4+ and CD8+ T cell count [Time Frame: Days 3, 7, and 14]
2	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)	On-going	April 15, to December 31, 2020	Phase IIb/III Randomized double-blind, placebo-controlled with 2:1 ratio (active drug to placebo ratio)	US	Severely ill COVID-19 cases male or female adult age ≥ 18 and < 65 years of age	Leronlimab (700 mg) for 2 weeks	Placebo	PRIMARY: All causes of mortality at day 28 - Blood levels of IL-6 and TNF-alpha at days 3 and 7 SECONDARY All-cause mortality at Day 14 [Time Frame: Day 14]Day 0 refers to the data of randomization/first treatment. Change in clinical status of subject at Day 14 (on a 7 point ordinal scale) [Time Frame: Day 14] 7-category

									ordinal scale of patient health status ranges from: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities. Change in clinical status of subject at Day 28 (on a 7 point ordinal scale) [Time Frame: Day 28]A 7-category ordinal scale of patient health status ranges from: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3)

									Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities. Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Day 14. [Time Frame: Day 14]. The SOFA score assessment will be based on PaO2/FiO2, platelets, Glasgow coma scale (GCS), bilirubin, Mean arterial pressure OR administration of vasoactive agents required, and Serum creatinine
