LERONLIMAB

RECOMMENDATION

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

Consensus Issues

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.

EVIDENCE SUMMARY

Should leronlimab be used for the treatment of COVID-19?

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

Key Findings

Very low-quality evidence based on three case series and one case study was found on the use of leronlimab for the treatment of COVID-19. Among the patients with severe-critical COVID-19 given leronlimab, 26.3% died, 21.1% were still hospitalized, and 52.6% were discharged. There were reductions in serial IL-6 measurements before and several days after administration. No thromboembolic events were reported. Well-conducted randomized controlled trials are still needed to assess the effectiveness of leronlimab as treatment for COVID-19.

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

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].

Results

The search strategy yielded twenty one articles. Full text review resulted in the exclusion of twelve theoretical/ review articles, four duplicates, and one preprint duplicate of a published study [3]. Four studies [3-6] provided clinical data on the use of leronlimab as treatment for COVID-19 patients: three case series and one case study (Appendix 1). These studies had very serious risk of bias due to the absence of comparison group and very small sample size (Appendix 2), thus providing very low quality of evidence.

The sample size ranged from 1 [5] to 23 [3], with a total of 38 COVID-19 patients who received leronlimab. All studies were on critically-ill COVID-19 patients. The age range of the patients was 42 to 79 years old. Leronlimab was given subcutaneously once a week for two weeks, except in one study [4] which gave it for four weeks. Yang et al [5] extended the administration of leronlimab with repeat dosing every one week if still admitted. The reported investigational products given alongside leronlimab were hydroxychloroquine/ chloroquine, azithromycin, lopinavir/ritonavir, zinc, tocilizumab, remdesivir, dexamethasone/ steroids, convalescent plasma, sarilumab, and selinexor.

Overall, after being given leronlimab, 10 patients died (26.3%), 8 are still hospitalized (21.1%), and 20 recovered (52.6%) in this combination of four studies. Two studies reported duration of ICU stay, which ranged from 10-21 days [6] to 91 days [4]. There were reductions in serial IL-6 measurement before and several days after leronlimab administration [3,5-6]. For adverse events, only a maculopapular rash was reported by Yang [5], which was attributed to the concurrent administration of a cephalosporin. No thromboembolic events were reported.

Recommendations from Other Groups

No recommendations on leronlimab have been released by the US NIH [7], WHO [8], Australian Living CPG [9], and PSMID [10]. Currently, it has been granted emergency Interventional New Drug (eIND) status by FDA, targeted to treat patients with respiratory complications associated with COVID-19 [11].

Research Gaps

High quality evidence is lacking on the efficacy of leronlimab in the treatment of COVID-19, which can be addressed by a well-conducted randomized controlled trial. There are 3 ongoing RCTs in *ClinicalTrials.gov* (Appendix 3), one each for mild-moderate COVID-19, severe-critical COVID-19, and long COVID-19.

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] Patterson BK, Seethamraju H, Dhody K, et al. CCR5 inhibition in critical COVID-19 patients decreases inflammatory cytokines, increases CD8 T-cells, and decreases SARS-CoV2 RNA in plasma by day 14. Int J Infect Dis. 2021;103:25-32. doi:10.1016/j.ijid.2020.10.101

[4] Elneil S, Lalezari JP, Pourhassan NZ. Case study of a critically ill person with COVID-19 on ECMO successfully treated with leronlimab [published online ahead of print, 2021 Mar 23]. J Transl Autoimmun. 2021;100097. doi:10.1016/j.jtauto.2021.100097

[5] Yang B, Fulcher JA, Ahn J, et al. Clinical Characteristics and Outcomes of COVID-19 Patients Receiving Compassionate Use Leronlimab [published online ahead of print, 2020 Oct 20]. Clin Infect Dis. 2020;ciaa1583. doi:10.1093/cid/ciaa1583

[6] Agresti N, Lalezari JP, Amodeo PP, et al. Disruption of CCR5 signaling to treat COVID-19-associated cytokine storm: Case series of four critically ill patients treated with leronlimab. J Transl Autoimmun. 2021;4:100083. doi:10.1016/j.jtauto.2021.100083

[7] US NIH. COVID-19 Treatment Guidelines. March 2021. Available from: https://www.covid19treatmentguidelines.nih.gov/. Accessed April 5, 2021.

[8] WHO. Therapeutics and COVID-19: Living Guideline. March 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.1. Accessed April 5, 2021.

[9] National COVID-19 Clinical Evidence Taskforce. Caring for people with COVID-19. April 2021. Available from: https://covid19evidence.net.au/. Accessed April 5, 2021.

[10] PSMID. Interim Guidance on the Clinical Management of Adult Patients with Suspected or Confirmed COVID-19 Infection (Version 3.1). July 2020. Available from: https://www.psmid.org/interim-management-guidelines-for-covid-19-version-3-1/. Accessed April 5, 2021.

[11] U.S. Food and Drug Administration (FDA) grants emergency IND for two coronavirus patients treated in New York with Cytodyn's leronlimab [news release]. Vancouver, Washington: CytoDyn, Inc; 2020. Available at: https://bit.ly/2R36K1B.

Appendix 1. Characteristics of Included Studies

Study	Study Design	Population	Intervention	Comparison	Outcome
Agresti 2020 USA	Case series	4 patients admitted to the intensive care unit with confirmed COVID-19 who received leronlimab Age range = 50-75 years old	2 doses of subcutaneous leronlimab 750 mg, with an interval of 7-18 days Other investigational drugs given: HCQ, Zinc, Azithromycin, Tocilizumab, Remdesivir	None	• Total days in ICU • Days in ICU after leronlimab treatment • Days removed from O2 after leronlimab treatment • Clinical status (discharged, died, admitted) • 14-day trend in laboratory tests, inflammatory markers, ventilatory settings and vasopressor requirements
Patterson 2021 USA	Case series	10 critically ill COVID-19 patients who received leronlimab Age range = 42-79 years old	2 doses of subcutaneous leronlimab 700 mg with one week interval Other investigational drugs given: HCQ/CQ, AZT, LPV/RTV	None	• Respiratory outcome • Clinical status • 14-day trend in laboratory tests, inflammatory markers
Elneil 2021 UK	Case study	Male patient with critical COVID-19 Age = late 50's	4 doses of leronlimab (700mg) with one week intervals Other investigational drugs given: Dexa, Remdesivir,	None	• Weaning off ECMO • Discharge from ECMO unit • adverse events
Yang 2020 USA	Case series	23 COVID-19 patients for whom other experimental therapeutic options were contraindicated or exhausted Mean age = 69.5 year	2 subcutaneous injections of 350 mg leronlimab (with repeat dosing if patients were still hospitalized after 7 days) Other investigational products given: convalescent plasma, HCQ, steroids, tocilizumab, remdesivir, sarilumab, selinexor	None	• Clinical status after 30 days of follow-up • Trend in inflammatory markers • Adverse events

Appendix 2. GRADE Evidence Profile

Author(s): Dan Louie Renz P. Tating, MS(cand), RN
Question: Leronlimab compared to placebo or standard of care for COVID-19 treatment
Setting: hospital
Bibliography:

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Clinical status									
4	observational studies	very serious [a]	not serious	not serious	not serious	none	After being given leronlimab, 10 patients died (26.3%), 8 are still hospitalized (21.1%), and 20 recovered (52.6%).	⨁◯◯◯ VERY LOW	
Duration of ICU stay									
2	observational studies	very serious [a]	not serious	not serious	not serious	none	The duration of ICU stay ranged from 10-21 days to 91 days.	⨁◯◯◯ VERY LOW	
Serial IL-6 measurements									
3	observational studies	very serious [a]	not serious	not serious	not serious	none	There were reductions in serial IL-6 measurement before and several days after leronlimab administration.	⨁◯◯◯ VERY LOW	
Adverse events									
3	observational studies	very serious [a]	not serious	not serious	not serious	none	Only a maculopapular rash was reported, but was attributed to the concurrent administration of a cephalosporin. No thromboembolic events were reported.	⨁◯◯◯ VERY LOW	

CI: Confidence interval

Explanations

a. absence of comparison group and very small sample size

Appendix 3. Table of Ongoing Studies

Study	Study Design	Population	Intervention	Comparison	Outcome	Estimated Completion Date
NCT04343651 Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate COVID-19	Phase 2 RCT	75 patients with mild to moderate symptoms of respiratory illness caused by coronavirus 2019 infection	weekly doses of 700 mg 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 ● Change in size of lesion area by chest radiograph or CT ● Change from baseline in serum cytokine and chemokine levels ● Change from baseline in CCR5 receptor occupancy levels for Tregs and macrophages ● Change from baseline in CD3+, CD4+ and CD8+ T cell count	August 31, 2020 Status: Active, Not Recruiting
NCT04347239	Phase 2b/3	394 patients	weekly doses of	Placebo	Primary outcome: All-cause mortality at Day 28	October 15, 2021

Study to Evaluate the Efficacy and Safety of Leronlimab for Patients With Severe or Critical Coronavirus Disease 2019 (COVID-19)	adaptive RCT	with severe or critical symptoms of respiratory illness caused by coronavirus 2019 infection	700 mg leronlimab (PRO 140) SQ		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	
NCT04678830 COVID-19 Long-Haulers Study	Phase 2 RCT	50 patients with prolonged symptoms (> 6 weeks) caused by COVID-19	weekly doses of 700 mg 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	July 23, 2021

					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 ● Change from baseline in serum cytokine and chemokine levels ● Change from baseline in CD4+ and CD8+ T cell count ● Change from baseline in Transgrowth factor beta 1 (TGF beta1) on Days 14, 28, 42, and 56 ● Change from baseline in CRP on Days 14, 28, 42, and 56 ● Incidence of treatment-related adverse events (TEAEs) ● Incidence and severity of treatment-emergent adverse events (TEAEs) ● Incidence of serious adverse events (SAEs) ● Incidence of TEAEs and SAEs leading to discontinuation of study medication. ● Changes in blood chemistry, hematology and coagulation parameter results ● Changes in vital signs including temperature, pulse, respiratory rate, systolic and diastolic blood pressure ● Changes in physical examination results ● Changes in electrocardiogram (ECG) results	