

Should protease inhibitors be used for COVID-19?

This write-up summarises a rapid evidence review of protease inhibitors for treating COVID-19. The information may be revised as new evidence emerges.

Background

Protease inhibitors developed to treat HIV infection, have previously been trialed as a treatment for patients with Severe Acute Respiratory Syndrome (SARS-CoV); however their clinical efficacy was inconclusive.¹ As SARS-CoV and COVID-19 both belong to the Coronavirus family, protease inhibitors are currently being studied as a potential antiviral treatment for COVID-19 infection. Most ongoing trials are focusing on lopinavir/ritonavir (brand names: Kaletra, Aluvia), following reports of its efficacy in a patient with COVID-19 in South Korea.²

Clinical evidence

A literature search of protease inhibitors used for treating COVID-19 was conducted on 23 March 2020.[†] Sixteen clinical trials identified are currently ongoing, with results pending (Table 1). Only one clinical trial (LOTUS China) by Cao et al. has published results to date.

Table 1: List of ongoing trials investigating protease inhibitors for treating COVID-19

Study identifier	Study Design	Intervention	Comparator(s)	Date of primary completion
LOTUS China trial, ³ ChiCTR2000029308	SC*, OL, phIV, RCT	Lopinavir/ritonavir	Standard of care	3 February 2020
NCT04307693 ⁴	MC, OL, phII, RCT	Lopinavir/ritonavir	Hydroxychloroquine sulfate	May 2020
NCT04286503 ⁵	MC, OL, phIV, RCT	Carrimycin	<ul style="list-style-type: none"> Lopinavir/ritonavir arbidol chloroquine phosphate 	February 2021
NCT04255017 ⁶	SC*, SB, phIV, RCT	Lopinavir/ritonavir	<ul style="list-style-type: none"> Abidol hydrochloride oseltamivir 	June 2020
NCT04295551 ⁷	MC, OL, RCT	Lopinavir/ritonavir	Lopinavir/ritonavir with Xiyanning injection	July 2020
NCT04303299 ⁸	MC, OL, phIII, RCT	<p><u>Mild COVID-19</u></p> <ul style="list-style-type: none"> oseltamivir and chloroquine lopinavir/ritonavir with favipiravir lopinavir/ritonavir with oseltamivir <p><u>Moderate to severe COVID-19</u></p> <ul style="list-style-type: none"> lopinavir/ritonavir with oseltamivir lopinavir/ritonavir with favipiravir darunavir/ritonavir with oseltamivir with chloroquine darunavir/ritonavir with favipiravir with chloroquine 	Standard of care	October 2020
NCT04291729 ⁹	SC*, OL, phIV, NRCT	Danoprevir and ritonavir with or without interferon atomisation	<ul style="list-style-type: none"> Long acting interferon recombinant cytokine gene-derived protein lopinavir/ritonavir Chinese medicines with interferon atomisation 	March 2020
NCT04261907 ¹⁰	MC, OL, RCT	ASC09 with ritonavir	Lopinavir/ritonavir	May 2020
NCT04315948 ¹¹	MC, OL, RCT	<ul style="list-style-type: none"> Remdesivir lopinavir/ritonavir lopinavir/ritonavir with interferon β-1a 	Standard of care	March 2023

[†] The literature search covered antiretroviral HIV-1 protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir); and hepatitis C virus NS3/4A protease inhibitors (asunaprevir, boceprevir, grazoprevir, glecaprevir, paritaprevir, simeprevir, telaprevir and danoprevir).

NCT04275388 ¹²	MC, OL, RCT	Xiyanping injection with lopinavir/ritonavir and interferon- α nebulisation	lopinavir/ritonavir and interferon- α nebulisation	May 2020
NCT04252274 ¹³	SC*, OL, pHIII, RCT	Darunavir and cobicistat	Standard of care	August 2020
NCT04251871 ¹⁴	SC*, OL, RCT	Traditional Chinese Medicines granules, lopinavir/ritonavir and interferon- α nebulisation	lopinavir/ritonavir and interferon- α nebulisation	January 2021
NCT04304053 ¹⁵	MC, OL, pHIII, CRCT	Chloroquine, darunavir and cobicistat	Standard of care	July 2020
NCT04276688 ¹⁶	SC*, OL, pHII, RCT	Lopinavir/ritonavir, ribavirin and interferon β -1b	Lopinavir/ritonavir	January 2022
NCT02735707 REMAP-CAP: COVID-19 Antiviral Therapy Domain ¹⁷	MC, OL, pHIV, ARCT	Lopinavir/ritonavir	Standard of care	December 2021
ASID Australia New South Wales trial	NA	<ul style="list-style-type: none"> • lopinavir/ritonavir • lopinavir/ritonavir and hydroxychloroquine • hydroxychloroquine 	Standard of care	NA
SOLIDARITY ¹⁸	NA	<ul style="list-style-type: none"> • Remdesivir • lopinavir/ritonavir • lopinavir/ritonavir and interferon β • chloroquine 	Standard of care	NA

Abbreviations: DB, double blind; SB, single blind; MC, multicenter; OL, open label, pHII, phase II; pHIII, phase III; pHIV, phase IV; RCT, randomised controlled trial; CRCT, cluster randomised controlled trial; ARCT, adaptive randomised controlled trial; SC, single centre; NA, not available;

† None of the listed trials include Singapore as a study site.

* China ‡ France

The LOTUS China trial reported that there was no significant difference in time to clinical improvement, mortality and viral load between patients who received lopinavir/ritonavir in addition to standard care versus standard of care alone. Standard of care comprised supplemental oxygen, ventilation, antibiotic agents, vasopressor support, renal-replacement therapy and extracorporeal membrane oxygenation (ECMO) as necessary. The proportion of patients who experienced grade 3 or 4 adverse events were comparable between the two treatment groups (lopinavir/ritonavir: 39%, standard of care: 42%). Nearly 14% of patients receiving lopinavir/ritonavir could not complete the full 14-day course due to gastrointestinal adverse events.

The authors noted that the enrolled patients were likely to be more ill than typical patients which may have affected the results. A post-hoc analysis concluded that patients who received lopinavir/ritonavir within 12 days of symptom onset may experience faster clinical recovery and lower mortality, but this finding was highly uncertain and required further research.³

The World Health Organization (WHO) has also recently announced that it will be conducting a large, global trial (SOLIDARITY)¹⁸ on the four most promising therapies identified to date to treat COVID-19, including lopinavir/ritonavir. The following countries are currently included in the trial: Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland and Thailand, with more countries likely to be included over time. The trial completion date has not been released yet.

Recommendations from professional bodies

The World Health Organization, US Centers for Disease Control and Prevention, European Medicines Agency, NHS (UK), Taiwan Centers for Disease Control, Singapore National Centre for Infectious Diseases and ministries of health of Australia, Canada, New Zealand and South Korea have reported that there is currently no approved targeted treatment for COVID-19 and symptom management is the best available option.^{19, 20, 21, 22, 23, 24, 25, 26, 27, 28}

Interim COVID-19 clinical guidelines from Belgium, China, France, Italy, Spain and Switzerland have included lopinavir/ritonavir as an option for investigational or compassionate use. Most guidelines propose lopinavir/ritonavir as a first-line treatment option for mild to moderate COVID-19 infection and

as a second-line option for severe infections.^{29, 30, 31, 32} No other protease inhibitors are currently recommended.

Conclusion

Lopinavir/ritonavir is the most common protease inhibitor listed for investigational or compassionate use for COVID-19 in international clinical guidelines. However, current evidence on the efficacy and safety of any protease inhibitors for treating COVID-19 infection is limited. Large multinational studies are currently underway to provide more evidence on the use of protease inhibitors in patients with different levels of disease severity.

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