Should protease inhibitors be used for COVID-19?

This clinical evidence summary outlines existing evidence on the use of protease inhibitors for treating COVID-19. The information may be revised as new evidence emerges. The summary is not exhaustive of the subject matter and does not replace clinical judgement. The responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.

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

Many trials assessing the use of protease inhibitors for COVID-19 are ongoing (Appendix I).

Lopinavir/ritonavir for severe COVID-19

The LOTUS open-label randomised controlled trial (RCT) [3] conducted in 199 patients with severe COVID-19 in China reported that there was no significant difference in time to clinical improvement between patients who received lopinavir/ritonavir in addition to standard care versus standard of care alone (median 16 days). There was also no significant difference in mortality between the two groups although the 28-day mortality rate was numerically lower with lopinavir/ritonavir compared with standard of care (19.2% vs 25%). 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 (HR 1.25; 95%CI 1.17 to 2.05) compared to later treatment, but this finding was highly uncertain and required further research.[3]

Lopinavir/ritonavir for mild to moderate COVID-19

The ELACOI open-label RCT[4, 5] conducted in 86 patients with mild to moderate COVID-19 reported that there was no significant difference in time to undetectable viral RNA load between patients who received lopinavir/ritonavir in addition to standard care versus arbidol in addition to standard of care versus standard of care alone (mean of 9 days). There was also no significant difference in the proportion of patients who achieved undetectable viral RNA load between the 3 treatment groups at day 14 (35.3% vs 37.1% vs 41.2%). No deaths occurred during the trial. The treatments were well tolerated, with the occurrence of one serious adverse event in a patient who received lopinavir/ritonavir resulting in treatment discontinuation (1/34, 2.9%). Due to the small sample size and short trial follow-up of 21 days, the significance of the reported outcomes is uncertain.

An open-label RCT by Hung et al. 2020[6, 7] conducted in 127 patients with mild to moderate COVID-19 with symptom duration of 14 days or less reported statistically significantly shorter time to negative nasopharyngeal swab from start of treatment for patients who received combination therapy (lopinavir/ritonavir, ribavirin and subcutaneous interferon beta-1b) with standard of care versus

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patients who received lopinavir/ritonavir monotherapy with standard of care (7 days versus 12 days, p<0.001). Patients in the combination therapy arm were around 4 times more likely to achieve negative viral load than patients in the lopinavir/ritonavir monotherapy arm. Clinical improvement, as measured by the National Early Warning Score 2 (NEWS2), were similarly improved, with patients in the combination therapy arm reporting statistically significantly shorter time to complete alleviation of symptoms compared to patients in the lopinavir/ritonavir monotherapy arm (4 days versus 8 days, p<0.0001), resulting in a significantly reduced median length of hospital stay of 5.5 days (9 days versus 14.5 days, p=0.016). No deaths occurred within 30 days post-treatment. There was no significant difference in safety profile between the 2 arms, with diarrhoea (41%), fever (38%), nausea (34%) and raised alanine transaminase level (14%) being the most commonly reported adverse events. No serious adverse events were reported in the combination arm. Authors concluded that early combination therapy is more efficacious and as safe as lopinavir/ritonavir monotherapy.

A single centre, open-label RCT by Huang et al. 2020 [8] conducted in 101 patients with mild to moderate COVID-19 reported no statistically significant difference in the time to undetectable viral RNA load for patients who received one of the following regimens: (1) lopinavir/ritonavir with interferon-α, (2) ribavirin with interferon-α or (3) lopinavir/ritonavir, ribavirin with interferon-α (median of 12 days, 13 days and 15 days respectively, p=0.23). There was also no statistically significant difference in the proportion of patients with COVID-19 negativity at day 14 between the three treatment arms (61.1%, 51.5% and 46.9% respectively, p-value not reported). No deaths or serious adverse events occurred during the 28-day study and there were no statistically significant differences in the proportion of patients who progressed to severe disease (5.6%, 3.0% and 6.3% respectively, p=0.58). More patients receiving treatment regimen 3 experienced grade 1 or 2 gastrointestinal adverse events compared to the other two treatment regimens (Proportion of patients taking regimen 1, 2 or 3 that experience grade 1 or 2 diarrhoea: 38.9%, 21.2% and 59.4% respectively, p<0.05 versus regimen 2 only; vomiting: 16.7%, 3.0% and 34.4% respectively, p<0.05 versus regimen 1 and 2). The authors concluded that there were no significant differences among the three regimens in terms of antiviral effectiveness in patients with mild to moderate COVID-19.

Lopinavir/ritonavir for hospitalised patients with COVID-19

The RECOVERY trial[9] is an open-label, adaptive design RCT that is ongoing in the UK. The trial is investigating a range of potential treatments, including lopinavir/ritonavir, for treating patients hospitalised with COVID-19. On 29 June 2020, the chief investigators of the trial announced that the lopinavir/ritonavir arm had been stopped due to lack of benefit.[10] When 1,596 patients who received lopinavir/ritonavir were compared with 3,376 patients who received usual care alone, preliminary results showed no statistically significant difference in 28-day mortality (22.1% vs. 21.3%, relative risk 1.04, 95% CI 0.91 to 1.18, p=0.58). The results were consistent in different subgroups of patients, the largest of which included patients who required oxygen alone, followed by those who did not require any respiratory intervention and those who required mechanical ventilation (70%, 26% and 4% respectively). There was also no evidence of benefit of lopinavir/ritonavir on hospital stay duration or risk of progression to mechanical ventilation. Publication of the full results in a peer-reviewed journal is currently pending.

The World Health Organization (WHO) initiated a large global trial (SOLIDARITY) on the four most promising therapies identified in early 2020 to treat COVID-19, including lopinavir/ritonavir as monotherapy or in combination with interferon beta-1a. Over 100 countries are currently included in the trial. The date of primary completion is March 2021, with findings expected to be reported by December 2021. On 4 July 2020, WHO accepted the recommendation from the SOLIDARITY Trial's International Steering Committee to discontinue the hydroxychloroquine and lopinavir/ritonavir monotherapy arms in the trial for hospitalised patients. The recommendation was based on the SOLIDARITY trial interim results, and from a review of the evidence from all trials presented at the July 2020 WHO Summit on COVID-19 Research and Innovation. These interim trial results showed that hydroxychloroquine and lopinavir/ritonavir produced little or no reduction in the mortality of hospitalised COVID-19 patients when compared to standard of care. The lopinavir/ritonavir with interferon beta-1a treatment arm is still ongoing. The Steering Committee for the AustralaSian COVID-

19 Trial (ASCOT)[11] has since discontinued the hydroxychloroquine and lopinavir/ritonavir treatment arms in view of the findings of the SOLIDARITY and RECOVERY trials.[12, 13, 14]

Danoprevir/ritonavir

A case series of 11 patients with moderate COVID-19 infection who received danoprevir/ritonavir with or without alpha-interferon nebulisation was published online by Chen et al.[15] The article, which has not been peer reviewed, reported that all 11 patients recovered following 4 to 12 days of treatment with danoprevir/ritonavir. Viral nucleic acids in nasal swabs turned negative at a median of 2 days (range 1 to 8 days) and the absorption of acute exudative lesions occurred at a median of 3 days (range 2 to 4 days) after the initiation of danoprevir/ritonavir treatment. Due to the small sample size, lack of control subjects and possible selection bias, the significance of the reported outcomes is unclear and not considered generalisable to all patients. Larger randomised controlled trials are required to determine the clinical benefit of danoprevir/ritonavir for treating COVID-19.

Darunavir/Cobicistat for mild COVID-19

A single-centre, open-label RCT by Chen et al. 2020[16, 17] conducted in 30 patients with mild COVID-19 reported that there was no statistically significant difference in the proportion of patients who achieved viral clearance at day 7 between those who received darunavir/cobicistat versus standard of care (46.7% and 60.0% respectively, p=0.72). There was also no statistically significant difference in the time to viral clearance between the two treatment arms (median duration of 8 and 7 days respectively, hazard ratio: 0.82, 95%CI 0.36 to 1.88). At day 14, one patient in the darunavir/cobicistat treatment arm progressed to critical illness while all patients in the standard of care arm remained stable. The authors reported that the frequencies of adverse events in the two groups were comparable and were all mild in severity. No patients discontinued darunavir/cobicistat due to adverse events. The authors concluded that darunavir/cobicistat did not increase the proportion of negative conversion versus standard of care alone.

Recommendations from professional bodies

Several international professional bodies, acknowledging the lack of robust scientific evidence, have provided advice on the use of protease inhibitors for patients with COVID-19:

- The WHO interim guidance for the clinical management of COVID-19 recommended against using lopinavir/ritonavir or other antivirals as treatment or prophylaxis for COVID-19, except in a clinical trial.[18, 19]
- The National Institutes of Health (NIH) in the US has recommended against using lopinavir/ritonavir or other HIV protease inhibitors for the treatment of COVID-19, except in a clinical trial.[20] Potential drug interactions with concurrent medicines should be reviewed before using lopinavir/ritonavir as the drug is a potent inhibitor of the cytochrome P450 3A, and many medications that are metabolised by this enzyme may cause severe toxicity.
- The Australian National COVID-19 Clinical Evidence Taskforce does not recommend the use of lopinavir/ritonavir or darunavir/cobicistat outside of randomised trials that have appropriate ethical approval.[21]
- On 17 July 2020, the Italian Medicines Agency (AIFA) has suspended the authorisation for the off-label use of lopinavir/ritonavir, except in clinical trials.[22]
- The Spanish Agency for Medicines and Health Products (AEMPS) notes that there is currently no evidence from controlled clinical trials to recommend a specific treatment for COVID-19. If lopinavir/ritonavir is used, the AEMPS recommends giving it within the context of an RCT.[23]
- Locally, the National Centre for Infectious Diseases (NCID) Singapore has recommended that if remdesivir or convalescent plasma is not available or contraindicated, subcutaneous interferon beta-1b in combination with lopinavir/ritonavir and ribavirin may be considered in early COVID-19 (<7 days from onset of illness), optimally within the context of a clinical study, and preferably a trial if available.[24]

Conclusion

Current evidence on the efficacy and safety of any protease inhibitors for treating COVID-19 infection is limited. For patients who are hospitalised with COVID-19, preliminary findings of the SOLIDARITY and RECOVERY trials have led trial investigators to conclude that lopinavir/ritonavir monotherapy is not an effective treatment versus standard of care. Although a few large multinational studies have discontinued their lopinavir/ritonavir treatment arms in response to the findings of the RECOVERY trials, many others are currently ongoing to provide more evidence on the use of protease inhibitors in patients with different levels of disease severity.

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Appendix 1: Table of registered studies for protease inhibitors in patients with COVID-19

Study identifier	Study Design	Intervention	Comparator(s)	Date of primary completion
LOTUS China trial, ChiCTR2000029308	SC*, OL, phIV, RCT	Lopinavir/ritonavir	Standard of care	Completed and published.[3]
NCT04291729 [25]	SC*, OL, phIV, NRCT	Danoprevir and ritonavir with or without interferon atomisation	NA	Completed and published.[15]
NCT04252885 [5]	SC, OL, phIV, RCT	• Lopinavir/ritonavir • Arbidol	Standard of care	Completed and published.[4]
NCT04276688 [6]	SC*, OL, phII, RCT	Lopinavir/ritonavir, ribavirin and interferon beta-1b	Lopinavir/ritonavir	Completed and published.[7]
NCT04252274 [17]	SC*, OL, phIII, RCT	Darunavir/cobicistat and interferon alpha 2b	Interferon alpha 2b	Completed and published.[16]
NCT04304053 [26] 2020-001031-27 [27]	MC, OL, phIII, CRCT	Hydroxychloroquine, darunavir/cobicistat	Patient cohort: standard of care Prevention cohort: no intervention	Completed and published.[28^]
ChiCTR2000029387	SC, OL, RCT	• Lopinavir/ritonavir and interferon-α • Lopinavir/ritonavir, ribavirin and interferon-α	Ribavirin and interferon-α	Completed and published.[8]
NCT04255017 [29]	SC*, SB, phIV, RCT	Lopinavir/ritonavir	• Abidol hydrochloride • Oseltamivir	June 2020
NCT04303299 [30]	MC, OL, phIII, RCT	<u>Mild COVID-19</u> • Oseltamivir and hydroxychloroquine • Darunavir/ritonavir and oseltamivir and hydroxychloroquine • Lopinavir/ritonavir and oseltamivir <u>Moderate to severe COVID-19</u> • Lopinavir/ritonavir and oseltamivir • Lopinavir/ritonavir and favipiravir • Darunavir/ritonavir and oseltamivir and hydroxychloroquine • Darunavir/ritonavir and favipiravir and hydroxychloroquine	Standard of care	December 2020
DisCoVeRy: NCT04315948 [31] 2020-000936-23 [32]	MC, OL, RCT	• Remdesivir • Lopinavir/ritonavir (**discontinued**) • Lopinavir/ritonavir and interferon beta-1a	Standard of care	March 2023
NCT02735707 [33] 2015-002340-14 [34] REMAP-CAP: COVID-19 Antiviral Therapy Domain [33, 34]	MC, OL, phIV, ARCT	• Lopinavir/ritonavir • Hydroxychloroquine and lopinavir/ritonavir • Hydroxychloroquine • Hydrocortisone • Ceftriaxone • Moxifloxacin or levofloxacin • Piperacillin-tazobactam • Ceftaroline • Amoxicillin-clavulanate • Oseltamivir • Interferon beta1a • Anakinra • Tocilizumab • Sarilumab • Vitamin C • Therapeutic anticoagulation • Simvastatin • Convalescent plasma	Standard of care	December 2021

NCT04483960 AustralaSian COVID-19 Trial (ASCOT) [11]	MC, OL, phIII, RCT	Intervention domain 1: • Lopinavir/ritonavir • Lopinavir/ritonavir and hydroxychloroquine The antiviral domain is now suspended (**no further enrolment**). Intervention domain 2: • Convalescent plasma	Standard of care	June 2021
ISRCTN83971151 SOLIDARITY [12, 13] NCT04330690 [35] 2020-001549-38 [36] 2020-002060-31 [37] 2020-001366-11 [38] 2020-001784-88 [39] 2020-000982-18 [40] 2020-001448-24 [41]	MC, OL, phIII, ARCT	• Remdesivir • Lopinavir/ritonavir * • Lopinavir/ritonavir and interferon beta-1a • Chloroquine or hydroxychloroquine * * **Discontinued** for hospitalised patients only.	Standard of care	March 2021
NCT04321174 [42]	MC, OL, phIII, RCT	• Lopinavir/ritonavir	Patient cohort: standard of care Prevention cohort: no intervention	March 2021
RECOVERY: 2020-001113-21 [43] NCT04381936 [9]	MC, OL, phIII, ARCT	• Lopinavir/ritonavir **(discontinued due to lack of efficacy)** • Corticosteroid **(discontinued due to benefit)** • Hydroxychloroquine **(discontinued due to lack of efficacy)** • Azithromycin • Convalescent plasma • Tocilizumab	Standard of care	NA
NCT04328285 [44]	MC, DB, phIII, RCT	• Hydroxychloroquine • Lopinavir/ritonavir	Standard of care	November 2020
NCT04331470 [45]	SC, OL, phII/III, RCT	• Levamisole and budesonide/formoterol inhaler and hydroxychoroquine and lopinavir/ritonavir	Hydroxychoroquine and lopinavir/ritonavir	April 2020
NCT04328012 [46]	SC, DB, phII/III, ARCT	• Lopinavir/ritonavir • Hydroxychloroquine sulphate • Losartan	Standard of care	January 2021
2020-001188-96 [47]	MC, DB, phIII, RCT	• Lopinavir/ritonavir • Hydroxychloroquine	Standard of care	NA
NCT04345276 [48]	SC, OL, phIV, SA	• Danoprevir and ritonavir	No comparator- single arm trial	Completed. No published report available.
NCT04343768 [49]	SC, OL, phIV, RCT	• Hydroxychloroquine, lopinavir/ritonavir and interferon beta-1a • Hydroxychloroquine, lopinavir/ritonavir and interferon beta-1b	Hydroxychloroquine and lopinavir/ritonavir	Completed. No published report available.
NCT04350671 [50]	SC, DB, phIV, RCT	• Interferon beta-1a, lopinavir/ritonavir and hydroxychloroquine	Lopinavir/ritonavir and hydroxychloroquine	April 2020
NCT04350684 [51]	SC, DB, phIV, RCT	• Umifenovir, interferon beta-1a, lopinavir/ritonavir and hydroxychloroquine	Interferon beta-1a, lopinavir/ritonavir and hydroxychloroquine	April 2020
NCT04346147 [52]	SC, OL, phII, RCT	• Hydroxychloroquine and baricitinib • Hydroxychloroquine and imatinib	Hydroxychloroquine and lopinavir/ritonavir	August 2020
NCT04351724 [53] 2020-001302-30 [54]	MC, OL, phII/III, ARCT	• Lopinavir/ritonavir • Chloroquine or hydroxychloroquine • Rivaroxaban • Thromboprophylaxis • Candesartan • Non-RAS blocking antihypertensives	Standard of care	December 2020

		• Clazakizumab		
2020-001448-24 [41] NCT04386070 [55]	MC, OL, phIII, RCT	• Hydroxychloroquine • Lopinavir/ritonavir • Lopinavir/ritonavir and hydroxychloroquine	Placebo and standard of care	May 2021
2020-001321-31 [56]	SC, OL, phII, RCT	• Hydroxychloroquine and imatinib • Hydroxychloroquine and baricitinib	Hydroxychloroquine and lopinavir/ritonavir	NA
NCT04359095 [57]	MC, OL, phII/III, RCT	• Hydroxychloroquine • Hydroxychloroquine and lopinavir/ritonavir • Hydroxychloroquine and azithromycin	Standard of care	October 2020
NCT04365582 [58]	MC, OL, phIII, RCT	• Hydroxychloroquine • Lopinavir/ritonavir • Azithromycin	Standard of care	August 2020
NCT04364022 [59]	MC, OL, phIII, RCT	• Hydroxychloroquine • Lopinavir/ritonavir	Active surveillance	October 2020
NCT04372628 [60]	MC, DB, phIII, RCT	• Lopinavir/ritonavir	Placebo	December 2020
2020-001723-13 [61]	MC, OL, phIII, RCT	• Hydroxychloroquine • Lopinavir/ritonavir • Azithromycin	Standard of care	NA
2020-001156-18 [62]	MC, OL, phIII, RCT	• Hydroxychloroquine • Lopinavir/ritonavir • Azithromycin	Standard of care	NA
NCT04409483 [63]	SC, OL, phIII, RCT	• Lopinavir/ritonavir	Standard of care	December 2020
NCT04403100 [64]	MC, DB, phIII, RCT	• Hydroxychloroquine • Lopinavir/ritonavir • Hydroxychloroquine and lopinavir/ritonavir	Standard of care	September 2020
2020-001605-23 [65]	SC, OL, phIV, RCT	• Lopinavir/ritonavir and hydroxychloroquine	Hydroxychloroquine and azithromycin	NA
NCT04468087 [66] (REVOLUTIOn)	MC, DB, phII/III, ARCT	• Atazanavir • Daclatasvir • Sofusbuvir and Daclatasvir	Standard of care	December 2021
NCT04459286 [67]	MC, OL, phII, RCT	• Nitazoxanide and atazanavir/ritonavir	Standard of care	October 2020
NCT04466241 [68] (INTENSE-COV)	MC, OL, phIIb, RCT	• Lopinavir/ritonavir and telmisartan • Lopinavir/ritonavir and atorvastatin	Lopinavir/ritonavir	November 2020
NCT04459702 [69]	DB, phIIa, RCT	• Hydroxychloroquine, lopinavir/ritonavir, and azithromycin	Hydroxychloroquine and azithromycin	July 2021

Note: As of 25 August 2020, only RCTs involving lopinavir/ritonavir as an intervention will be tracked in this appendix. For other protease inhibitors, all study types will continue to be monitored.
Abbreviations: DB, double blind; SB, single blind; MC, multicentre; OL, open label, phII, phase II; phIII, phase III; phIV, phase IV; RCT, randomised controlled trial; CRCT, cluster randomised controlled trial; SA, single-arm trial; ARCT, adaptive randomised controlled trial; SC, single centre; NA, not available; † None of the listed trials include Singapore as a study site. * China
^ Study was published online and has not been peer-reviewed. Study was not retrieved as only around half the patients originally randomised to the intervention arm received darunavir/cobicistat with hydroxychloroquine due to a protocol amendment (90 of 168 patients). Additionally, important outcomes such as time to negative viral load and proportion of patients who recovered from COVID-19 were not reported.