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. 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.

Clinical evidence

The World Health Organization (WHO) has also begun conducting a large global trial (SOLIDARITY) on the four most promising therapies identified to date to treat COVID-19, including lopinavir/ritonavir. Over 70 countries are currently included in the trial, with more countries likely to be included over time. The date of primary completion is March 2021, with findings expected to be reported by December 2021.

Lopinavir/ritonavir for severe COVID-19

The LOTUS China trial conducted in 199 patients with severe COVID-19 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.

Lopinavir/ritonavir for mild to moderate COVID-19

The ELACOI trial 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.
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.8 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.

Recommendations from professional bodies

WHO, US Centers for Disease Control and Prevention (CDC), European Medicines Agency, National Health Service UK (NHS), Taiwan Centers for Disease Control, Singapore National Centre for Infectious Diseases (NCID) and governments in Australia, Canada, New Zealand and South Korea have reported that there is currently no approved targeted treatment for COVID-19 and symptom management is currently the best available option.9, 10, 11, 12, 13, 14, 15, 16, 17, 18

Interim COVID-19 clinical guidelines from Belgium, China, France, India, 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.19, 20, 21, 22, 23, 24 No other protease inhibitors are currently recommended.

Locally, in interim guidelines on the management of COVID-19, NCID recommend that if lopinavir/ritonavir (either alone or in combination with interferon beta-1b) is considered, it should be used in early illness (<12 days).25

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.

References

15. Page 53. 48. 47. 46. 45. 44. 43. 42. 40. 39. 38. 37. 36. 35. 34. 33. 32. 31. 30. 29. 28. 27. 26. 25. 24. 23. 22. 20. 19. 18. 17. 16. 15. 14. 13. 12. 11. 10. 9. 8. 7. 6. 5. 4. 3. 2. 1. van Iersel S, Dauby N, Bottlaert E et al. Interim clinical guidance for patients suspected of/ confirmed with COVID-19 in Belgium. 19 March 2020. Report No.: Version 4.


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

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Date of primary completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOTUS China trial, ChCTR2000029308</td>
<td>SC*, OL, phIV, RCT</td>
<td>Lopinavir/ritonavir</td>
<td>Standard of care</td>
<td>3 February 2020</td>
</tr>
<tr>
<td>NCT04291729</td>
<td>SC*, OL, phIV, NRCT</td>
<td>Danoprevir and ritonavir with or without interferon atomisation</td>
<td>NA</td>
<td>March 2020</td>
</tr>
<tr>
<td>NCT04252885</td>
<td>SC, OL, phIV, RCT</td>
<td>Lopinavir/ritonavir, Arbidol</td>
<td>Standard of care</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04307693</td>
<td>MC, OL, phIII, RCT</td>
<td>Lopinavir/ritonavir</td>
<td>Hydroxychloroquine sulphate</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04286503</td>
<td>MC, OL, phIV, RCT</td>
<td>Lopinavir/ritonavir, Arbidol, Chloroquine phosphate</td>
<td>Standard of care</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04295551</td>
<td>SC*, SB, phIV, RCT</td>
<td>Lopinavir/ritonavir</td>
<td>Abidol hydrochloride, Oseltamivir</td>
<td>June 2020</td>
</tr>
<tr>
<td>NCT04295551</td>
<td>MC, OL, RCT</td>
<td>Lopinavir/ritonavir</td>
<td>Lopinavir/ritonavir with Xyayanping injection</td>
<td>July 2020</td>
</tr>
<tr>
<td>NCT04261907</td>
<td>MC, OL, RCT</td>
<td>ASC09 with ritonavir</td>
<td>Lopinavir/ritonavir</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04315948</td>
<td>MC, OL, RCT</td>
<td>Remdesivir, Lopinavir/ritonavir, Lopinavir/ritonavir with interferon β-1a</td>
<td>Standard of care</td>
<td>March 2023</td>
</tr>
<tr>
<td>NCT04275388</td>
<td>MC, OL, RCT</td>
<td>Xyayanping injection with Lopinavir/ritonavir and interferon-α nebulisation</td>
<td>Lopinavir/ritonavir and interferon-α nebulisation</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04252274</td>
<td>SC*, OL, phIII, RCT</td>
<td>Darunavir and cobicistat</td>
<td>Standard of care</td>
<td>August 2020</td>
</tr>
<tr>
<td>NCT04251877</td>
<td>SC*, OL, RCT</td>
<td>Traditional Chinese Medicines granules, Lopinavir/ritonavir and interferon-α nebulisation</td>
<td>Lopinavir/ritonavir and interferon-α nebulisation</td>
<td>January 2021</td>
</tr>
<tr>
<td>NCT04304053</td>
<td>MC, OL, phIII, CRCT</td>
<td>Chloroquine, darunavir and cobicistat</td>
<td>Standard of care</td>
<td>July 2020</td>
</tr>
<tr>
<td>NCT04276688</td>
<td>MC, OL, phIII, RCT</td>
<td>Lopinavir/ritonavir, ribavirin and interferon β-1b</td>
<td>Lopinavir/ritonavir</td>
<td>January 2022</td>
</tr>
<tr>
<td>ASID Australia New South Wales trial</td>
<td>NA</td>
<td>Lopinavir/ritonavir, Lopinavir/ritonavir and hydroxychloroquine, Hydroxychloroquine</td>
<td>Standard of care</td>
<td>NA</td>
</tr>
</tbody>
</table>
| ISRCTN83971151 | NA | • Remdesivir  
• Lopinavir/ritonavir  
• Lopinavir/ritonavir and interferon beta-1a  
• Chloroquine or hydroxychloroquine | Standard of care | March 2021 |
| NCT04330690 | MC, OL, phIII, ARCT | • Lopinavir/ritonavir | Standard of care | March 2022 |
| 2020-001366-11 | MC, OL, phIII, ARCT | • Remdesivir  
• Chloroquine  
• Hydroxychloroquine sulfate  
• Lopinavir/ritonavir  
• Interferon-beta-1a | Standard of care | NA |
| NCT04321993 | OL, phII, NRCT | • Lopinavir/ritonavir  
• Hydroxychloroquine sulphate  
• Baricitinib  
• Sarilumab | Standard of care | February 2021 |
| NCT04321174 | MC, OL, phII, RCT | • Lopinavir/ritonavir | Patient cohort: standard of care  
Prevention cohort: no intervention | March 2021 |
| NCT04328285 | MC, DB, phII, RCT | • Hydroxychloroquine  
• Lopinavir/ritonavir | Placebo | November 2020 |
| NCT04331470 | SC, OL, phII/III, RCT | • Levamisole and budesonide/formoterol inhaler and hydroxychloroquine and lopinavir/ritonavir | Hydroxychloroquine and lopinavir/ritonavir | April 2020 |
| NCT04328012 | SC, DB, phII/III, ARCT | • Lopinavir/ritonavir  
• Hydroxychloroquine sulphate  
• Losartan | Placebo | January 2021 |
| 2020-001188-96 | MC, DB, phII, RCT | • Lopinavir/ritonavir | Placebo | NA |
| 2020-001031-27 | SC, OL, phII, CRCT | • Darunavir/cobicistat  
• Hydroxychloroquine | Patient cohort: standard of care  
Prevention cohort: no intervention | NA |
| NCT04345276 | SC, OL, phIV, SA | • Danoprevir and ritonavir | No comparator- single arm trial | April 2020 |
| NCT04343768 | SC, OL, phIV, RCT | • Hydroxychloroquine, lopinavir/ritonavir and interferon beta-1a  
• Hydroxychloroquine, lopinavir/ritonavir and interferon beta-1b | Hydroxychloroquine and lopinavir/ritonavir | April 2020 |
| NCT04350671 | SC, DB, phIV, RCT | • Interferon-beta-1a, lopinavir/ritonavir and hydroxychloroquine | Lopinavir/ritonavir and hydroxychloroquine | April 2020 |
| NCT04350684 | SC, DB, phIV, RCT | • Umifenovir, interferon-beta-1a, lopinavir/ritonavir and hydroxychloroquine | Interferon-beta-1a, lopinavir/ritonavir and hydroxychloroquine | April 2020 |
| NCT04346147 | SC, OL, phII, RCT | • Hydroxychloroquine and baricitinib  
• Hydroxychloroquine and imatinib | Hydroxychloroquine and lopinavir/ritonavir | August 2020 |
| NCT04351724 | MC, OL, phII/III, RCT | • Hydroxychloroquine  
• Lopinavir/ritonavir | Standard of care | December 2020 |
| 2020-001302-30 | MC, OL, phII, RCT | • Hydroxychloroquine  
• Lopinavir/ritonavir | Placebo and standard of care | 2025 |
| 2020-001321-31 | SC, OL, phII, RCT | • Hydroxychloroquine and imatinib  
• Hydroxychloroquine and baricitinib | Hydroxychloroquine and lopinavir/ritonavir | 2026 |

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; 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