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

A literature search of protease inhibitors used for treating COVID-19 was conducted on 23 March 2020. Twenty 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

<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, † ChiCTR2000029308</td>
<td>SC*, OL, phIV, RCT</td>
<td>Lopinavir/ritonavir</td>
<td>Standard of care</td>
<td>3 February 2020</td>
</tr>
<tr>
<td>NCT042891729 ‡</td>
<td>SC*, OL, phIV, NRCT</td>
<td>Darunavir and ritonavir with or without interferon atomisation</td>
<td>NA</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04307693 ‡</td>
<td>MC, OL, phII, RCT</td>
<td>Lopinavir/ritonavir</td>
<td>Hydroxychloroquine sulfate</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04286503 ‡</td>
<td>MC, OL, phIV, RCT</td>
<td>Carimycin</td>
<td>Lopinavir/ritonavir + arbidol + chloroquine phosphate</td>
<td>February 2021</td>
</tr>
<tr>
<td>NCT04255017 ‡</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 Xiyanping injection</td>
<td>July 2020</td>
</tr>
<tr>
<td>NCT04303299 ‡</td>
<td>MC, OL, phIII, RCT</td>
<td>Mild COVID-19</td>
<td>OSeltamivir and chloroquine</td>
<td>October 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</td>
<td>Standard of care</td>
<td>March 2023</td>
</tr>
<tr>
<td>NCT04275388 † ‡</td>
<td>MC, OL, RCT</td>
<td>Xiyanping 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, phII, RCT</td>
<td>Darunavir and cobicistat</td>
<td>Standard of care</td>
<td>August 2020</td>
</tr>
</tbody>
</table>

† 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).
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.\textsuperscript{23} 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, European Medicines Agency, NHS (UK), Taiwan Centers for Disease Control, Singapore National Centre for Infectious Diseases 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.24, 25, 26, 27, 28, 29, 30, 31, 32, 33

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.34, 35, 36, 37 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.

References

31. Taiwan Centers for Disease Control. COVID-19 [https://www.cdc.gov.tw/En/Category/QAPage/LndBFJsuJwF3JnscwO4Yw, Assessed 23 March 2020].