Does lopinavir measure up in the treatment of COVID-19?
Sheila A. Doggrell
Faculty of Health, Queensland University of Technology, Brisbane, Australia

ABSTRACT
Introduction: Lopinavir in combination with ritonavir is approved for the treatment of HIV and has recently been subject to a clinical trial in severe COVID-19.
Areas covered: This evaluation is of LOTUS China (the Lopinavir Trial for Suppression of SARS-Cov-2 in China), which was a randomized trial in hospitalized subjects with COVID-19 in a respiratory sample and pneumonia. As, in severe COVID-19, lopinavir/ritonavir had no beneficial effects but increased gastrointestinal adverse effects, this combination should not be used at this stage of COVID-19.
Expert opinion: In my opinion, the rationale for undertaking a trial of lopinavir/ritonavir in COVID-19 was poor. The analysis of a modified intention to treat group analysis in LOTUS China may have introduced bias. After LOTUS China, there is probably no future for lopinavir in the treatment of severe COVID-19, but some clinical trials for prevention or in various stages of COVID-19 have recently started or are ongoing. The major limitation of these trials is that as lopinavir does not inhibit COVID-19, it is unlikely to prevent infection, reduce viral load, or reduce the severity. However, these trials may be worthwhile in finally determining whether lopinavir has any role in preventing or treating COVID-19.

1. Introduction
The emergence of new viruses, such as the coronavirus SARS-CoV-2 (COVID-19), requires both vaccines for the prevention and drugs for the treatment of the infection. As a vaccine is probably a year away at least, drugs for the treatment of the symptoms of COVID-19 are urgently needed. The development of new drugs for COVID-19 will require extensive preclinical testing followed by clinical trials. In contrast, drugs that are already approved for clinical use in conditions other than COVID-19 can be tested immediately in COVID-19. However, clinical trials of such drugs will be required to determine benefits and adverse effects.

Lopinavir is an HIV type 1 aspartate protease inhibitor approved for use against HIV infections in combination with ritonavir. Ritonavir is also a protease inhibitor, which was initially developed to treat HIV infections. However, ritonavir is now predominantly used in doses that do not inhibit proteases but do inhibit cytochrome P450 CYP3A4 to boost the levels of drugs metabolized by this enzyme, such as lopinavir.

Lopinavir was identified as a registered drug that may have potential in treating COVID-19. In vitro, lopinavir inhibits SARS-CoV [1], which causes severe acute respiratory syndrome (SARS), and MERS-CoV [2], which causes Middle East Respiratory syndrome (MERS). Preliminary clinical testing has suggested, but not proven, that lopinavir with ritonavir may have small benefits in the treatment of SARS [1] and/or MERS [3]. LOTUS China (Lopinavir Trial for Suppression of SARS-Cov-2 in China) is the first published trial of lopinavir/ritonavir in the treatment of COVID-19 [2020] and is the subject of this evaluation.

2. LOTUS China
LOTUS China was a randomized, controlled, open-label trial of the lopinavir–ritonavir combination, which was performed in a Wuhan hospital, with subjects testing positive for COVID-19 in a respiratory tract sample. As this trial was performed quickly in a difficult situation, no placebo tablets were available.

In addition to having the virus, to be enrolled, adult subjects had to have pneumonia and an oxygen saturation of ≤94% while breathing air or a ratio of partial pressure of oxygen to fraction of inspired oxygen ≤300 mg Hg. Randomization was stratified according to respiratory support, and the resulting groups were well-matched for demographics and clinical parameters. Median age was 58 years, and ~21% had coexisting conditions, which were not respiratory.

Subjects (199) received either lopinavir-ritonavir 400/100 mg orally and standard care or standard care alone for 14 days. Standard care included, if required, supplemental oxygen, ventilation, antibiotics, vasopressor support, renal-replacement therapy, and extracorporeal life support (ECLS).

The primary end point was time to clinical improvement from randomization by two points on a 7-point scale:

1. Not hospitalized with resumption of normal activities.
2. Not hospitalized but unable to resume normal activities.
3. Hospitalized, not requiring supplementary oxygen.
4. Hospitalized, requiring supplementary oxygen.
5. Hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation or both.
Most of the subjects (~70%) were at point 4 at the start of the trial. Most subjects were treated with antibiotics (~95%), and some were treated with glucocorticoids (~34%) during the trial. The primary end point was reached in 16 days in the lopinavir-ritonavir group, which was the same as in the standard care group. There was also no difference between groups, when the clinical outcomes were assessed on the National Early Warning Score 2, which is a scale used in the assessment and response of acute illness.

Several secondary outcomes indicated numerically, but not significantly, that there may be small benefits with lopinavir-ritonavir in reducing mortality, stay in the intensive care unit, and duration from randomization to hospital discharge. Lopinavir-ritonavir did not alter the duration of oxygen therapy, duration of hospitalization, or time from randomization to death.

Viral RNA load of COVID-19 did not differ between the lopinavir-ritonavir and standard care groups over the course of the trial. Nausea, vomiting, and diarrhea were more common with lopinavir-ritonavir than in the standard care group.

Although the authors concluded that lopinavir–ritonavir added to standard care was not associated with clinical improvement or mortality in COVID 19, they did suggest that there was some evidence from a modified intention-to-treat group that lopinavir-ritonavir may reduce time to clinical improvement; 15 vs 16 days [2020].

4.2. Potential bias in the LOTUS China trial
In addition to the analysis from the intention to treat groups, the authors of LOTUS China also presented some data from analyzing a modified intention to treat group that lopinavir-ritonavir may reduce the time to clinical improvement [2020]. It has been well-documented that the only way to prevent bias in randomized controlled trials is to use intention to treat analysis [6]. In LOTUS China, three subjects assigned to the lopinavir-ritonavir group died within 24 hours and without receiving any lopinavir-ritonavir and were not included in the modified intention to treat group [2020]. Demographic data from the intention to treat and the standard treatment groups were well-matched, but as this data for the modified intention to treat group versus standard treatment group is not given, we do not know whether these groups were well-matched. Removing the subjects who died before being treated with lopinavir-ritonavir may have introduced bias in the results. Thus, analysis using the modified intention to treat group should be given low value and probably should not have been included in the study.

4.3. A positive from LOTUS China – the establishment of a primary end point
One positive from the LOTUS China trial was the establishment of a primary end point to be used in severe COVID-19. As COVID-19 is a new viral disease, the authors had to create a primary end point, which was time to clinical improvement from randomization by two points on a 7-point scale. This scale seems clear-cut and easy to use, and may be useful in the determination of the effectiveness of other drugs being investigated in severe COVID-19.

4.4. Adverse effects of drugs in COVID-19
It is important to reposition drugs that have been clinically tested and approved for other conditions for possible use in COVID-19. However, given that when this testing starts, the drugs will not have established benefits in COVID-19, attention needs to be given to their adverse effects. Thus, it must be asked whether clinical trials with drugs that are being repositioned for COVID-19 are likely to fail the principle of ‘first, do no harm’. With lopinavir/ritonavir, beneficial effects in SARS, MERS, and COVID-19 are yet to be established. However, it is known that this combination causes gastrointestinal adverse effects, and these were observed in LOTUS China. Thus, lopinavir/ritonavir fails the ‘first, do no harm’ principle.

4.5. Ongoing clinical trials of lopinavir in COVID-19
Although, it seems to me that, after LOTUS China, there is no future for lopinavir in the treatment of severe COVID-19, some clinical trials of lopinavir/ritonavir for prevention in various stages of COVID-19 have recently started. The major limitation of these trials is that, as lopinavir does not inhibit SARS-CoV-2 in vitro [5], it seems unlikely that it will prevent infection,
reduce viral load, or reduce the severity. However, these trials may be worthwhile in finally determining whether lopinavir has any role in preventing or treating any stage of COVID-19.

4.5.1. Trials comparing lopinavir with other drugs
In a placebo-controlled trial, lopinavir is being compared to hydroxychloroquine, which is used to treat malaria, rheumatoid arthritis, and lupus erythematosus, as a preventative treatment for COVID-19 in exposed health-care workers with the primary outcome being the occurrence of the infection (NCT04328285) [7].

There are two phase 2 studies comparing lopinavir/ritonavir with hydroxychloroquine in pre-emergency treatment of COVID-19. In the first of these, 150 subjects with mild COVID-19 are being recruited and the primary outcome is viral load, and secondary outcomes relate to clinical outcomes (e.g., time to clinical improvement) and adverse effects (NCT04307693) [8]. However, there are several problems with this trial including that there is no placebo group, and it is not powered to give a definitive result on clinical outcomes. Without a placebo group, it is possible that the adverse effects with lopinavir may seem mild compared to hydroxychloroquine, which has considerable toxicity, including cardiac toxicity [9]. The second phase 2 trial comparing lopinavir/ritonavir with hydroxychloroquine (NCT04372628) in the early treatment of COVID-19 is in the outpatient setting. This trial is recruiting 900 participants and the primary outcome measures include death and in-hospital stages [10]. This trial has a placebo group and will be important in determining the adverse effects of lopinavir and hydroxychloroquine.

The SOLIDARITY open-label clinical trial was launched by the WHO and is comparing lopinavir/ritonavir with the local standard of care, remdesivir, or chloroquine/hydroxychloroquine in subjects hospitalized with COVID-19. Lopinavir is being included as ‘studies so far in COVID-19 patients have been inconclusive’ [11]. Rather than inconclusive, LOTUS China was conclusive in showing lopinavir had no benefit in severe COVID-19, and, in my opinion, lopinavir should not be undergoing further testing in hospitalized subjects. It will also be difficult to obtain conclusive results in the SOLIDARITY trial, as it has the major limitation of being open label.

Three phase 4 clinical trials are comparing lopinavir/ritonavir with other drugs in subjects with COVID-9. Two of these trials are in subjects with pneumonia due to COVID-19; a comparison with two anti-influenza drugs (umifenovir, oseltamivir) (NCT04255017) [12], and a comparison with umifenovir, interferon-β 1a, and a single dose of hydroxychloroquine (NCT04350684) [13]. The third phase 4 trial is in subjects with mild to severe COVID-19 and is a comparison with the anti-biotic carrimycin and basic treatment (NCT04286503) [14].

Given that in LOTUS China no benefits were found with lopinavir in severe COVID-19, the continuation of the lopinavir arm in these trials is questionable.

4.5.2. Trials of lopinavir in combination with hydroxychloroquine
There are at least two clinical trials comparing lopinavir/ritonavir in combination with hydroxychloroquine to other drugs. One is a phase 2 trial comparing lopinavir/ritonavir in combination with hydroxychloroquine to two other drugs (imatinib and baricitinib), also in combination with hydroxychloroquine, in subjects with pneumonia due to COVID-19 (NCT04346147). It is claimed that ‘The therapeutic effect of ritonavir and lopinavir could be mainly due to its inhibitory effect on coronavirus endopeptidase C30’ [15]. In this description, it is not clear to me what therapeutic effect of lopinavir is being referred to, maybe HIV, as no beneficial effect has been shown in COVID-19. The inhibitory effect on endopeptidase C30, the SARS-CoV-2 3 C-like proteinase, by lopinavir has been predicted in a model [16] but has not been confirmed in vitro or in vivo.

The second is a phase 2/3 clinical trial (NCT04359095) comparing lopinavir/ritonavir and hydroxychloroquine to hydroxychloroquine alone, hydroxychloroquine in combination with azithromycin or standard care in subjects with pneumonia associated with COVID-19 requiring hospital management. The first part of this trial will have 400 participants to identify treatments with better potential, and to discontinue treatments with higher toxicity. The second part of the trial will have 1200 participants to evaluate the effectiveness of the selected treatments [17]. The first part of the trial will be useful in determining the adverse effects of hydroxychloroquine alone, compared to standard care. If the first part of this trial establishes an excess of adverse effects with hydroxychloroquine alone, which is likely, it will be difficult to continue using it with other drugs, unless marked benefits can also be demonstrated with hydroxychloroquine alone.

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