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Original article

The protease inhibitor lopinavir, boosted with ritonavir, as treatment for COVID-19: a rapid review

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Background: The HIV protease inhibitor lopinavir, boosted with ritonavir, has been used off-label to treat COVID-19. We aimed to synthesize the clinical evidence for lopinavir/ritonavir as a treatment for COVID-19.

Methods: We performed a rapid review by searching databases including PubMed, GoogleScholar, medRxiv, ClinicalTrials.gov and the Cochrane COVID-19 Study Register, for COVID-19 studies comparing outcomes between patients who did and did not receive lopinavir/ritonavir. The quality of evidence was assessed using the GRADE criteria.

Results: We identified five completed randomized controlled trials (RCTs) and 14 retrospective cohort studies. Two large RCTs of 5,040 and 2,771 hospitalized adults with COVID-19 found no evidence that lopinavir/ritonavir influenced the primary outcome of mortality, or secondary outcomes including progression to mechanical ventilation or time to discharge. Results remained similar in all subgroup analyses including by age, gender, baseline ventilation and time since symptom onset. The three smaller RCTs (*n*=86–199) also found no evidence of a benefit in the primary outcomes of time to clinical improvement or time to viral clearance. The 14 observational studies included between 50 and 415 participants, and were limited by a lack of adjustment for potential confounding variables. The majority of these studies found no evidence that lopinavir/ritonavir was associated with improved mortality or other clinical outcomes, although results regarding viral clearance were mixed.

Conclusions: Good evidence from large clinical trials does not support using lopinavir/ritonavir to treat COVID-19 amongst hospitalized patients.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes novel coronavirus disease 2019 (COVID-19), is known to have infected over 51 million people globally at the time of writing, with over 1.2 million reported deaths [1]. Due to limited SARS-CoV-2 testing, the true numbers of cases are likely far higher. Currently, there are few effective treatments for COVID-19 that have been rigorously tested in randomized controlled trials. The rapid spread of the pandemic and urgent need for effective treatments has led to interest in re-purposing currently available drugs for immediate use [2]. The antiretroviral drug lopinavir is a protease inhibitor, which is widely used for the treatment of HIV and is a potential candidate for treatment of COVID-19. Lopinavir is formulated in combination with another protease inhibitor, ritonavir (lopinavir/ritonavir, branded as Kaletra or Aluvia). Ritonavir inhibits the metabolizing enzyme cytochrome P450 3A and thereby increases the half-life of lopinavir [3].

There is preliminary clinical evidence of effectiveness of lopinavir/ritonavir against other coronaviruses such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). During the SARS-CoV outbreak in 2003, an open-label, non-randomized study found reduced risk of severe hypoxia or death in 41 SARS-CoV patients who were treated with lopinavir/ritonavir and ribavirin, compared with 111 historical controls treated with ribavirin alone [4]. However, there has been no evidence from randomized clinical trials to demonstrate the efficacy of lopinavir/ritonavir in treating SARS-CoV or MERS-CoV.

Potential mechanism of action

SARS-CoV-2 is a single-stranded RNA-enveloped betacoronavirus, similar to SARS-CoV and MERS-CoV. These viruses enter host cells and replicate, producing strands of the viral RNA which are translated by host cell ribosomes into polypeptides [2,5]. The enzyme 3-chymotrypsin-like protease ($3CL^{pro}$) cleaves these polypeptides into non-structural proteins. These then replicate and transcribe the viral genome, prior to assembly and release of new progeny viruses [5–7]. As lopinavir is a protease inhibitor, it may inhibit the action of $3CL^{pro}$, which would in turn disrupt the process of viral replication and release from host cells [6,7]. Lopinavir has antiviral activity against SARS-CoV [4] and MERS-CoV [8], and has *in vitro* activity against SARS-CoV-2 with a half-maximal effective concentration (EC_{50}) at 26.63 μM [9]. However, this indicates that SARS-CoV-2 is less susceptible to lopinavir than HIV, as the EC_{50} for lopinavir against HIV is between 0.01–0.03 μM [3]. One reason for the reduced potency may be that coronavirus proteases like $3CL^{pro}$ do not contain a C2-symmetric pocket, which is the target of HIV protease inhibitors [8,10]. Darunavir, another HIV protease inhibitor, was not active against SARS-CoV-2 in an unpublished *in vitro* study [11]. A recent study using *in vitro* and mouse models found stronger evidence for anti-MERS-CoV activity for another antiviral, the RNA-dependent RNA polymerase inhibitor remdesivir, compared with lopinavir/ritonavir [8].

Dosing, safety, side effect profile and drug interactions

The recommended dose of lopinavir/ritonavir for HIV treatment is 400 mg/100 mg twice daily [3]. For COVID-19, the same dose has commonly been used, generally for 14 days [2]. Lopinavir/ritonavir is contraindicated in porphyria and caution is advised in patients with haemophilia, cardiac conduction disorders, pancreatitis, structural heart disease and those with increased risk of cardiovascular disease [12]. Common side effects include gastrointestinal disturbance, in particular diarrhoea, which is often worse in the first few weeks and can be treated with loperamide. Dyslipidaemia, diabetes mellitus, pancreatitis and hepatic disorders have also been reported, but these complications are usually only experienced after several months of therapy [12,13]. Drug interactions with lopinavir/ritonavir are common due to their inhibition of cytochrome P450, which can lead to increased levels of co-administered drugs that are metabolized by this enzyme. Drugs that interact with lopinavir/ritonavir and are commonly used in primary care include the lipid lowering simvastatin, combined oral hormonal contraceptives, anti-epileptic drugs and the inhaled corticosteroid fluticasone [14].

Global use and price

Lopinavir/ritonavir is currently recommended by the World Health Organization as a second-line treatment of HIV, and is used by approximately 580,000 people globally for this indication [15]. With the current interest in repurposing its use for COVID-19, there have been concerns regarding ensuring adequate supply for people living with HIV. Currently, a 2-week course costs approximately £140 (USD 170) in the UK [12], and approximately £6.50 (USD 8) in certain low- and middle-income countries under pooled patent agreements [15].

Here, we used rapid review methods [16] to synthesise the evidence for the use of lopinavir/ritonavir as a treatment for COVID-19.

Methods

We adhered as closely as possible to the PRISMA guidelines for systematic reviews [17]. We searched for clinical trials or observational studies comparing the efficacy of lopinavir/ritonavir against standard care or other drugs, for the treatment of COVID-19 in humans. We excluded studies which had fewer than 15 participants in either the lopinavir/ritonavir or the comparator group, as these studies were unlikely to have statistical power to detect any difference in treatment outcomes. We did not use any language restrictions and included pre-prints. Systematic reviews were used as a point of reference.

Search strategy and selection criteria

We conducted electronic searches in PubMed, GoogleScholar, the Cochrane COVID-19 Study Register, ClinicalTrials.gov and medRxiv on the 13 October 2020. We excluded articles published before 2019. We used search terms including coronavirus*, COVID-19, SARS-CoV-2, lopinavir and Kaletra. Full search terms are listed in Additional file 1. We searched the reference lists of identified articles to find further relevant articles. After removing duplicates, one author conducted title, abstract and full text screening, with any uncertainties checked by a second author. We used the Population, Intervention, Comparator, Outcomes, Study design (PICOS) framework to extract relevant data from selected articles using a standardized form (Table 1) [18]. We assessed the quality of the evidence using the GRADE criteria [19].

Results

We identified a total of 879 records, including 386 through PubMed, 85 through medRxiv, 264 through the Cochrane COVID-19 Study Register, 87 through ClinicalTrials.gov and 57 through GoogleScholar. From these, 175 duplicates were identified, and a

Table 1. PICOS items to guide data extraction

PICOS item	Description
Population	People with suspected or confirmed SARS-CoV-2 infection
Intervention	Lopinavir/ritonavir
Comparisons	No treatment, or other treatments
Outcomes	Clinical outcomes including but not limited to death, intensive care admission, ventilation, hospitalization, oxygen use, clinical signs and symptoms, SARS-CoV-2 viral shedding
Study designs	Randomized controlled trials, observational studies

PICOS, Population, Intervention, Comparator, Outcomes, Study.

further 631 records were excluded through title and abstract screening. 54 studies were further excluded in the full-text screening, including 45 studies that did not compare clinical outcomes between patients receiving lopinavir/ritonavir and those not receiving lopinavir/ritonavir, and 9 studies with sample sizes too small to allow meaningful comparisons. We finally included 19 studies, including 5 completed clinical trials and 14 observational studies (Table 2). Two of the clinical trials provided good quality evidence, one provided moderate quality evidence, and the other included studies were assessed as being at high risk of bias, mainly due to small sample sizes and the lack of adjustment for potential confounders. We present our findings in narrative format as heterogeneity of outcomes and study designs made quantitative synthesis inappropriate.

Clinical trial findings

The RECOVERY trial is an open-label, randomized platform trial of patients hospitalized with clinically suspected or laboratory confirmed SARS-CoV-2 infection in 176 UK hospitals [20]. As part of this study, 5,040 patients were randomized to receive either usual care plus lopinavir/ritonavir 400 mg/100 mg twice daily for 10 days (n=1,616), or usual care alone (n=3,424). Median days from symptom onset to enrolment was similar in both arms (lopinavir/ritonavir 8 days [IQR 5–12], usual care 8 days [IQR 4–12]). There was no difference between the two groups in the primary outcome of mortality by 28 days (rate ratio 1.03, 95% CI 0.91, 1.17; P=0.60). Analyses of pre-specified sub-groups by age, sex, ethnicity, time since symptom onset, respiratory support at randomization and baseline predicted risk also found no evidence of benefit. Secondary outcomes of hospital discharge (risk ratio [RR] 0.98, 95% CI 0.91, 1.05; P=0.53) and a composite of mechanical ventilation or death by 28 days (RR 1.09, 95% CI 0.99, 1.20; P=0.092), were similar between groups. There was one serious adverse event of elevated serum alanine aminotransferase in the lopinavir/ritonavir group, although the authors note that they did not record non-serious adverse reactions.

The SOLIDARITY trial, led by the World Health Organization, is a large, international, randomized platform trial of adults admitted with COVID-19 to 405 hospitals in 30 countries [21]. 1,399 participants randomized to receive lopinavir/ritonavir 400 mg/200 mg twice daily for 14 days, were compared with 1,372 participants who were randomized to receive usual care. The primary outcome of in-hospital mortality was similar in both groups (148/1,399 versus 146/1,372, RR 1.00, 95% CI 0.79, 1.25; P=0.97), and there were no differences in sub-group analyses stratified by age or ventilation status at randomization. Proportions achieving the secondary outcome of progression to requiring ventilation were similar in the lopinavir/ritonavir group (9.6%) and the control group (9.5%). The proportion remaining in hospital at 7 and 14 days (68% versus 59%, 31% versus 22%, respectively) was higher in the lopinavir/ritonavir arm, but the authors hypothesize that this was due to patients being asked to remain in hospital to complete the lopinavir/ritonavir treatment course, and this resolved by 21 days (12% versus 11%). 95% CIs and P-values were not presented for secondary outcomes. Serious adverse events were not reported, but there were no deaths from hepatic failure in the lopinavir/ritonavir arm.

Cao *et al.* [22] conducted an open-label randomized controlled trial at a single hospital in Wuhan, China at the peak of the epidemic there. They enrolled 199 hospitalized adults with a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test, pneumonia and oxygen saturations ≤94% on ambient air, and randomized them to receive lopinavir/ritonavir 400 mg/100 mg twice a day for 14 days (n=99) or standard care (n=100). Median time from onset of illness to randomization was 13 days (interquartile range [IQR] 11–16). Baseline characteristics were similar between the two groups. The median age was 58 years (IQR 49–68). Most patients (55%) were enrolled >12 days after symptom onset, and were severely unwell, requiring urgent clinical attention. After 28 days, intention to treat (ITT) analysis revealed no difference in the primary outcome of time to clinical improvement between the two arms (16 days in both groups; hazard ratio 1.31; 95% CI: 0.95, 1.85; P=0.09). Restricting the analysis to patients enrolled within 12 days of symptom onset did not alter results. When modified ITT analysis was conducted, in which three patients who died within 24 h of randomization and did not receive lopinavir/ritonavir were excluded, there was weak evidence of a small improvement in the time to clinical improvement with lopinavir/ritonavir (median of 15 days versus 16 days, respectively; hazard ratio 1.39 [95% CI: 1.00, 1.91]). There was no effect of lopinavir/ritonavir on the

Table 2. Completed clinical studies of lopinavir/ritonavir treatment for COVID-19 patients

No	Study details	Location	Study population	Design	Interventions	Results	Grade
1	RECOVERY Collaborative Group 2020 [20], NCT04381936	Multi-site, UK	5,040 hospitalized patients with COVID-19. Mean age 66.2 years (SD 15.9). 26% no oxygen, 70% oxygen only, 4% mechanical ventilation. Median 8 days (IQR 4–12) since symptom onset	Open-label RCT	1. Standard care (*n*=3,424); 2. LPV/r 400/100 twice a day for 10 days (*n*=1,616)	Primary outcome: 374 (23%) died by 28 days in LPV/r arm versus 767 (22%) in usual care arm, rate ratio 1.03 (95% CI 0.91, 1.17; *P*=0.60). No differences in subgroup analyses by age, gender, ethnicity, time since symptom onset, respiratory support at randomization or baseline risk. Secondary outcomes: no difference in time to discharge (median 11 days in both groups), nor composite outcome of mechanical ventilation or death (risk ratio 1.09, 95% CI 0.99, 1.2; *P*=0.092)	Good quality due to large sample size and objective primary outcome
2	SOLIDARITY trial consortium [21], NCT04315948	Multi-site, all 6 WHO regions	2,771 adults ≥18 years old hospitalized with COVID-19. 28% no oxygen, 63% oxygen only, 8% ventilated	Open-label RCT	1. Standard care (*n*=1,372); 2. LPV/r 400/100 twice a day for 14 days (*n*=1,399)	Primary outcome: 148 (10.6%) died during admission in LPV/r arm versus 146 (10.6%) in usual care arm (rate ratio, 1.00, 95% CI 0.79, 1.25; *P*=0.97). No difference in subgroup analyses by age, ventilation at admission, geographic region, corticosteroid use. Secondary outcomes: no difference in progression to ventilation (9.6% in lopinavir/ritonavir group versus 9.5% in control group, 95% CIs and *P*-values not presented)	Good quality due to large sample size and objective primary outcome
3	Cao 2020 [22], NCT02845843	Single site, China	199 hospitalized adults ≥18 years with laboratory confirmed SARS-CoV-2, pneumonia and oxygen saturation <94%. 55% enrolled >12 days after symptom onset. Median age 58, 60.3% men, median NEWS =5	Open-label RCT	1. Standard care (*n*=100); 2. LPV/r 400/100 twice a day for 7 days (*n*=99)	Primary outcomes: time to clinical improvement was median of 16 days in each arm. No difference in analysis restricted to those initiated within 12 days of symptom onset. No difference in NEWS score or clinical deterioration. Secondary outcomes: mortality at 28 days lower in LPV/r versus SOC: 19.2% versus 25.0% (difference, -5.8%; 95% CI, -17.3, 5.7). Clinical improvement at 14 days 15% higher in LPV/r versus SOC (95% CI 2.2, 28.8), but no difference at 7 or 28 days. Time in ICU (-5 days, 95% CI -9, 0) and time to discharge	Moderate quality due to small sample size, subjective nature of primary end point, open-label design

AE, adverse event; aHR, adjusted hazard ratio; ARDS, acute respiratory distress syndrome; CT, computed tomography; ICU, intensive care unit; IFN, interferon; LPV/r, lopinavir/ritonavir; NEWS, National Early Warning Score; OR, odds ratio; RBV, ribavirin; RCT, randomized controlled trial.

Table 2. Continued

No	Study details	Location	Study population	Design	Interventions	Results	Grade
						(-1 day, 95% CI -3, 0) shorter in LPV/r arm versus SOC arm. No difference in proportion with clinical improvement at 28 days, time from randomization to death, or duration of oxygen therapy and duration of mechanical ventilation. Virology: no difference in viral RNA over time between arms. Safety: gastrointestinal disturbances were more common in the LPV/r arm. Serious adverse events were numerically lower in the LPV/r versus SOC arm (32.3% versus 20.0%), with lower frequency of ARDS (12.6% versus 27.3%). LPV/r was stopped early in 13.8% due to AEs	
4	Huang 2020 [25], ChiCTR2000029387	Single site, China	101 adults aged 18–65 with mild/moderate, laboratory confirmed SARS-CoV-2. Median 4 days (IQR 1.5–7.0) since symptom onset	Open-label RCT	1. RBV+IFN-α (*n*=33); 2. LPV/r+IFN-α (*n*=36); 3. RBV+LPV/r+IFN-α (*n*=32)	Primary outcome: time to negative SARS-CoV-2 PCR test similar in three arms (13, 12 and 15 days respectively; *P*=0.23). Secondary outcomes: proportion with negative SARS-CoV-2 test at 14 days similar in both arms (51.5% [17/33], 61.1% [22/36] and 46.9% [15/32], respectively). Progression to severe disease also similar between arms (3.0% [1/33] versus 5.6% [2/36], versus 6.3% [2/32], respectively)	Very low due to small sample size, open-label design
5	Li 2020 [23], NCT04252885	Single site, China	86 adults aged 18–80 years with mild/moderate, laboratory confirmed SARS-CoV-2. Mean age 49.4, range 19–79. Median 3.5 days (IQR 2–6) since symptom onset in LPV/r arm	Open-label RCT	1. LPV/r (*n*=34); 2. Umifenovir (*n*=35); 3. No antiviral (*n*=17)	Primary outcome: time to negative pharyngeal SARS-CoV-2 RNA test in LPV/r, umifenovir and control groups was 9.0 (SD 5.0), 9.1 (SD 4.4) and 9.3 (SD 5.2) days, respectively; *P*=0.981. Secondary outcomes: no differences in pyrexia, cough or CT scan improvement at 7 and 14 days. In LPV/r arm, 23.5% deteriorated to severe/critical clinical status, compared with 8.6% in the umifenovir arm and 11.8% in the control arm (*P*=0.186)	Very low due to small sample size, open-label design
6	Grimaldi 2020 [26]	Multi-site, Belgium & France	415 patients with moderate to severe laboratory confirmed COVID-19 ARDS receiving mechanical ventilation. Median 8 days (IQR 7–10) since symptom onset in LPV/r group	Prospective cohort study	1. No treatment (*n*=85); 2. Hydroxychloroquine (*n*=220); 3. LPV/r (*n*=57); 4. Other treatments (*n*=53)	No difference between LPV/r group and no treatment group in proportions alive and extubated by day 28, after adjustment for age, sex, comorbidity, and ventilatory requirements (OR 0.48, 95% CI 0.18, 1.25). Need for renal replacement therapy higher	Very low due to risk of confounding

Table 2. Continued

No	Study details	Location	Study population	Design	Interventions	Results	Grade
						in LPV/r group versus no treatment group (39% versus 17%)	
7	Hu 2020 [29]	Single site, China	323 hospitalized adults with laboratory/radiologically diagnosed COVID-19. Median age 61, range 23–91. Median 9 days (range 1–60) since symptom onset	Retrospective cohort study	1. LPV/r (*n*=28); 2. No LPV/r (*n*=295)	Mortality/severe disease 53.6% in LPV/r-exposed versus 21.4% in unexposed (calculated from data presented in paper; *P*-value and confidence intervals not presented). 12/26 (46.2%) patients with critical disease severity at baseline received LPV/r compared with 5/151(3.3%) with non-severe and 11/146 (7.5%) with severe (*P*<0.001)	Very low due to risk of confounding
8	Cai 2020 [36]	Single site, China	298 hospitalized patients with COVID-19	Retrospective cohort study	1. LPV/r (*n*=229); 2. Favipiravir (*n*=30); 3. No antiviral (*n*=39)	Mortality (overall 0) and ICU admission (overall 10.7%) not described by drug treatment. Median time to viral clearance was similar amongst those who received antivirals (15 days, IQR 10–19) versus those with no antivirals (14 days, IQR 10–19)	Very low due to risk of confounding
9	Chen 2020 [37]	Single site, China	267 patients admitted with laboratory confirmed COVID-19	Retrospective cohort study	1. LPV/r (*n*=75); 2. No LPV/r (*n*=192)	Time to viral clearance was longer in LPV/r group, 14.0 days (IQR 10.0–19.0) versus median 12.0 days, (IQR 8.0–16.0) in control group. Similarly, the hazard of viral clearance was lower in LPV/r group in adjusted analysis taking into account age, disease severity and other clinical factors (aHR 0.70 [0.52–0.94]; *P*=0.017)	Very low due to risk of confounding
10	Rivera-Izquierdo [30]	Single site, Spain	238 adults hospitalized with laboratory confirmed COVID-19	Retrospective cohort study	1. LPV/r (*n*=191); 2. No LPV/r (*n*=47)	No difference in mortality between LPV/r and no LPV/r groups (HR 0.87, 95% CI 0.44, 1.73) when adjusted by calendar time, age, sex, comorbidities and clinical status on admission	Very low due to risk of confounding
11	Zhou 2020 [31]	Two sites, China	191 hospitalized adults with laboratory confirmed COVID-19. Median 11.0 (IQR 8.0–14.0) days since symptom onset	Retrospective cohort study	1. LPV/r (*n*=41); 2. No LPV/r (*n*=150)	Mortality 29.3% in LPV/r exposed and 28% in unexposed, *P*=0.87. Median time to viral clearance was similar amongst those who received LPV/r (19 days, IQR 17–22, *n*=29) versus the whole study population (20 days, IQR 17–24)	Very low due to risk of confounding
12	Wen 2020 [33]	Single site, China	178 patients hospitalized with COVID-19	Retrospective cohort study	1. LPV/r (*n*=59); 2. Umifenovir (*n*=36); 3. LPV/r + umifenovir (*n*=25); 4. No antiviral (*n*=58)	Days to SARS-CoV-2 clearance was similar across all groups (LPV/r =10.20 ±3.49, umifenovir =10.11 ±4.68, LPV/r+ umifenovir =10.86 ±4.74, no antiviral =8.44 ±3.51.	Very low due to small sample size and risk of confounding

Table 2. Continued

No	Study details	Location	Study population	Design	Interventions	Results	Grade
						There were no differences between groups in time to improvement of clinical symptoms or lung CT changes	
13	Gao 2020 [28]	Single site, China	129 adults hospitalized with non-severe, laboratory confirmed COVID-19. Median 5 (IQR 3–7) days from symptom onset	Retrospective cohort study	1. Standard care (*n*=59); 2. LPV/r (*n*=51); 3. Chloroquine (*n*=19)	Time to negative SARS-CoV-2 test was similar in the 3 groups (standard care 21.0 [15.0–28.8] days, LPV/r 23.0 [17.0–35.5] days, chloroquine 16.0 [14.0–41.0] days)	Very low due to small sample size and risk of confounding
14	Yu 2020 [34]	Single site, China	128 adults admitted with laboratory confirmed SARS-CoV-2 (64 adults also coinfected with influenza). Median 8.5 (IQR 7.0–12.0) days since symptom onset	Retrospective cohort study	1. No LPV/r (*n*=91); 2. LPV/r (*n*=37)	Patients receiving LPV/r had higher rate of resolution of lung involvement on CT scan (HR 1.878, *P*=0.020) and shorter time to SARS-CoV-2 negativity (median 13.0 days, IQR 10.0–16.0 in LPV/r group versus median 16.5 days, IQR 12.25–23.75 in control group; *P*=0.003)	Very low due to small sample size and risk of confounding
15	Yan 2020 [38]	Single site, China	120 patients with laboratory confirmed COVID-19	Retrospective cohort study	1. LPV/r (*n*=78); 2. No LPV/r (*n*=42)	Risk of prolonged viral shedding over 23 days was higher in those not exposed to LPV/r, adjusted for age and sex (adjusted OR 2.42, 95% CI 1.10, 5.36; *P*=0.03). Patients initiated on LPV/r within 10 days of symptom onset had shorter viral shedding versus those not on LPV/r (19 days versus 28.5 days; *P*<0.001). Patients on LPV/r more likely to have severe COVID-19	Very low due to risk of confounding
16	Lecronier 2020 [27]	Single site, France	80 patients with laboratory confirmed SARS-CoV-2 infection admitted to ICU and requiring high level oxygen. Median 8 (IQR 6–11) days since symptom onset	Retrospective cohort study	1. Standard care (*n*=22); 2. LPV/r (*n*=20); 3. HCQ (*n*=38)	Treatment escalation (defined as initiation of mechanical ventilation, renal replacement therapy or ECMO) was similar in the three groups (standard care =9 [41%], LPV/r =10 [50%], HCQ =15 [39%], *P*=0.567). No evidence for a difference between groups in ventilator free days, mortality, SARS-CoV-2 negativity at 7 days, liver function tests and acute renal failure were also similar between groups	Very low due to small sample size and risk of confounding
17	Karolyi 2020 [32]	Single site, Austria	67 adults hospitalized with laboratory confirmed severe COVID-19 (requiring oxygen or with bilateral lung consolidation and 2 comorbidities). Median 7 days (IQR 3–10) since symptom onset	Retrospective cohort study	1. LPV/r (*n*=47); 2. HCQ (*n*=20)	No difference between LPV/r and HCQ groups by in-hospital mortality (8.5% versus 15%; *P*=0.418), ICU admission (12.8% versus 20%; *P*=0.470) or length of hospital stay (11 versus 9 days; *P*=0.340). 64.5% were SARS-CoV-2-negative in LPVr group at median 17 days versus 58.3% negative in HCQ group	Very low due to small sample size and risk of confounding

Table 2. Continued

No	Study details	Location	Study population	Design	Interventions	Results	Grade
						at median 15 days. In LPV/r group, 25.2% complained of nausea, 14.9% developed diarrhoea and 15.4% stopped LPV/r due to side effects. 14.9% developed liver enzyme elevation	
18	Kim 2020 [35]	Single site, Korea	65 hospitalized patients with laboratory confirmed COVID-19. Median 7 days (IQR 4–12) since symptom onset	Retrospective cohort study	1. LPV/r (*n*=31); 2. HCQ (*n*=34)	Time to SARS-CoV-2 clearance was significantly lower in the LPV/r group versus the HCQ group (median 21 versus 28 days; *P*=0.029). LPV/r use was associated with SARS-CoV-2 clearance after adjusting for age (aHR 2.28, 95% CI 1.24, 4.21; *P*=0.008). No difference in time to clinical improvement between the two groups. Adverse events (especially increased bilirubin and lymphopenia) were higher in the LPV/r group	Very low due to small sample size and risk of confounding
19	Zhu 2020 [39]	Single site, China	50 patients hospitalized with laboratory confirmed COVID-19. Median 2.5 days (IQR 0–5.0) since fever onset in LPVr group	Retrospective cohort study	1. LPV/r (*n*=34); 2. Umifenovir (*n*=16)	Proportion with negative SARS-CoV-2 RNA test by 14 days was lower in umifenovir group (0/16, 0%) versus the LPV/r group (15/34 44.1%; *P*<0.01). Time to negative test was quicker in the umifenovir group (9.5 days, IQR 5.3–11.0) versus the LPV/r group (11.5 days, IQR 8.8–17.0; *P*<0.01)	Very low due to small sample size and risk of confounding

proportion of patients with clinical improvement at 28 days, time from randomization to death, nor duration of oxygen therapy or mechanical ventilation. There was also no difference in viral clearance between groups. Gastrointestinal symptoms were more common in the lopinavir/ritonavir arm, and 13.8% of patients stopped treatment early due to adverse events. Overall, serious adverse events were higher in the usual care arm (32 versus 19 events), largely due to a higher frequency of acute respiratory distress syndrome (27 versus 12 events).

Li *et al.* [23] report findings from a single-blind randomised controlled trial in China. The investigators initially aimed to enrol 125 adults with laboratory confirmed SARS-CoV-2, but due to control of the epidemic, the trial was limited to 86 participants. Patients with mild or moderate clinical status (with or without signs of pneumonia) were suitable for inclusion. The mean age of was 49.4 years (range 19-79). 34 participants were randomized to receive lopinavir/ritonavir for 14 days, 35 to receive umifenovir (a fusion inhibitor [24]) and 17 to standard care with no antiviral. There was no difference in the primary outcome of mean time to negative pharyngeal SARS-CoV-2 PCR test between the lopinavir/ritonavir, umifenovir and control groups (9.0 [standard deviation (SD) 5.0], 9.1 [SD 4.4] and 9.3 [SD 5.2] days, respectively). There were no differences in pyrexia, cough or lung computed tomography (CT) scan findings at 7 and 14 days. 12 (35.3%) patients in the lopinavir/ritonavir group experienced adverse events (gastrointestinal and deranged liver function), compared with five (14.3%) in the umifenovir group and zero patients in the control group.

Huang *et al.* [25] conducted a single-site, open-label, randomized controlled trial amongst 101 adults hospitalized with laboratory confirmed SARS-CoV-2 infection and mild to moderate COVID-19, defined as respiratory rate <30 breaths per min, oxygen saturations >93% and FiO2 >39.9 kPa. Participants were randomized to receive ribavirin plus interferon-α (*n*=33), or lopinavir/ritonavir plus interferon-α (*n*=36), or lopinavir/ritonavir plus ribavirin plus interferon-α (*n*=32). There was no evidence of a difference in the primary outcome of time to SARS-CoV-2 negativity between the groups (13 versus 12 versus 15 days respectively; *P*=0.23). Secondary outcomes of proportions who were SARS-CoV-2 negative by day 14 (51.5% versus 61.1% versus 46.9% respectively; *P*-value not given), and progression to severe disease (3.0% versus 5.6% versus 6.3%; *P*=0.58) were similar between the three groups.

Observational study findings

We identified 14 observational studies that provided some empirical data for the association of lopinavir/ritonavir with outcomes in patients with COVID-19 (Table 2). These studies were characterized by high risk of bias with respect to the question posed by this review. All studies were among hospitalized patients, with two studies restricted to patients in intensive care units [26,27], and one study limited to 'non-severe' cases (defined as not hypoxic) [28]. Seven studies reported time from symptom onset as being a median of 7 days or longer, while two studies reported a median of less than 7 days. Outcomes reported included mortality (*n*=6 studies) [26,27,29–32], clinical deterioration in COVID-19 severity (*n*=3 studies) [26,27,32], clinical improvement (*n*=4 studies) [32–35] and SARs-CoV-2 RT-PCR clearance (*n*=11 studies) [27,28,31–39]. Only five studies adjusted for potential confounders [26,30,37,38].

Most studies found no association between lopinavir/ritonavir treatment and COVID-19 outcomes. Lopinavir/ritonavir use was not associated with a change in mortality outcomes in five studies [26,27,30–32], or with preventing clinical deterioration in three studies [26,27,32], nor with clinical improvement in three studies [32,33,35]. One Chinese study found that amongst patients receiving lopinavir/ritonavir (*n*=28) a higher proportion developed unfavourable outcomes, including death or disease progression (53.6% versus 21.4%; *P*<0.001), compared with those not on lopinavir/ritonavir (*n*=295) [29]. However, patients with critical disease severity at baseline were more likely to receive lopinavir/ritonavir compared with those with non-severe and severe disease (*P*<0.001), meaning that the worse outcomes amongst those receiving lopinavir/ritonavir could be explained by this bias. Another Chinese study found an association between receiving lopinavir/ritonavir and faster resolution of lung involvement on computed tomography (CT) scan, but patients receiving lopinavir/ritonavir were also more likely to have influenza coinfection, and the scheduling of CT scans was not clear [34]. Regarding clearance of SARS-CoV-2 in RT-PCR testing, results were more mixed. Of the 11 studies, 6 found no association between lopinavir/ritonavir use and SARS-CoV-2 clearance [27,28,31–33,36], while lopinavir/ritonavir was associated with better SARS-CoV-2 clearance in 3 studies [34,35,38] and worse clearance in 2 studies [37,39]. The two studies with shorter time since symptom onset did not find an association between lopinavir/ritonavir use and shorter time to viral clearance [28,35]. Three studies reported increased side effects (gastrointestinal disturbances) [32] and adverse events (liver and renal function derangement) [26,32,35] among patients receiving lopinavir/ritonavir.

Discussion

We identified five randomized clinical trials, including 8,197 hospitalized patients, which assessed lopinavir/

ritonavir as a treatment for COVID-19. Two of these studies provided good quality evidence due to their large sample size and objective primary outcome [20,21], although neither were placebo controlled and results from one of these trials had not yet been peer-reviewed. The remaining three trials had a higher risk of bias; none were blinded and two were under-powered. No randomized trial found a benefit from lopinavir/ritonavir with regard to their primary outcomes which included mortality, time to clinical improvement and negative pharyngeal SARS-CoV-2 PCR test. There was no clear benefit in secondary outcomes, nor in sub-analyses broken down by patients who received treatment earlier in the course of the disease. Gastrointestinal side effects were more common in patients treated with lopinavir/ritonavir compared with controls. We also reviewed 14 observational studies including 2,549 patients, of whom 1,003 received lopinavir/ritonavir. There was no association between use of lopinavir/ritonavir and reduced mortality nor clinical improvement. Results regarding viral shedding were mixed, and in general were unadjusted for potential confounders such as disease severity or concomitant treatments.

Comparison with existing literature

We did not find any other published systematic reviews reporting results of recent, large trials of lopinavir/ritonavir for COVID-19. Our rapid review, containing five RCTs and 14 observational studies, therefore provides an important update.

Strengths and limitations

We used a broad search strategy, and rapid, pragmatic approach that allowed identification of emerging evidence in the evolving COVID-19 pandemic. We adhered as closely as possible to the PRISMA checklist for systematic reviews. We specifically searched for and included pre-prints, because much of the current evidence is being made available in this form in the interest of data sharing during this pandemic. We did not apply language restrictions in order to capture COVID-19-related research being conducted in China. Due to the rapid nature of the review, we did not attempt to contact authors, meaning we were unable to clarify or confirm data where we had queries.

Limitations of the current evidence

We did not find any randomized trials of lopinavir/ritonavir use among patients with COVID-19 in the community, where earlier treatment may be more effective. However, amongst hospitalized patients, there was no evidence of a benefit in sub-group analyses among those treated with lopinavir/ritonavir earlier in the course of the disease. Our review included a large number of observational studies which, by virtue of their design, are more prone to bias. None of the included studies adjusted their analyses for concomitant medication use or COVID-19 severity, which are likely to have affected outcomes. Lack of adjustment for important co-variates (potential confounders) can increase risk of bias. We also excluded many cohort studies from this analysis as they did not specifically describe the number of patients treated with lopinavir/ritonavir for COVID-19, or did not describe a comparator group. This represents a missed opportunity to increase the evidence base to identify treatment strategies for COVID-19.

Implications for research and clinical practice

Ongoing platform randomized trials should continue to assess alternative treatments for COVID-19 in order to determine safety and efficacy [40–42]. Ideally, these would be double blinded, but the urgency and constraints of conducting research in pandemic settings means this has not always been possible [42–44]. These studies are mainly focused on hospital inpatients, and trials of treatments in primary care, where patients are likely to present earlier, should also be prioritized. Developing studies in community settings would allow assessment of whether earlier treatment with repurposed drugs such as lopinavir/ritonavir could prevent the development of serious complications of COVID-19 [45]. Treatments that are hypothesized to have an antiviral effect may be more likely to work earlier during the replicative phase of SARS-CoV-2 infection, rather than later during the inflammatory stage of COVID-19.

In conclusion, we found evidence that lopinavir/ritonavir should not be used to treat COVID-19 amongst hospitalized patients. Further trials of community-based lopinavir/ritonavir treatment may be warranted.

Disclosure statement

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Additional file

Additional file 1: A list of search terms can be found at https://www.intmedpress.com/uploads/documents/AVT-20-OA-4692_Dorward_Addfile_1.pdf

References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020; **20:**533–534.
2. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020; **323:**1824–1836.
3. AbbVie. Kaletra prescribing Information 2020. (Accessed 11 November 2020.) Available from www.rxabbvie.com/pdf/kaletratabpi.pdf
4. Chu CM, Cheng VC, Hung IF, *et al*. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; **59:**252–256.
5. Vastag B. Old drugs for a new bug. *JAMA* 2003; **290:**1695–1696.
6. Zhang L, Lin D, Sun X, *et al*. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors. *Science* 2020; **368:**409–412.
7. Anand K, Ziebuhr J, Wadhwani P, Mesters JR, Hilgenfeld R. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. *Science* 2003; **300:**1763–1767.
8. Sheahan TP, Sims AC, Leist SR, *et al*. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020; **11:**222.
9. Choy KT, Yin-Lam Wong A, Kaewpreedee P, *et al*. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication *in vitro*. *Antiviral Res* 2020; **178:**104786.
10. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov* 2020; **19:**149–150.
11. Johnson & Johnson. Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2. 2020. (Accessed 11 November 2020.) Available from https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus
12. Joint Formulary Committee. British National Formulary 2020. (Accessed 3 April 2020.) Available from https://bnf.nice.org.uk/
13. Domingo P, Suarez-Lozano I, Torres F, *et al*. First-line antiretroviral therapy with efavirenz or lopinavir/ritonavir plus two nucleoside analogues: the SUSKA study, a non-randomized comparison from the VACH cohort. *J Antimicrob Chemother* 2008; **61:**1348–1358.
14. The University of Liverpool. HIV drug interactions. (Accessed 11 November 2020.) Available from https://www.hiv-druginteractions.org/
15. Clinton Health Access Initiative. HIV market report: the state of HIV treatment, testing, and prevention in low- and middle-income countries. Boston, USA; 2019. (Accessed 11 November 2020.) Available from https://www.clintonhealthaccess.org/the-state-of-the-hiv-market-in-low-and-middle-income-countries-2/
16. Plüddemann A, Aronson JK, Onakpoya I, Heneghan C, Mahtani KR. Redefining rapid reviews: a flexible framework for restricted systematic reviews. *BMJ Evid Based Med* 2018; **23:**201–203.
17. PRISMA. PRISMA: transparent reporting of systematic reviews and meta-analyses 2020. (Accessed 11 November 2020.) Available from http://www.prisma-statement.org/
18. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007; **7:**16.
19. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336:**924–926.
20. The RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2020; **396:**1345–1352.
21. Pan H, Peto R, Karim QA, *et al*. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. *N Engl J Med* 2021; **384:**497–511.
22. Cao B, Wang Y, Wen D, *et al*. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020; **382:**1787–1799.
23. Li Y, Xie Z, Lin W, *et al*. Efficacy and safety of lopinavir/ritonavir or Arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. *Med (N Y)* 2020; **1:**105–113.e4.
24. Haviernik J, Stefanik M, Fojtikova M, *et al*. Arbidol (umifenovir): a broad-spectrum antiviral drug that inhibits medically important arthropod-borne flaviviruses. *Viruses* 2018; **10:**184.
25. Huang YQ, Tang SQ, Xu XL, *et al*. No statistically apparent difference in antiviral effectiveness observed among ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha, and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate coronavirus disease 2019: results of a randomized, open-labeled prospective study. *Front Pharmacol* 2020; **11:**1071.
26. Grimaldi D, Aissaoui N, Blonz G, *et al*. Characteristics and outcomes of acute respiratory distress syndrome related to COVID-19 in Belgian and French intensive care units according to antiviral strategies: the COVADIS multicentre observational study. *Ann Intensive Care* 2020; **10:**131.
27. Lecronier M, Beurton A, Burrel S, *et al*. Comparison of hydroxychloroquine, lopinavir/ritonavir, and standard of care in critically ill patients with SARS-CoV-2 pneumonia: an opportunistic retrospective analysis. *Crit Care* 2020; **24:**418.
28. Gao G, Wang A, Wang S, *et al*. Brief report: retrospective evaluation on the efficacy of lopinavir/ritonavir and chloroquine to treat nonsevere COVID-19 patients. *J Acquir Immune Defic Syndr* 2020; **85:**239–243.
29. Hu L, Chen S, Fu Y, *et al*. Risk factors associated with clinical outcomes in 323 coronavirus disease 2019 (COVID-19) hospitalized patients in Wuhan, China. *Clin Infect Dis* 2020; **71:**2089–2098.
30. Rivera-Izquierdo M, Valero-Ubierna MDC, Rd JL, *et al*. Therapeutic agents tested in 238 COVID-19 hospitalized patients and their relationship with mortality. *Med Clin (Barc)* 2020; **155:**375–381.
31. Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395:**1054–1062.
32. Karolyi M, Pawelka E, Mader T, *et al*. Hydroxychloroquine versus lopinavir/ritonavir in severe COVID-19 patients: Results from a real-life patient cohort. *Wien Klin Wochenschr* 2020; doi: 10.1007/s00508-020-01720-y.
33. Wen CY, Xie ZW, Li YP, *et al*. [Real-world efficacy and safety of lopinavir/ritonavir and arbidol in treating with COVID-19: an observational cohort study]. *Zhonghua Nei Ke Za Zhi* 2020; **59:**E012. Chinese.
34. Yu C, Zhang Z, Guo Y, *et al*. Lopinavir/ritonavir is associated with pneumonia resolution in COVID-19 patients with influenza coinfection: a retrospective matched-pair cohort study. *J Med Virol* 2021; **93:**472–480.
35. Kim JW, Kim EJ, Kwon HH, *et al*. Lopinavir-ritonavir versus hydroxychloroquine for viral clearance and clinical improvement in patients with mild to moderate coronavirus disease 2019. *Korean J Intern Med* 2021; **36 Suppl 1:**S253–S263.
36. Cai Q, Huang D, Ou P, *et al*. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. *Allergy* 2020; **75:**1742–1752.
37. Chen X, Zhu B, Hong W, *et al*. Associations of clinical characteristics and treatment regimens with the duration of viral RNA shedding in patients with COVID-19. *Int J Infect Dis* 2020; **98:**252–260.
38. Yan D, Liu XY, Zhu YN, *et al*. Factors associated with prolonged viral shedding and impact of lopinavir/ritonavir treatment in hospitalised non-critically ill patients with SARS-CoV-2 infection. *Eur Respir J* 2020; **56:**2000799.

39. Zhu Z, Lu Z, Xu T, *et al*. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. *J Infect* 2020; **81:**e21–e23.

40. Horby P. Randomised Evaluation of COVID-19 Therapy (RECOVERY) Study Protocol. University of Oxford; 2020. (Accessed 11 November 2020.) Available from https://www.recoverytrial.net

41. REMAP-CAP. REMAP-CAP response to the novel COVID-19 pandemic. (Accessed 11 November 2020.) Available from https://www.remapcap.org/coronavirus

42. Henao Restrepo AM, Moorthy V, Preziosi M-P. ISRCTN83971151: Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients 2020. (Accessed 11 November 2020.) Available from http://www.isrctn.com/ISRCTN83971151

43. Cook DJ, Marshall JC, Fowler RA. Critical illness in patients with COVID-19: mounting an effective clinical and research response. *JAMA* 2020; **323:**1559–1560.

44. Angus DC. Optimizing the trade-off between learning and doing in a pandemic. *JAMA* 2020; **323:**1895–1896.

45. Butler CC, Ogburn E, Allen J, Bongard E, Swazye H, Tonner D. ISRCTN86534580: a trial evaluating treatments for suspected coronavirus infection in people aged 50 years and above with pre-existing conditions and those aged 65 years and above 2020. (Accessed 11 November 2020.) Available from http://www.isrctn.com/ISRCTN86534580.

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