Should hydrochloroquine (HCQ) or chloroquine (CQ) in combination with lopinavir/ritonavir (LPV/r) be used in the treatment of COVID-19?

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KEY FINDINGS

There is currently no evidence to support the use of HCQ or CQ in combination with LPV/r in the treatment of COVID-19 infection.

- Hydrochloroquine (HCQ) or chloroquine (CQ), and lopinavir/ritonavir (LPV/r) are separately being investigated as repurposed investigational drugs for the treatment of COVID-19 infection. HCQ and CQ are antimalarial drugs that are also used in the treatment of rheumatologic conditions LPV/r is a fixed dose combination drug used primarily for the prevention and treatment of HIV infection.
- HCQ and CQ "appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification." Meanwhile, LPV/r inhibits 3-chymotrypsin-like protease for preoteolysis.[1]
- One in-vivo study in a mouse model found that the LPV/r combination enhanced the antimalarial activity of amodiaquine, a drug similar to chloroquine, against *Plasmodium berghei*.[2] A study with both in-vitro and in-vivo components showed that ritonavir had the greatest synergistic effect on the antimalarial action of chloroquine against *P. falciparum* and *P. chabaudi*, among the HIV protease inhibitors studied, including lopinavir.[3]
- There are no published clinical studies investigating the combination of HCQ or CQ plus LPV/r. However, six ongoing clinical trials were found on this combination (See Table 1).
- A single case study and a case series reported lowered or heightened tacrolimus levels, and severe gastrointestinal symptoms during the use of the combination of HCQ or CQ plus LPV/r in patients with solid transplants, necessitating discontinuation of the antiviral therapy.
- The COVID-19 clinical practice guidelines in New South Wales indicated that clinicians could prescribe this combination, off-label antiviral therapy on a case-by-case basis for deteriorating and critically ill patients.

RESULTS

There are no published clinical studies investigating the combination of HCQ or CQ plus LPV/r. However, six ongoing clinical trials were found on this combination (See Table 1). These studies were being conducted in China. Iran, Japan and Australia. One study, the REMCAP study, was being done in multiple countries. The specific comparators to this specific combination included monotherapy CQ, monotherapy LPV/r, monotherapy interferon (INF) β 1a, monotherapy interleukin-1 (IL-1) receptor antagonist, combination therapy with INF β 1a and 1b, combination with oseltamivir, levamisole + budesonide/formoterol, no antiviral, no immune modulation and usual care. The common outcomes included in these studies were mortality, negative PCR testing, length of hospital stay and ICU admission, time to negative testing and clinical improvement, and incidence of serious adverse events.

A case study reported extremely elevated tacrolimus trough levels in a COVID-19 patient who had kidney transplant four days after starting hydroxychloroquine 200 mg bid, lopinavir/ritonavir 400/100 mg bid and ceftriazone 2 g daily.[4] Similarly, a case series of 18 patients with solid organ transplant found that out of the eight patients who had lopinavir/ritonavir and hydroxychloroquine, two had to prematurely discontinue lopinavir/ritonavir due to inability to reach target tacrolimus levels and severe gastrointestinal symptoms.[5]

The New South Wales Department of Health, in its *Health Interim Guidance on the Use of Antiviral Therapy in COVID-19*[6], mentions that for deteriorating or critically ill patients, "good supportive care is current best practice… and in the interim, treating clinicians who elect to prescribe off-label antiviral therapy on a case-by-case basis in NSW should only consider Kaletra (lopinavir / ritonavir) +/- hydroxychloroquine." There is no mention of this combination treatment in any available COVID-19 clinical practice guidelines from the WHO, Canada, US, Europe, Italy, UK, Spain, Japan, and China. It is also not included in the WHO R&D Blueprint document on *Informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection*[7].

CONCLUSION

There is currently no evidence to support the use of HCQ or CQ in combination with LPV/r in the treatment of COVID-19 infection. Adverse events reported in patients with solid organ transplants who used this combination include lowered or heightened tacrolimus levels, and severe gastrointestinal symptoms.

DECLARATION OF CONFLICT OF INTEREST

LPV is participating in the ACT-COVID trial, which will investigate HCQ or CQ + Azithromycin for the treatment of COVID-19. DLRPT declares no relevant conflict of interest.

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Table 1. Characteristics of clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	ChCTR2000029609 A prospective, open-label, multiple center study for the efficacy of chloroquine phosphate in pateints with novel coronavirus pneumonia (COVID-19)	Not yet recruiting	Febuary 12, 2020 to December 31, 2020	prospective, open-label, multiple center study	China	205 adults ≥ 18 years, diagnosed with 2019 nCoV pneumonia according to national guidelines mild to moderate pneumonia: 177 pxs severe pneumonia: 28 pxs	Mild to Moderate Group: lopinavir/ritonavir	Mild to Moderate Group: Oral CQ phosphate vs. Oral Lopinavir/ritonavir Severe Oral CQ phosphate vs. Oral Lopinavir/ritonavir	Viral nucleic acid negative-tranforming time 28-day all-cause mortality total length of hospitalization ICU admission ratio Length of ICU stay
2	NCT04331470 Evaluation of Efficacy of Levamisole and Formoterol+Budesonide in Treatment of COVID-19	Recruiting	Estimated completion date: May 20, 2020	Double blind, parallel, randomized controlled trial	Iran	30 participants with confirmed COVID-19 Ages 15 to 100 years	Levamisole 50 mg 1-2 tables every 8 hours + Budesonide+Formoterol 1-2 puff every 12 hours Plus HCQ 200 mg single dose + LPV/r 2 tablets every 12 hours	HCQ 200 mg single dose + LPV/r 2 tablets every 12 hours	1: negative chest CT, negative PCR test within 3-7 days 2: Symptom relief within 3-7 days
3	NCT04343768 An Investigation Into Beneficial Effects of Interferon Beta 1a, Compared to Interferon Beta 1b And The Base Therapeutic Regiment in Moderate to Severe COVID-19: A Randomized Clinical Trial	Enrolling by invitation	April 10-24, 2020	Open label, RCT with three arms	Iran	Confirmed COVID-19 cases by either RT-PCR or CT-Scan, aged 18 years and older, with tympanic temperature of ≥37.5 and at least one of the ff: cough, sputum production, nasal discharge, myalgia, headache or fatigue; onset of symptoms should be ≤ 10 days; NEWS2 ≥ 1 on admission (National Early Warning Score 2)	Experimental Arm 1: Hydroxychloroquine + Lopinavir / Ritonavir + Interferon-β 1a Experimental Arm 2: Hydroxychloroquine + Lopinavir / Ritonavir + Interferon-β 1b	Active Comparator Arm: hydroxychloroquine + Lopinavir / Ritonavir	Primary: Time to clinical improvement until 14 days later (Improvement of two points on a seven-category ordinal scale or hospital discharge) Secondary: Mortality until 14 days later SpO2 improvement at days 1,2,3,4,5,6,7,14 Incidence of new MV use until 14 days later Duration of hospitalization from randomization until discharge or death, up to 14 days Cumulative incidence of any serious adverse

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
									events (not specified)
4	NCT02735707 Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP)	Recruiting	April 11, 2016 to June 2022	randomized, embedded, multifactorial, adaptive platform trial	Multiple countries	Total of 6800 participants Adult patients admitted to an ICU for severe CAP within 48 hours of hospital admission with: i. symptoms or signs or both that are consistent with lower respiratory tract infection AND ii. Radiological evidence of new onset consolidation (in patients with pre-existing radiological changes, evidence of new infiltrate) 2. Requiring organ support with one or more of: i. Non-invasive ii. Invasive ventilatory support; iii. Receiving infusion of vasopressor or inotropes; Aged 18 years old and older COVID Specific Inclusion Criteria: •COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing • Microbiological testing for SARS-CoV-2 infection of upper or lower	Aside from the corticosteroid and antibiotic domains for community-acquired pneumonia, the following interventions are specific for COVID-19: 1. Lopinavir/ritonavir 2. Hydroxychloroquine 3. Hydroxychloroquine + Lopinavir/ritonavir 4. Interferon-β1a 5. Anankira (IL-1 receptor antagonist)	Aside from the corticosteroid and antibiotic domains for community-acquired pneumonia, the following comparators are specific for COVID-19: 1. No antiviral 2. No immune modulation	Primary: All cause mortality until 90 days Days alive and outside of ICU until 21 days (primary endpoint for patients with suspected or proven pandemic infection) Secondary: ICU Mortality ICU length of stay Hospital length of stay Ventilator free days Organ failure free days All-cause mortality Health-related Quality of life assessment (EQ5D-5L and WHODAS 2.0) Proportion of intubated patients who receive a tracheostomy Destination at time of hospital discharge Readmission to the index ICU during the index hospitalization Other COVID specific outcomes: Occurrence of serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
						respiratory tract secretions or both has occurred or is intended to occur			Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinical testing)
5	jRCTs031190227 A prospective multi-center open trial to evaluate the safety and efficacy of triple combination therapy of lopinavir , ritonavir and hydroxychloroquine sulfate in patients infected with COVID-19.	Recruiting	April 1, 2020-present	prospective multi-center open trial	Japan	Individuals aged 20 years old and above, positive result for COVID-19 detection test, fever above 37.5 degree Celsius, or pneumonia shadow on chest X-ray or CT-scan, hospital admission	lopinavir, ritonavir and hydroxychloroquine with oseltamivir	lopinavir, ritonavir and hydroxychloroquine without oseltamivir	ratio of C-reactive protein before versus after the treatment disappearance rate of COVID-19
6	ACTRN12620000445976 Australasian COVID-19 Trial (ASCOT). A multi-centre randomised clinical trial to assess clinical, virological and immunological outcomes in patients with SARS-CoV-2 infection (COVID-19) treated with lopinavir/ritonavir and/or hydroxychloroquine compared to standard of care	Not yet recruiting	April 10, 2020 to present	Randomised controlled trial	Australia and New Zealand	1. Age 18 years and over 2. Confirmed SARS-CoV-2 by nucleic acid testing in the past 12 days 3. Able to be randomised within 12 days of symptom onset 4. Expected to be remain an inpatient for at least 48 hours from the time of randomization	1. Lopinavir (400mg)/ritonavir (100mg) twice daily for 10 days 2. Hydroxychloroquine800mg twice a day (4x200mg administered 12 hours apart) on Day 1, followed by 400mg twice a day for 6 days 3. Lopinavir (400mg)/ritonavir (100mg) twice daily for 10 days plus hydroxychloroquine 800mg twice a day (4x200mg administered 12 hours apart) on Day 1, followed by 400mg twice a day for 6 days	Control: usual routine medical care	Primary outcome: Proportion of participants alive and not having required intensive respiratory support (invasive or non-invasive ventilation or humidified high flow nasal oxygen flow) at 15 days after enrolment. Secondary outcomes: WHO 7-point outcome scale; Mortality at 7, 15, 28, 90 days; Time to death; Length of hospital stay; Receipt of invasive or non-invasive ventilation in first 28 days; Length of receipt of invasive or non-invasive ventilation; Length of ICU stay; Presence of chest infiltrates on CXR or

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
									CT at day 3 and day 7; Time to defervescence from randomization; Biomarker levels – C-reactive protein (CRP), Lactate dehydrogenase (LD or LDH), D-Dimer; Antibiotic use – number of days of use in first 10 days; Safety. Any of the following adverse events in first 10 days. - Diarrhoea – grade 2 or greater - Nausea – grade 2 or greater - Vomiting – grade 2 or greater - Pancreatitis – grade 2 or greater - QTc prolongation (>500ms) 24 hours following initial dose of study drugs; Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital; Viral clearance. Proportion of patients with negative SARS-CoV-2 RT-PCR at day 3 and day 7 from upper or lower respiratory tract samples.;

Appendix 2. Literature search

DATABASE	SEARCH STRATEGY / SEARCH TERMS
Medline	(((((Lopinavir) OR "lopinavir"[MESH])) AND ((ritonavir) OR "ritonavir"[MESH]))) AND (((("hydrochloroquine"[MESH] OR ""chloroquine"[MESH] OR hydroxychloroquine OR chloroquine)))
CENTRAL	Lopinavir [all text] AND ritonavir [all text] AND (chloroquine [all text] OR hydroxychloroquine [all text])
Trial Registries	
ClinicalTrials.gov	Lopinavir/Ritonavir[intervention] Kaletra [intervention]
Chinese Clinical Trial Registry	Lopinavir Ritonavir Chloroquine [intervention] AND COVID-19 [disease] OR Lopinavir Ritonavir Hydroxychloroquine [intervention] AND COVID-19 [disease]
EU Clinical Trials Register	lopinavir AND ritonavir AND (chloroquine OR hydroxychloroquine)
Republic of Korea - Clinical Research Information Service	Lopinavir Ritonavir Chloroquine [intervention] AND COVID-19 [disease] OR Lopinavir Ritonavir Hydroxychloroquine [intervention] AND COVID-19 [disease]
Japan Primary Registries Network/ NIPH Clinical Trials Search	Lopinavir
WHO ICTRP Database (COVID-19 trials)	Lopinavir AND chloroquine [intervention]