European Review for Medical and Pharmacological Sciences 2020; 24: 8592-8605

Lopinavir/ritonavir for the treatment of SARS, MERS and COVID-19: a systematic review

M. VARGAS[1], G. SERVILLO[1], S. EINAV[2]

[1]Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", Naples, Italy
[2]General Intensive Care Unit of the Shaare Zedek Medical Center and Hebrew University Faculty of Medicine, Jerusalem, Israel

Abstract. – OBJECTIVE: Lopinavir/ritonavir has been used for the treatment of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) coronavirus infections. It has been suggested that, based on this experience, this drug should also be studied in SARS-CoV2 infection.

MATERIALS AND METHODS: We performed a systematic review of the literature regarding the use of lopinavir/ritonavir for the treatment of these three infections. We systematically searched the PubMed database from inception to April 30th, 2020, to identify *in-vitro* and animal studies and any reports of human use of lopinavir/ritonavir for the treatment of SARS, MERS and COVID-19. We also searched the Clinicatrial.gov to identify ongoing trials.

RESULTS: Five in-vitro studies evaluated the effect of lopinavir/ritonavir in SARS. Three additional *in-vitro* studies reported the EC50 of the antiviral activity of lopinavir/ritonavir in MERS. We identified no *in vitro* studies evaluating the effect of lopinavir/ritonavir on the novel coronavirus. Two retrospective matched-cohort studies reported the use of lopinavir/ritonavir in combination with ribavirin for SARS patients. Three case reports and one retrospective study described the use of lopinavir/ritonavir in MERS. Twenty-two papers describe the use of lopinavir/ritonavir in adult patients with COVID-19.

CONCLUSIONS: The existing literature does not suffice for assessing whether Lopinavir/ritonavir has any benefit in SARS, MERS or COVID-19.

Key Words:
COVID-19, SARS, MERS, Lopinavir/ritonavir.

PROSPERO registration number: CRD42020180990.

Introduction

As of April 18th, 2020, the World Health Organization (WHO) reported more than 2 million confirmed cases of SARS coronavirus-2 and more than 150,000 deaths attributable to coronavirus disease 2019 (COVID-19)[1]. Pulmonary radiological examination of patients with COVID-19 often reveals patchy infiltrates, and in some patients, the initial manifestation progresses to extensive bilateral ground-glass opacities[2]. Among those patients developing a critical illness, two-thirds develop a severe form of pulmonary disease that was initially thought to be acute respiratory distress syndrome (ARDS)[3] but is now understood to be somewhat different in at least some of the patients[3]. The reported mortality of COVID-19 disease among confirmed cases approximates 6% globally and may be even higher in Europe[1].

At this time, there is no proven treatment for COVID-19 disease and questions have arisen regarding the justification for administering specific antiviral therapies in infected patients. Severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS) and COVID-19 are infections caused by the same family of coronaviruses that causes COVID-19, all of which possess a positive-sense single-stranded RNA genome[4].

Lopinavir is an antiretroviral protease inhibitor widely used for the treatment of HIV[5]. Ritonavir was the second protease inhibitor approved in 1996 for the treatment of HIV in the United States. Ritonavir was originally designed to inhibit HIV protease but its ability to inhibit cytochrome P450-3A4 is nowadays considered of greater value as it is more often used to increase the bioavailability of other antiretroviral drugs which it is co-administered with[5]. The combina-

Corresponding Author: Maria Vargas, MD; e-mail: vargas.maria82@gmail.com

tion of Lopinavir/Ritonavir has been proposed for the treatment of coronaviruses because of its potential effect on viral replication at the cellular level. Therefore, we performed a systematic review of the evidence regarding the use of Lopinavir/Ritonavir for SARS, MERS and COVID-19.

Materials and Methods

This systematic review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.

We systematically searched the PubMed database from inception to 30 April 2020 to identify *in-vitro* and animal studies and any reports of human use of Lopinavir/Ritonavir for the treatment of SARS, MERS and COVID-19. English language restrictions were imposed (see detailed search strategy in **Supplementary Figure 1**). We also searched the Clinicatrial.gov registry to identify ongoing trials. Two authors (MV, GS) independently screened the databases and the trial registries and extracted relevant information. Discrepancies and doubts regarding the relevance of the sources were solved by consensus or, when required, by the adjudication of a third author (SE).

This review protocol has been registered in PROSPERO International Prospective Register of systematic reviews (www.crd.york.ac.uk/PROSPERO) (registration number: CRD42020180990).

Overall, 39 studies were identified, one of which was a randomized controlled trial. See PRISMA flow chart for the inclusion-exclusion process (**Supplementary Figure 1**)

Data From Preclinical Studies on SARS, MERS and COVID-19

The assumption underlying the conduction of preclinical studies was that Lopinavir/Ritonavir may inhibit specific proteases involved in viral RNA replication (e.g., the enzyme 3-chymotrypsin-like protease)[6]. Table I presents the data from preclinical studies on lopinavir/ritonavir.

Three computerized biochemical models have suggested a possible effect of Lopinavir/Ritonavir specifically on SARS CoV and SARS CoV2 proteinase[7-9].

Three *in-vitro* studies evaluated whether Lopinavir/Ritonavir affects the SARS coronavirus[10-12]. One *in-vitro* study[10] sought inhibition of the main proteinase of SARS-CoV by Lopinavir/Ritonavir but found no such effect (see details in Table I). Two other *in-vitro* studies identified the EC_{50} (i.e., the drug concentration which induces a response halfway between the baseline and maximum after a specified exposure time; a measure of drug potency) of the antiviral activity of Lopinavir/Ritonavir in SARS[11,12]. One study identified the EC50 of Lopinavir/Ritonavir in susceptible isolates to be 6 μg/ml[11] and the second study showed it was 4 μg/ml[12], more than 1000-fold less effective than the effect of this drug on HIV[5].

Three additional *in-vitro* studies reported the EC_{50} of the antiviral activity of lopinavir/ritonavir in MERS[13-15]. One study showed that an EC50 of 8 μg/ml of Lopinavir/Ritonavir inhibited *in-vitro* replication of MERS-CoV at low molecular range[13]. Another study showed that an EC50 of 8.5 μg/ml had lower antiviral activities compared with ribavirin and interferon-b[14]. The third study reported no cytopathic effect of Lopinavir/Ritonavir on MERS-CoV but did not report the EC50[15]. Finally, two animal studies evaluated the use of Lopinavir/Ritonavir combined with interferon-β in MERS and noted both laboratory and clinical effects[14,16]. One study was conducted in a mice model of MERS and reported that prophylactic use of Lopinavir/Ritonavir slightly reduced viral loads without affecting lung function while therapeutic use of Lopinavir/Ritonavir improved pulmonary function but did not reduce virus replication or severe lung pathology[14]. The second study showed that marmosets treated with Lopinavir/Ritonavir had improved clinical scores, fewer pulmonary infiltrates and bronchointerstitial pneumonia and had lower mean viral loads in necropsied lung and extrapulmonary tissues[16].

We identified no *in-vitro* studies evaluating the effect of Lopinavir/Ritonavir on SARS coronavirus-2.

Data from Clinical Studies on SARS and MERS

Table II summarizes the data from clinical studies regarding the effect of Lopinavir/Ritonavir on SARS and MERS. Two retrospective matched-cohort studies reported the use of Lopinavir/Ritonavir in combination with ribavirin for SARS patients[17,12]. One study included overall 152 patients infected with SARS (41 treated patients *vs.* 111 historical controls) and reported a much lower unadjusted incidence of the composite outcome as ARDS or death (2.4% *vs.* 28.8% respectively) at day 21 after symptom

Table I. Preclinical studies evaluating the role of lopinavir/ritonavir in SARS, MERS. And COVID-19. MERS: Middle East Respiratory Syndrome, SARS: Severe Acute Respiratory Syndrome.

Biochemical modelling studies				
References	**Disease**	**Antiviral activity (EC_{50})**	**Aim of the study**	**Results**
Nukoolkan et al[7]	SARS	-	Biochemical modeling of potential inhibition of main SARS-CoV-proteinase ($3CL^{pro}$)	The results show that flap closing was clearly observed when the inhibitors bind to the active site of SARS-CoV 3CL(pro). The binding affinities of LPV and RTV to SARS-CoV 3CL(pro) do not show any significant difference. In addition, six hy-drogen bonds were detected in the SARS-LPV system, while seven hydrogen bonds were found in SARS-RTV complex.
Zhang et al[8]	SARS	-	Biochemical modeling of potential inhibition of main SARS-CoV-proteinase ($3CL^{pro}$)	The binding analysis of SARS-CoV main proteinase with HIV, psychotic and para-site drugs (lopinavir, ritonavir, niclosamide and promazine) suggests that these ex-isting drugs can be used as starting points for designing SARS-CoV proteinase in-hibitors.
Nutho et al[9]	COVID-19	-	Biochemical modeling of potentia inhibition of main inhibitor and SARS-CoV-2 $3CL^{pro}$	The binding pattern and susceptibility of lopinavir and ritonavir in complex with SARS-CoV-2 $3CL^{pro}$ were pro fully revealed by all-atom MD simulations, binding free energy estimation, and PIEDA based on the MM/PB(GB)SA and FMO-MP2/PCM/6-31G* calculations.
***In-vitro* studies**				
Yamamoto et al[10]	SARS	-	Activity of compounds against SARS associated coronavirus in Vero cell cultures	Lopinavir did not affect the replication of SARS-CoV
Chen et al[11]	SARS	6 μg/ml	*In-vitro* antiviral susceptibility of 10 isolates of SARS coronavirus to commercially available antiviral agents	Lopinavir has detectable antiviral activities on the Vero cell lines
Chu et al[12]	SARS	4 μg/ml + 50 μg/ml ribavirin	*In-vitro* antiviral activity against SARS associated coronavirus	*In-vitro* antiviral activity against SARS associated coronavirus was demonstrated for lopinavir and ribavirin at concentrations of 4 micro g/ml and 50 micro g/ml, respectively, only at 48 hours.
De Wilde et al[13]	MERS	8.0 μM	Inhibition of MERS replication	Lopinavir inhibits the *in vitro* replication of MERS-CoV at low-micromolar range (50% effective concentrations [EC(50)s], 3 to 8 μM)
Sheahan et al[14]	MERS	8.5 μM	*In-vitro* antiviral activity against MERS-CoV	Ritonavir does not significantly enhance the *in-vitro* antiviral activity of lopinavir. Lopinavir/ritonavir less antiviral activities compared with ribavirin and interferon-b.
Chan et al[15]	MERS	-	Cytopathic effect inhibition	Lopinavir was not found to be active on MERS-CoV CPE inhibition essay

Table continued

Table I *(Continued)*. Preclinical studies evaluating the role of lopinavir/ritonavir in SARS, MERS. And COVID-19. MERS: Middle East Respiratory Syndrome, SARS: Severe Acute Respiratory Syndrome.

Animal studies				
Reference	**Disease**	**Drugs studied**	**Aim of the study**	**Results**
Sheahan et al[14]	MERS	Lopinavir/ritonavir + interferon-β	Prophylactic and therapeutic use of lopinavir/ritonavir combine with interferon-β in a mice model	Prophylactic Lopinavir/ritonavir + interferon-β slightly reduces viral loads without affecting lung function. Therapeutic lopinavir/ritonavir + interferon-β improves pulmonary function but does not reduce virus replication or severe lung pathology
Chan et al[16]	MERS	Lopinavir/ritonavir + interferon-β1b	Use of lopinavir/ritonavir alone or in combination with interferon β1b in one marmoset	The lopinavir/ritonavir-treated and interferon-β1b-treated animals had better out-come than the untreated animals, with improved clinical (mean clinical scores ↓50.9%-95.0% and ↓weight loss than the untreated animals), radiological (minimal pulmonary infiltrates), and pathological (mild bronchointerstitial pneumonia) find-ings, and lower mean viral loads in necropsied lung (↓0.59-1.06 log10 cop-ies/glyceraldehyde 3-phosphate dehydrogenase; $p < .050$) and extrapulmonary (↓0.11-1.29 log10 copies/GAPDH; $p < .050$ in kidney) tissues

Table II. Characteristics of clinical studies evaluating lopinavir/ritonavir for the treatment of SARS and MERS.

Reference	Virus studied	Number of patients (study/controls)*	Type of study	Lopinavir/ritonavir dose	Outcome
Chan et al[17]	SARS	1052 (75/977)	Retrospective matched cohort study	Given as treatment or as salvage therapy. Study group: 400 mg/100 mg, orally twice a day for 10 to 14 days, and ribavirin 1.2 g three time daily for 10-14 days	Overall mortality: 5/75 in treatment group and 147/977 in control group with early treatment mortality 2.3% *vs.* 15.6% and in intubation rate 0% *vs.* 11%.
Chu et al[12]	SARS	152 (41/111)	Retrospective matched cohort study	Given as treatment. Study group: 400 mg/100 mg, orally twice a day for 14 days, and ribavirin 1.2 g three time daily for 14 days	Rate of death or ARDS by day 21: 0/41 in treatment group and 7/111 in control group
Meyer et al[18]	MERS	1 (1/0)	Case report	Given as treatment. Dose not reported	Patient survived with complete clinical recovery
Kim et al[19]	MERS	1 (1/0)	Case report	Given as treatment. 400 mg/100 mg, orally twice a day for 7 days	Patient survived
Spanakis et al[20]	MERS	1 (1/0)	Case report	Given as treatment. 400 mg/100 mg, orally twice a day, for 10 days	Patient died
Park et al[21]	MERS	43 (22/43)	Retrospective matched cohort study	Given as prophylaxis. 400 mg/100 mg, orally twice a day, for 11 to 13 days	40% decrease in the risk of infection
Choi et al[22]	MERS	138 (120/138)	Retrospective study	Given as treatment in 120 patients. Dose not reported	24/120 died

*Number of treated patients/total number of patients included in the antiviral treatments. ARDS: Acute Respiratory Distress Syndrome, MERS: Middle East Respiratory Syndrome, SARS: Severe Acute Respiratory Syndrome.

onset[12]. The second study included 75 patients treated with Lopinavir/Ritonavir. Among these, 44 patients received Lopinavir/Ritonavir as initial treatment and were compared to 634 controls, and 31 received Lopinavir/Ritonavir as rescue therapy and were compared to 343 controls. All controls were matched for age, sex, comorbidity, and the initial LDH level within 5 days of onset of symptoms. Only early (rather than rescue) use of Lopinavir/Ritonavir with ribavirin was associated with lower intubation (0% *vs.* 11%) and mortality (2.3% *vs.* 15.6%) rates[17].

Three case reports and one retrospective study described the use of Lopinavir/Ritonavir in MERS patients[18-20]. Lopinavir/Ritonavir was used in combination with ribavirin and interferon in two case reports; one patient died and two survived[18-20]. One retrospective matched-cohort study evaluated the use of Lopinavir/Ritonavir as post-exposure prophylaxis in 43 healthcare workers at a high risk of MERS exposure[21]. Post-exposure prophylaxis was associated with a 40% reduction in the risk of infection[21]. One retrospective study used Lopinavir/Ritonavir as treatment in 120 out of 138 patients and 24 of the 120 patients died[22]. At this time a randomized controlled trial is ongoing regarding the use of lopinavir/ritonavir in MERS (ClinicalTrials.gov, NCT02845843. Registered on July 27th, 2016)[23].

Data from Clinical Studies on COVID-19

Table III summarizes the data from clinical studies regarding the effect of Lopinavir/Ritonavir on COVID-19. Six case reports described the use of 400/100 mg twice daily of Lopinavir/Ritonavir for 9-10 days and all of

Table III. Characteristics of included studies evaluating the use of Lopinavir/Ritonavir in patients with COVID-19. NR: information not reported.

Author	Study design	N patients who received Lopinavir/Ritonavir in intervention group	N patients in control group	Intervention/s	Drug dosage/s	Duration of treatment (days)	Outcome
Kim et al[24]	Case report	1	0	1 patient received Lopinavir/Ritonavir	Lopinavir/Ritonavir 400/100 mg twice daily	10	Discharged alive
Lim et al[25]	Case report	1	0	1 patient received Lopinavir/Ritonavir	Lopinavir/Ritonavir 400/100 mg twice daily	9	Discharged alive
Guillen et al[26]	Case report of patient with kidney transplantation	1	0	1 patient received Lopinavir/Ritonavir	Lopinavir/Ritonavir 400/100 mg twice daily	10	After 10 days of supportive and anti-viral treatment, the patient presented a worsening in respiratory symptoms, with hypoxia in spite of the use of high-flux nasal oxygen delivery, and a progression to diffuse bilateral infiltrates on chest X-ray. Interferon Beta was initiated at this moment
Bartiromo et al[27]	Case report of kidney transplanted patient with Senior-Loken syndrome	1	0	1 patient received Lopinavir/Ritonavir	Lopinavir/Ritonavir 400/100 mg twice daily	NR	Lopinavir/ritonavir was suspended after 2 days and replaced by darunavir/cobicistat due to the onset of nausea and diarrhea
Ghiasvand et al[28]	Case report	1		1 patient received Lopinavir/Ritonavir	Lopinavir/Ritonavir 400/100 mg twice daily, oseltamivir 75 mg twice daily, hydroxychloroquine 400 mg daily	NR	Discharged alive
Zhang et al[29]	Case report of patient with lung cancer	1	0	1 patient received Lopinavir/Ritonavir	NR	14	Discharged alive
Wang et al[30]	Case series	4	0	4 patients received Lopinavir/Ritonavir	Lopinavir/Ritonavir 400/100 mg twice a daily	6-16	2 patients were discharged alive while 2 patients were still hospitalized
Liu et al[31]	Case series	5+4+1/10	0	5 patients received Lopinavir/Ritonavir + immunoglobulin + interferon 2b, 4 patients received Lopinavir/Ritonavir + interferon 2b, 1 patient received Lopinavir/Ritonavir alone	Lopinavir/Ritonavir 400/100 mg twice daily, interferon-2b 5 million U twice daily, immunoglobulin 20 g every day	NR	3/10 transferred 7/10 discharged Three patients stopped lopinavir because of adverse effects, two of them deteriorated, one was hospitalized longer than others who with sustained lopinavir use

Table continued

Table III *(Continued)*. Characteristics of included studies evaluating the use of Lopinavir/Ritonavir in patients with COVID-19. NR: information not reported.

Author	Study design	N patients who received Lopinavir/Ritonavir in intervention group	N patients in control group	Intervention/s	Drug dosage/s	Duration of treatment (days)	Outcome
Young et al[32]	Case series	5/18	0	5 patients received Lopinavir/Ritonavir alone	NR	14	0/5 died 3/5 improved 2/5 developed Progressive respiratory failure 4/5 patients developed nausea, vomiting, and/or diarrhea 3-7 developed abnormal liver function test results, only 1 completed the full 14-day treatment
Cheng et al[33]	Case series	2/5	3	2 patients received Lopinavir/Ritonavir alone	Lopinavir/Ritonavir 400/100 mg twice daily	6-8	Lopinavir/ritonavir did not shorten the duration of SARS CoV-2 viral shedding in patients with mild pneumonia.
Fernandez-Ruiz et al[34]	Case series of patients after solid organ transplantation	9/18	0	9 patients received Lopinavir/Ritonavir alone	Lopinavir/Ritonavir 200/100 mg twice daily and/or hydroxychlo-roquine 200 mg twice daily	14	4/9 died Lopinavir/ritonavir was prematurely discontinued in two patients due to the impossibility to reach the target tacrolimus levels and severe gastrointestinal symptoms
Xu et al[35]	Retrospective case series	25+21/62	0	25 patients received Lopinavir/Ritonavir 21 patients received Lopinavir/Ritonavir + arbidol	Lopinavir/Ritonavir 400/200 mg twice daily, arbidol 200 mg three time daily	NR	1 patient was discharged 1 patient was still hospitalized
Ye et al[36]	Retrospective Case control	42/47	5	42 patients received Lopinavir/Ritonavir alone 5 patients received arbidol and interferon	Lopinavir/Ritonavir 400/200 mg twice daily. Interferon 5 million U daily, arbidol 200 mg three time daily	10	Compared with controls, patients treated with Lopinavir/Ritonavir had: - More rapid decrease in body temperature - Less abnormal alanine aminotransferase and aspartate aminotransferase. - Decrease in the number of days to negative nCoV-RNA testing
Chen et al[37]	Retrospective cohort study	75/99	0	75 patients received Lopinavir/Ritonavir + oseltamivir + ganciclovir	Lopinavir/Ritonavir 400/100 mg twice daily, oseltamivir 75 mg twice daily, ganciclovir 250 mg twice daily	3-14	11/99 died 31/99 discharged 57/99 still hospitalized
Wan et al[38]	Retrospective cohort study	135	0	135 patients received Lopinavir/Ritonavir + interferon	NR	NR	1/135 died

Table continued

Table III *(Continued)*. Characteristics of included studies evaluating the use of Lopinavir/Ritonavir in patients with COVID-19. NR: information not reported.

Author	Study design	N patients who received Lopinavir/Ritonavir in intervention group	N patients in control group	Intervention/s	Drug dosage/s	Duration of treatment (days)	Outcome
Deng et al[39]	Retrospective cohort study	33	0	16 patients received Lopinavir/Ritonavir + arbidol 17 patients received Lopinavir/Ritonavi alone	NR	5-21	SARS-CoV-2 not detected in the nasopharyngeal specimens: After 7 days – in 75% of patients (12/16) with combination treatment *vs*. 35% (6/17) with monotherapy ($p < 0{\cdot}05$). After 14 days – in 94% (15/16) *vs*. 52·9% (9/17) ($p < 0{\cdot}05$). Chest CT scans were improving: After 7 days – in 69% (11/16) *vs*. 29% (5/17) ($p < 0{\cdot}05$)
Zhou et al[40]	Retrospective, multicenter cohort study	41/191	0	41 patients received Lopinavir/Ritonavir	NR	NR	12/41 died Among 29 patients who received lopinavir/ritonavir and were discharged, the median time from illness onset to initiation of antiviral treatment was 14.0 days (IQR 10.0-17.0) and the median duration of viral shedding was 22.0 days (18.0-24.0). The median duration of viral shedding was 19.0 days (17.0-22.0) in patients with severe disease status and 24.0 days (22.0-30.0) in patients with critical disease status.
Zhu et al[41]	Retrospective study	34/50	16 patients received arbidol	34 patients received Lopinavir/Ritonavir	Lopinavir/Ritonavir 400/100 mg twice daily Arbidol 200 md three time daily	7	All comparisons unadjusted. Fever duration similar in the two groups ($p = 0.61$). On post-admission day 14: - Viral load undetectable in arbidol group but still found in 44.1% (15/34) of Lopinavir/Ritonavir group. - Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group ($p < 0.01$). No side effects apparent found in either group

Table continued

Table III ***(Continued).*** Characteristics of included studies evaluating the use of Lopinavir/Ritonavir in patients with COVID-19. NR: information not reported.

Author	Study design	N patients who received Lopinavir/Ritonavir in intervention group	N patients in control group	Intervention/s	Drug dosage/s	Duration of treatment (days)	Outcome
Sun et al[42]	Retrospective study	165/217	54	165 patients received Lopinavir/Ritonavir and umifenovir	NR	NR	76 adverse drug reactions and 16 severe adverse drug reactions were found in antiviral group. 18 adverse drug reactions and 1 severe adverse drug reaction was found in the other group treated with chloroquine or antibacterial drugs.
Zhou et al[43]	Observational study	26/26	0	26 asymptomatic patients received 1 patient received Lopinavir/Ritonavir	NR	NR	3 patients developed clinical symptoms of COVID-19
Cai et al[44]	Open label non randomized control study	45/80	35 patients received favipiravir + interferon-alpha	45 patients received Lopinavir/Ritonavir + interferon- alpha,	Lopinavir/Ritonavir 400/100 mg twice daily, favipiravir 1600 mg twice daily, interferon-alpha 5 million U twice daily	1-14	Shorter viral clearance [4 (2.5-9) *vs.* 11 (8-13) days] and more rapid resolution of chest imaging abnormalities (91.43% *vs.* 62.22%) with faviripavir compared with Lopinavir/Ritonavir
Cao et al[45]	Randomized, controlled, open-label trial	99/199	100 patients received, standard care comprised as necessary, supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation	99 patients received Lopinavir/Ritonavir	Lopinavir/Ritonavir 400 /100 mg twice daily	14	14/99 died in Lopinavir/Ritonavir group *vs.* 25/100 in control group. Lopinavir/ritonavir not associated with a statistically significant difference in time to clinical improvement

the patients described in these reports were discharged alive[24-29]. Six case series reported the use of Lopinavir/Ritonavir, either alone or in combination[30-34]. In three case series where Lopinavir/Ritonavir was used alone, none of the patients died[29,30,32,33]. Lopinavir/Ritonavir was used alone in nine COVID-19 patients after solid organ transplantation and four patients died[34]. In the one case series where Lopinavir/Ritonavir was used in combination with interferon, no patients died[31].

Eight retrospective cohort studies reported the use of Lopinavir/Ritonavir, either alone or in combination with other drugs[35-42]. In two retrospective studies, 36 patients received Lopinavir/Ritonavir in combination with arbidol. No deaths were reported among patients receiving Lopinavir/Ritonavir with or without arbidol[35,39]. The authors also reported improved resolution in lung computed tomography, assessed by the degree of involvement of different lobes, in the lopinavir/ritonavir plus arbidol group[35,39]. The third retrospective study described the use of Lopinavir/Ritonavir concomitantly with oseltamivir and ganciclovir in 75 of 99 patients (no control group). The outcomes of patients receiving antiviral therapy were described together with those who received none and at the time of publication, the majority of patients were still being treated[37]. In the fourth retrospective study, 42 patients who received Lopinavir/ritonavir plus arbidol and interferon were compared to 5 patients treated only with arbidol and interferon. The time to normalization of systemic temperatures, lymphocyte count and C-reactive protein was briefer in patients receiving Lopinavir/ritonavir and viral RNA became undetectable earlier[36]. In the fifth retrospective study, 135 patients received Lopinavir/ritonavir in conjunction with interferon and 1/125 patients died[38]. In the sixth retrospective study, 41/191 patients were noted to have been treated with Lopinavir/Ritonavir but the report was unclear as whether these patients were also treated with steroids or intravenous immune globulin. However, 12/41 patients died and 29/41 were discharged[40]. In the seventh retrospective study, 34 patients who received Lopinavir/Ritonavir were retrospectively compared to 16 patients who received arbidol. No difference was observed in the clinical parameters sought but viral shedding was briefer with arbidol[41]. The eighth retrospective study aimed to identify adverse drug reactions in patients with COVID-19. The prevalence of such reactions was 37.8% (most commonly gastrointestinal and liver system disorders) and 63.8% of these were attributed to the use of Lopinavir/Ritonavir[42].

An observational study described prophylactic use of Lopinavir/Ritonavir in 26 asymptomatic participants at high-risk of COVID-19 infection and noted that three patients developed clinical symptoms nonetheless[43].

Finally, one open-label non-randomized study compared treatment with Lopinavir/Ritonavir to alternative treatment options. This study compared patient outcomes following 14 days of treatment with either Lopinavir/Ritonavir (400/100 twice daily, n=45 patients) or favipiravir (1600 mg twice daily, n= 35 patients)[44]. A shorter duration of time to viral clearance and more rapid resolution of lung computed tomography findings were observed with favipiravir[44]. One open-label randomized controlled trial evaluated the use of Lopinavir/Ritonavir (400 mg/100 mg orally twice a day for 14 days) in 99 patients compared to 100 patients treated with standard care[45]. No differences were observed between the groups in the rates of clinical improvement, hospital discharge or 28-day viral clearance[45]. However, 48% of the patients randomized to Lopinavir/Ritonavir had an adverse event and gastrointestinal symptoms were more common in the Lopinavir/Ritonavir group[45].

Ongoing Studies

We identified 16 registered clinical trials that intend to evaluate the effectiveness and the safety of Lopinavir/Ritonavir alone or in combination for treating COVID-19 (Table IV).

Discussion

The recent interim guidance from the American Thoracic Society made no suggestion either for or against treatment with lopinavir-ritonavir for patients with COVID-19 and pneumonia[46]. This the first systematic review of the existing literature regarding treatment with lopinavir/ritonavir in coronavirus infections, including COVID-19 disease. In human case reports, series and studies of SARS, MERS or Covid-19, Lopinavir/ritonavir was most commonly used at a dose of 400 mg/100 mg twice daily for a period of 7-14 days. Data synthesis was not possible due to the poor quality of the studies identified.

Table IV. Ongoing trials evaluating antiviral drugs against COVID-19 that include Lopanivir/Ritonavir in one of their treatment arms. https://clinicaltrials.gov.

Drug	Mechanisms of action	Clinical trials (n°)	N participants planned/Randomized
Lopinavir-Ritonavir	• Lopinavir/ritonavir – protease inhibitors for HIV/AIDS	NCT04295551 NCT04286503 NCT04255017 NCT04321174	80/? 520/yes 400/yes 1220/yes
ASC09/Ritonavir, Lopinavir/Ritonavir, and/or Umifenovir	• ASC09 – HIV-1 protease inhibitor; • Ritonavir and lopinavir/ritonavir-protease Inhibitors for HIV/AIDS; • Umifenovir – entry inhibitor against influenza	NCT04261907 NCT04350684	160/yes 40/yes
ASC09/Oseltamivir, Ritonavir/Oseltamivir, Oseltamivir	• Oseltamivir – asialidase inhibitor for influenza	NCT04261270	60/yes
Darunavir/Cobicistat alone or with Lopinavir/Ritonavir and Thymosin α1	• Darunavir and cobicistat – an HIV-1 protease inhibitor and inhibitor of cytochrome P450 (CYP)3A enzyme, approved as a combination against HIV-1/AIDS • Thymosin α1 – immune response boosting agent	NCT04252274	30/yes
Interferon alfa-2b alone or in combination with Lopinavir/Ritonavir and/or Ribavirin	• Interferon alfa-2b – recombinant cytokine with antiviral properties; • Ribavirin – guanine derivative	NCT04254874 NCT04276688 NCT04291729 NCT04275388 NCT00578825 NCT04251871 NCT04350671	100/yes 70/yes 50/no 348/yes 340/yes 150/yes 40/yes
Arbidol and/or Lopinavir/Ritonavir	• Ardidole – immunomodulating agent	NCT04252885	125/yes
Chloroquine and/or Lopinavir/Ritonavir and/or remdesivir	• Cloroquine – antimalarial drug	NCT04330690 NCT04346147 NCT04328285 NCT04359095 NCT04331470 NCT04328012 NCT04364022 NCT04321993 NCT04351724 NCT04365582 NCT04343768 NCT04315948 NCT04366245	400/yes 165/yes 1200/yes 1600/yes 30/yes 4000/yes 400/yes 1000/no 500/yes 640/yes 60/yes 3100/yes 72/yes

Lopinavir/ritonavir has been evaluated as a potential treatment for SARS and MERS. Clinical studies performed on patients with SARS showed an association between treatment and reduced mortality and intubation rates. But these were retrospective, observational studies which did not enable inference of causation[12,17]. A systematic review of lopinavir/ritonavir for the treatment of SARS and MERS also found that the studies available do not suffice to draw meaningful conclusions[47].

Strikingly, more than 750 patients have already been treated with Ritonavir-lopinavir and still there is limited evidence regarding the use of lopinavir/ritonavir in COVID-19 disease. Our systematic review identified only one randomized

controlled trial. This randomized controlled trial which included 199 patients did not find that the use of lopinavir/ritonavir conferred any clinical or laboratory advantage when compared with standard care but did raise some concern regarding potential side effects[45].

Although at this time no single therapy has been proven unarguably effective for treating COVID-19[29], the variety of combination drug therapies further confound analysis. The timing of Lopinavir/Ritonavir has also been proposed to be an important determinant of effectivity as this drug combination may only be effective when administered in the early phase of peak viral replication (initial 7-10 days)[16,18]. The ever-growing number of clinical trials launched to investigate potential therapies for COVID-19 highlights both the urgency and the need to produce high-quality evidence on the topic[48]. Several randomized clinical trials have been registered regarding treatment with Lopinavir/Ritonavir in patients with COVID-19 disease and their estimated completion dates range between March 2020 and March 2022. Until more data is forthcoming, we encourage the use of Lopinavir/ritonavir alone or in combination for COVID-19 only within the framework of registered clinical studies and with concomitant data collection regarding adverse events.

Conclusions

The existing literature does not suffice for assessing whether Lopinavir/ritonavir has any benefit in SARS, MERS and COVID-19. Additional RCTs which are expected to yield more data on the use of lopinavir/ritonavir are ongoing for both MERS infection and COVID-19.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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