Should lopinavir/ritonavir combined with interferon-beta be used in the treatment of COVID-19?

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KEY FINDINGS

Currently, there is **NO EVIDENCE** on combined lopinavir/ritonavir and interferon-beta among patients with COVID-19. There are on-going clinical trials on this combined antiviral therapy: two randomized and a non-randomized controlled trial for patients with COVID-19.

- Lopinavir/ritonavir (LPV/r) is one of the repurposed drugs combined with interferon-beta (IFN-β1b) suggested to be used as antiviral therapy for patients with COVID-19 [1].
- Lopinavir-ritonavir (LPV/r) is used primarily in HIV infections while interferon-beta is well-known in treating patients with multiple sclerosis and is considered as the most potent interferon in reducing Middle East respiratory syndrome coronavirus (MERS-CoV) [2, 5-7].
- The combination of LPV/r and IFN-β1b when used *in vitro* and *in vivo* resulted to an indistinguishable effect to viral loading when compared with that of interferon-beta alone [4]. Nevertheless, the lack of drug interactions in LPV/r and IFN-β1b combination made it seem safe for future clinical trials [8].
- Currently, there is no completed clinical trial on combined lopinavir/ritonavir and interferon-beta among patients with COVID-19.
- However, there are on-going trials investigating specifically the effects of LPV/r plus interferon-beta among patients with COVID [13, 14, 15] and MERS [16].
- Antiviral therapies are not currently recommended by international institutions for routine use [17,18, 20] in acute respiratory failure among patients with COVID-19.

RESULTS

Currently, there is no completed clinical trial on combined lopinavir/ritonavir and interferon-beta among patients with COVID-19. However, there are on-going trials investigating specifically the effects of LPV/r plus interferon-beta among adult patients with COVID-19 in various countries including China and Europe [13, 14, 15]. In these trials, lopinavir/ritonavir will be taken orally (400mg/100mg) every 12 hours for 14 days with daily injection of interferon-beta for 6 days. The study in China is expected to end in December 2020 while the other two clinical trials will end within four years.

Table 1 contains the table for characteristics of these on-going trials.

CONCLUSION

Combined lopinavir/ritonavir and interferon-beta still lacks evidence in improving clinical outcomes among patients even with coronavirus in general. However, randomized clinical trials are already underway and their results are needed to determine its effects among patients with COVID-19.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of on-going 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	ChiCTR2000031196 Clinical efficacy of novel coronavirus infection treated by combination of interferon regimen and ritonavir tablets	On-going	January 10, 2020 – December 31, 2020	Prospective non-randomized control	China	n = 60 • 16-85 years old • nCoV was detected by real-time fluorescence RT-PCR in sputum, throat swabs, and lower respiratory tract secretions based on the novel coronavirus infection suspected case standard • sequencing of viral genes homologous to known nCoV	lopinavir/ritonavir (Kaletra) tablets and interferon	routine medical treatment	1. time till the SARS-COV-2 clearance 2. novel coronavirus nucleic acid clearance rate 3. adverse reaction rate
2	ISRCTN83971151 Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients	On-going, Recruiting	March 1, 2020 – March 25, 2021	open-label randomized, clinical trial	Multicountry	• adults (aged ≥ 18 years) recently hospitalized,or already in the hospital with definite COVID-19	Local standard of care and any of the study drugs: • remdesivir (daily infusion for 10 days) • chloroquine or hydroxychloroquine (2 oral loading doses, then orally twice daily for 10 days) • Lopinavir/ ritonavir (orally twice daily for 14 days) • Lopinavir/ ritonavir (orally twice daily for 14 days) PLUS interferon-beta (daily injection for 6 days)	local standard of care	1. all-cause mortality 2. duration of hospital stay (hours) 3. Time to first receiving ventilation (or intensive care) (hours)
3	NCT04315948 Multi-centre, Adaptive, Randomized Trial of the Safety and Efficacy of Treatments of COVID-19 in Hospitalized Adults (DisCoVeRy)	On-going, Recruiting		randomized controlled trial parallel, open label stratification based on European region, severity of illness at enrolment	Multicenter in Europe	n = 3100 • adults (aged ≥ 18 years) • with laboratory-confirmed SARS-CoV-2 infection using PCR or other public health assay in any specimen < 72 hours prior to randomization • has at least one of the ff: - evidence of	Standard of care and any of the following • Remdesivir • Lopinavir/ritonavir (200mg/50mg) • Lopinavir/ritonavir and interferon-beta 1A • Hydroxychloroquine	Standard of care	1. Percentage of subjects reporting severity using 7-point ordinal scale 2. Time to discharge 3. No. of oxygenation free days in 28 days 4. Incidence and duration of high

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						rales/crackles - SpO2 ≤ 94% on room air • women of childbearing potential must agree to use contraception			flow oxygen device use 5. Incidence and duration of mechanical ventilation use 6. Duration of hospitalization 7. Mortality 8. Cumulative incidence of SAEs 9. Cumulative incidence of Grade 3 or 4 AEs 10. changes in laboratory results
4	NCT02845843 MERS-CoV Infection treated with a combination of lopinavir /ritonavir and interferon beta-1b: a multicenter, placebo-controlled, double-blind randomized trial	On-going, Recruiting	July 2016 – December 2020	parallel, double-blind, two-stage group sequential, multicentre, placebo controlled	Saudi Arabia	n = 194 • adults (aged ≥ 18 years) • laboratory confirmed MERS-CoV infection using RT-PCR from any diagnostic sampling source • new organ dysfunction clinically-related to MERS including: - hypoxia - hypotension - renal impairment - risk stage by RIFLE criteria - thrombocytopenia - gastrointestinal symptoms	Lopinavir/ritonavir (400mg +100 mg / ml twice daily for 14 days) and interferon beta-1b (0.25 mg subcutaneous every alternate day for 14 days)	Placebo	1. 90-day mortality 2. organ support-free days for 28 days 3. RT-PCR cycle threshold value in lower respiratory samples 4. sequential organ failure assessment (SOFA) scores 5. length of ICU stay 6. length of hospitalization 7. duration of mechanical ventilation use 8. serial chest radiograph findings