EVIDENCE SUMMARY

Should lopinavir/ritonavir be used as chemoprophylaxis among individuals exposed to patients with COVID-19?

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RECOMMENDATION

We recommend against the use of lopinavir/ritonavir for chemoprophylaxis in individuals exposed to COVID-19 patients. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues

The panel strongly recommends against the use of lopinavir/ritonavir for chemoprophylaxis because of very low quality of evidence. The drug combination is not commercially available and can only be availed of through the HIV program. In addition to the limited accessibility, there might also be competition with HIV patients who need it as regular regimen. Given the limited supply in the country, it is not deemed to be a feasible intervention for prophylaxis since a large quantity of lopinavir/ritonavir will be required in such cases.

Key Findings

There is currently no available direct evidence on the use of lopinavir/ritonavir in the prevention of COVID-19 among healthy individuals, particularly those exposed to confirmed COVID-19 individuals. There is very low quality indirect evidence of lopinavir/ritonavir as post-exposure prophylaxis for an outbreak of MERS-CoV.

Introduction

Several measures have been recommended on how to prevent and mitigate the spread of COVID-19 such as wearing of masks, personal protective equipment, social distancing, testing and contact tracing. The use of pharmacologic agents as pre-exposure and post-exposure prophylaxis as a preventive strategy in COVID-19 are still being investigated. Lopinavir/ritonavir has been utilized as post-exposure chemoprophylaxis among Korean health care workers during the outbreak of Middle East Respiratory syndrome (MERS) [1]. As such, it is one of the anti-viral agents being investigated as a potential agent for chemoprophylaxis for COVID-19.

Review Methods

We sought articles investigating the use of lopinavir/ritonavir (I) in the prevention of COVID-19 (O) among healthy individuals or health care workers exposed to COVID-19 patients (P).

We performed a systematic literature search in online databases such as MEDLINE, CENTRAL, and Google Scholar. Additional searches in MedRxiv, clinicaltrials.gov, and WHO ICTRP were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used search terms such as “lopinavir,” “ritonavir,” “kaletra,” “prevention,” “prophylaxis” and “COVID-19.” References from review articles were also manually searched for additional articles.

Results

The initial search from all the databases retrieved 571 references. After removal of duplicates, letters, narrative reviews, screening of abstracts and studies not meeting the inclusion criteria, we retrieved 21 full text articles. There is one COVID clinical practice guideline that was retrieved while the rest were narrative reviews and ongoing clinical trials. After a comprehensive and systematic search, we found no direct completed studies on the use of lopinavir/ritonavir in the prevention COVID-19

During the MERS-COV outbreak in Korea, a non-randomized clinical trial assessed the efficacy of lopinavir/ritonavir (with ribavirin) as post-exposure prophylaxis (PEP) among health care workers (n=43) exposed to a confirmed MERS-COV case. None of the HCW in the PEP group developed MERS compared to six (28%) in the non-PEP group (OR 0.05, CI 0.0028, 1.01). No adverse events were observed in the use of lopinavir/ritonavir with ribavirin for two weeks [2].

The use of lopinavir/ritonavir as PEP was also evaluated for its associated adverse events. A randomized clinical trial evaluated the rate of discontinuation and tolerability of two PEP regimens for HIV infection: zidovudine/lamivudine plus either lopinavir/ritonavir (n=131) or atazanavir (n=124). Both arms experienced similar rates of adverse events (49% lopinavir/ritonavir vs 43% atazanavir), majority of which were mild. The use of lopinavir/ritonavir, compared to atazanavir, was not associated with increased risk of adverse events (OR 1.2 CI 0.7, 2.2) [3].

Recommendations from Other Groups

A clinical practice guideline from Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM) and Chinese Research Hospital Association (CRHA) [4] found insufficient evidence for or against any agents as both pre-exposure or pre-exposure prophylaxis for COVID-19.

Clinical practice guidelines from WHO, IDSA, US NIH, UK NHS, or PSMID made no recommendation on the use of SNI in the prevention of COVID-19.

Ongoing Studies

Currently, there are three clinical trials being conducted in Canada, France, and Switzerland on the use of lopinavir/ritonavir as chemoprophylaxis for COVID-19 that are awaiting completion (Appendix).

References

[1] Gentile I, Maraolo AE, Piscitelli P. COVID-19 : Time for Post-Exposure Prophylaxis ? 2020;17–9.

[2] Park SY, Lee JS, Son JS, Ko JH, Peck KR, Jung Y, et al. Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. J Hosp Infect [Internet]. 2019 Jan;101(1):42–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0195670118304845

[3] Diaz-Brito V, Leon A, Knobel H, Peraire J, Domingo P, Dalmau D, et al. Post-exposure prophylaxis for HIV infection: a clinical trial comparing lopinavir/ritonavir versus atazanavir each with zidovudine/lamivudine. 2012;346:337–46.

[4] Jin Y, Zhan Q, Peng Z, Ren X, Yin X, Cai L, et al. and discharge management of COVID-19 : An evidence-based clinical practice guideline (updated version). 2020;1–33.

Appendix 1: Characteristics of Included Studies

Title/Author	Study design	Sample Size	Population	Intervention Group(s)	Control	Outcomes
Park, 2018	Non-RCT	N=43	Health care workers	Lopinavir+ritonavir+ ribavirin post exposure prophylaxis	post exposure prophylaxis	Attack rate of MERS COV
Diaz-Brito, 2012 (for adverse events)	Randomized controlled trial	N=255	Emergency room patients exposed to HIV, receiving PEP	Lopinavir/ritonavir	Atazanavir	Adverse events reported in 50/102 [49%] in the lopinavir/ritonavir arm, 42/98 [43%] in the atazanavir arm. Difference not significant (p=0.38).

Appendix 2: GRADE Evidence Profile

Author(s):
Question: Lopinavir/ritonavir compared to minimum health standards for prevention of COVID-19
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	lopinavir/ritonavir	minimum health standards	Relative (95% CI)	Absolute (95% CI)		
Incidence of infection												
1	observational studies	serious	not serious	very serious	not serious	none	0/22 (0.0%)	6/21 (28.6%)	**OR 0.0500** (0.0028 to 1.0100)	**266 fewer per 1,000** (from 285 fewer to 2 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events												
1	randomised trials	very serious	not serious	serious	not serious	none	50/102 (49.0%)	42/98 (42.9%) (Control: Azatanavir)	**OR 1.2** (0.7 to 2.2)	**45 more per 1,000** (from 84 fewer to 194 more)	⨁◯◯◯ VERY LOW	CRITICAL

Appendix 3: Summary of Ongoing Studies

Registration Number	Title	Population	Interventions	Comparator	Outcome
NCT04321174 (recruiting)	COVID-19 Ring-based Prevention Trial With Lopinavir/Ritonavir (CORIPREV-LR)	High risk close contact with a confirmed COVID-19 case during their symptomatic period	Lopinavir/ ritonavir x 14 days	none	microbiologic evidence of infection
NCT04328285 (active, not recruiting)	Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers (COVIDAXIS)	Adult healthcare workers (HCWs) involved at the time of enrolment in the care and the management of patients with confirmed or suspected SARS-CoV-2 infection	Lopinavir/ ritonavir	placebo	occurrence of SARS-COV2 infection
NCT04364022 (recruiting)	Efficacy of Pragmatic Same-day COVID-19 Ring Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland (COPEP)	Documented close contact with a PCR-confirmed SARS-CoV-2 positive individual	Lopinavir/ ritonavir	none	21-day incidence of COVID-19 in individuals exposed to SARS-CoV- 2 who are asymptomatic at baseline