Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

3CL^{pro} inhibitors as a potential therapeutic option for COVID-19: Available evidence and ongoing clinical trials

The genus Betacoronavirus includes severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Historically, these two coronaviruses had got great clinical importance in infecting humans [1]. At present, the novel coronavirus strain, SARS-CoV-2, the causative agent of COVID-19 emerged in Wuhan, China, in December 2019 [2] and has rapidly spread throughout the world.

According to European Center for Disease prevention and Control (ECDC) report, since 31 December 2019 and as of 20 March 2020, 242,488^{+} cases of COVID-19 (in accordance with case definitions of affected countries) have been reported, including 9885 deaths reported from 59 countries. The top three countries highly affected with COVID-19 are China, Italy, and Spain [3]. As of 20 March 2020, 34 African countries have also reported COVID-19 cases [3]. As per the World Health Organization (WHO) report, the total number of cases and deaths outside China has overtaken the total number of cases in China [4]. WHO has declared COVID-19 a worldwide pandemic and Europe as a new epicenter of COVID-19 with worst situations being observed in Italy. WHO has recommended laboratory tests for any suspected cases alongside quarantining suspects, applying social distancing and frequent handwashing to contain the spread of 2019-nCoV [4]. Despite such preventive measures, there is no recommended drug therapy officially approved by United States Food and Drug Administration (FDA) for COVID-19. At present, there are several classes of drugs undergoing clinical trials including RNA polymerase inhibitors (Remdesivir and Favipiravir), protease inhibitors (Lopinavir/ritonavir), anti-inflammatory agents, angiotensin converting enzyme type 2 (ACE 2) blockers, convalescent plasma, RNA antisense technologies, monoclonal antibodies, and Chinese traditional medicines (http://www.chictr.org.cn/index.aspx and https://clinicaltrials.gov/ct2/home).

Protease inhibitors including lopinavir and ritonavir are currently available in both first and second-line antiretroviral therapy regimens in pediatrics and adult HIV/AIDS patients, respectively. China's national health commission has recommended using these agents as an *ad-hoc* treatment against COVID-19. Since 2019-nCoV infection is an RNA virus similar to HIV, lopinavir/ritonavir is proposed for management of 2019-nCoV infection despite the absence of official approval of these drugs for the treatment of COVID-19. At present, lopinavir/ritonavir is widely used for possible treatment of 2019-nCoV infection in countries that the emerging infection exists [5]. Countries like Belgium has prepared interim clinical guidance for the treatment of patients suspected of/confirmed with COVID-19. In this guideline, lopinavir/ritonavir may be used as one alternative despite the absence of sufficient efficacy data. https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf.

The SARS-CoV main proteinase (M^{pro}), also called 3-Chymotrypsin like protease (3CL^{pro}), plays a key role in proteolytic processing of viral polyproteins, essential proteins for viral replication and function, is considered as a key drug target. Previous molecular dynamic simulation analysis indicated that there was equavalent binding affinities of lopinavir and ritonavir towards SARS-CoV 3CL^{pro}. In addition, six and seven hydrogen bonds were detected in the SARS-CoV-lopinavir and SARS-CoV–ritonavir complexes, respectively [6]. Accordingly, inhibitors that block the cleavage function of 3CL^{pro} can be expected to inhibit virus replication, making this enzyme one of the most attractive targets for treatment of COVID-19. Though the SARS-CoV-2 (2019-nCoV) could be quite different in structure, lopinavir and ritonavir may have clinical efficacy against SARS-CoV-2, as seen in the response against SARS-CoV [6].

As per the China's treatment recommendations, pediatric respiratory infections caused by SARS-CoV-2 infection can be treated by combination of protease inhibitors, most importantly lopinavir/ritonavir (LPV/r) (per kg basis) and/or Interferon-α2b nebulization (based on severity) [5]. A case report regarding the treatment of COVID-19 patient in Korea indicated that administration of LPV/r (Kaletra®) to the patient significantly reduced the viral loads and no or little coronavirus titers were observed upon further treatment [7].

With visiting the US National Library of Medicine (NLM) (https://clinicaltrials.gov/ct2/home) and Chinese clinical trial registries (http://www.chictr.org.cn/index.aspx), 25 registered clinical trials were retrieved in total since the outbreak of COVID-19 (12 and 13 from US, and Chinese clinical trial registry, respectively).

Out of 12 registered trials in the US NLM, 11 of them are randomized, open label controlled trials whereas the remaining is a non-randomized, open label clinical trial (Supplemental Table 1). There is no registered randomized, blinded and placebo controlled clinical trial to fully evaluate the safety and efficacy of protease inhibitors in real clinical settings till the time of this review. Out of 13 clinical trials registered in China, 11 of which are randomized, open label clinical trials whereas the rest two are non-randomized, open label clinical trials showing no randomized, blinded, and placebo controlled trial registered yet (Supplemental Table 2). One randomized, open label clinical trial registered in China (http://www.chictr.org.cn/showprojen.aspx?proj=48684) with trial identifier No: ChiCTR2000029308 was completed and the finding has been published at the New England Journal of Medicine on 18 March, 2020. As stated in the table, the primary end point of this trial was clinical improvement time within 28 days following randomization. According to the finding, treatment with lopinavir/ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio: 1.24; 95 % confidence interval, 0.90–1.72). Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group though a secondary outcomes measures were found promising in lopinavir/ritonavir group [8]. This trial was initiated in severe COVID-19 patients lately and lacks blinding and well established placebo. Hence, it is too infant to conclude the poor clinical benefits of

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lopinavir/ritonavir as it requires randomized, multicenter, double blind, placebo controlled clinical trials in large cohort of patients and in all stage of the disease (mild, moderate and severe) to fully investigate the safety and efficacy of these drugs in real scenario.

With regard to the recruitment status and phases of the study, 6 out of 12 in US and 11 out of 13 in Chinese registries have recruited participants. Two phase 2, three phase 3 and three phase 4 trials were identified from US clinical trial registry. Two phase 4 trials were also identified from Chinese clinical trial registry. Regarding the intervention, 4 trials (including discovery trial) from the US and 4 from Chinese registry enrolled participants in experimental arms in which protease inhibitors, primarily lopinavir/ritonavir, as one of the sole interventions. Besides, a total of 12 trials (6 from US and Chinese each) enrolled participants in the experimental arms where protease inhibitors are provided in combination with other agents including interferons, Favipiravir, Chinese traditional medicine, Xiyanping injection and conventional therapies. Six trials from US and 5 trials from Chinese registry have Lopinavir/ritonavir as active comparator either alone or in combination with other agents. The summary of ongoing clinical trials including their primary outcome measures is presented in supplemental Table 1 and 2.

On the top of this, the National Institute of Health and Medical Research (INSERM) of France has planned to initiate DisCoVeRy trial (phase 3 randomized open label clinical trial). The trial protocol has already been registered on 20 March, 2020 and available at https://clinicaltrials.gov/ct2/show/NCT04315948. The recruiting of participants has not been started but estimated to enroll 3200 patients in 4 arms in which the two interventional arms to be lopinavir/ritonavir alone (14 days regimen) and with interferon-β compared to the standard care. WHO has also planned to launch Solidarity trial (randomized open label) very recently to evaluate the safety and efficacy of lopinavir/ritonavir in one of the interventional arms https://www.statnews.com/2020/03/18/who-to-launch-multinational-trial-to-jumpstart-search-for-coronavirus-drugs/. The registration of the trial protocol has not yet commenced till the time of this review.

In conclusion, though there are several promising studies with regard to the mechanism of action and activity of protease inhibitors against SARS-CoVs, there is no sufficient in vitro and in vivo studies against SARS-CoV-2 to confidently use them for COVID-19. They are being used in *ad-hoc* and compassionate manner based on case reports and previous experiences because of the absence of officially approved drug for this life threatening condition. Even if it could be taken as a bench mark, the recently published trial report is not sufficient and too early to conclude the poor clinical utility of Lopinavir/ritonavir without conducting multi-centered, randomized, blinded and well-established placebo controlled clinical trials.

Declaration of Competing Interest

There are no conflicts to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.104779.

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