Lopinavir/Ritonavir

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Definition

Lopinavir-ritonavir (LPV/RTV) is a human immunodeficiency virus (HIV) antiviral combination that has been considered for the treatment of COVID-19 disease.

1. Introduction

Since the emergence of an unknown viral infection with its first cases in China in December 2019 and following the identification of this infection as 2019-new coronavirus disease (2019-nCoV, also known as COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], the world has worked to find effective therapeutics and vaccinations to treat hundreds of thousands of affected patients and to reduce the spread of this global pandemic [2].

As of 2 June 2020, there were 1104 registered clinical trials of COVID-19 therapeutics or vaccinations worldwide that either had ongoing or were recruiting patients; however, at that stage no drug or vaccine had officially been approved for COVID-19 [2][3]. These trials have produced mixed and conflicting results of positive or negative outcomes and inclusive evidence of efficacy or safety, that render the suspension of some trials inevitable, as in the hydroxychloroquine trials, which was suggested by the World Health Organization (WHO) in light of safety concerns [4]. This decision was reversed on 3 June 2020 [5], following a retraction of the research article by the Lancet as certain authors were not granted access to the underlying data [6]. As the pandemic evolves, the amount of evidence regarding the benefit of hydroxychloroquine in the treatment of COVID-19 patients has grown. A recent systematic review included 32 studies for a total 29,192 studied participants found treatment with hydroxychloroquine confers no benefit in terms of mortality in hospitalized patients with COVID-19 compared to standard care [7].

Lopinavir-ritonavir (LPV/RTV) is a protease inhibitor and nucleoside analog combination used for human immunodeficiency virus (HIV-1) and was also thought to be a potential treatment for COVID-19 [8], as its therapeutic value in the treatment of COVID-19 was assessed by in-vitro studies that claimed inhibition of several viral corona respiratory illnesses, including severe acute respiratory syndrome (SARS-CoV), and Middle East Respiratory Syndrome (MERS) [9][10][11]. Only recently, LPV/RTV therapy was hypothesized to be of no antiviral efficacy against SARS-CoV or MERS-CoV because the recommended dosages supplied to patients included in the published studies were subtherapeutic [12] and doses higher than 400 mg/100 mg twice daily are suggested[13].

Lopinavir (LPV) is an aspartic acid protease inhibitor of HIV, where inhibition of proteases enzymes is essential for the intervening of the viral infectious cycle. LPV is co-formulated with ritonavir (RTV) to boost the pharmacokinetic activity and half-life of LPV through the inhibition of cytochromes P450, providing adequate suppression of viral load and constant improvements in CD4+ cell counts, as demonstrated in randomized trials in naïve and experienced adult and child HIV patients [8].

There is conflicting evidence regarding the use of LPV/RTV for the treatment of COVID-19 patients; and evidence is currently scarce and of low quality. LPV/RTV is available as a single-tablet formulation (Kaletra®, North Chicago, IL, USA) in dosage strengths of 400/100 mg or 200/50 mg, and in clinical trials, this combination reduced rates of acute respiratory distress syndrome (ARDS) or death compared to supportive care or ribavirin alone in a matched cohort group during the early phase of viral acquisition [11].

LPV/RTV is being examined in several international clinical trials, including the RECOVERY trial and SOLIDARITY WHO trial [14], but did not gain authorization to be used emergently in the current pandemic in the USA by the Food and Drug Administration (FDA), which has approved only three pharmacologically different therapeutics for treatments of COVID-19, including antibiotic-hydroxychloroquine, immunotherapy-convalescent plasma therapy, and antiviral-

remdesivir [2][14].

Among the clinical trials that did not find positive results for LPV/RTV, a study conducted by Bin Cao et al. published in the New England Journal of Medicine [15] revealed that treatment with LPV/RTV was not associated with clinical improvement beyond standard care or reduction in mortality rate at 28 days in hospitalized adult patients with severe COVID-19.

To date, LPV/RTV combination is available in some countries' therapeutics guidelines including USA[16], Saudi Arabia [17], and Ireland [18], which means that the medicine has tenable evidence of efficacy; however, considering that early negative and conflicting results have emerged [15], there is a need to assess the efficacy and safety of this COVID-19 treatment in a systematic manner.

2. Lopinavir/Ritonavir in Treatment of COVID-19

To address the efficacy and safety of LPV/RTV combined with other drugs in patients with COVID-9, LPV/RTV plus IFN combination in addition to ribavirin was found to be superior and safer than LPV/RTV alone by shortening the time to negative nasopharyngeal swab compared to the LPV/RTV arm alone [19]. Additionally, a combined treatment regimen of LPV/RTV plus IFN and umifenovir resulted in a shorter time by normalizing body temperature and turning PCRs negative compared to the umifenovir plus IFN arm with reasonable safety profile [20]. However, the use of LPV/RTV plus IFN combination resulted in less therapeutic responses on COVID-19 in terms of viral clearance and chest CT changes compared to the favipiravir plus IFN combination. Favipiravir arm patients had fewer AEs than patients in the LPV/RTV arm [21]. Additionally, there was no significant difference in average PCR negative conversion times among IFN plus LPV/RTV or IFN plus LPV/RTV plus ribavirin treatment arms [22]. The combination of LPV/RTV, in addition to standard care, or standard care alone revealed no difference in the time to clinical improvement, duration of hospitalization, initiation of invasive mechanical ventilation and death [15][23][24]. A serious case of elevated alanine aminotransferase (ALT) was reported [23], GI AEs were more common in the LPV/RTV group and treatment was stopped early in 13.8% because of AEs [15].

In a recent systematic review that included 41 studies which considered therapeutics for COVID-19, LPV/RTV was found to be the third therapy associated with positive outcomes (54.9%) with less negative outcomes (12.3%) compared to systemic corticosteroids (21.3%), remdesivir (16.9%), moxifloxacin (13.4%) and oseltamivir (12.5%) [2]; however, further controlled studies were needed to draw a valid conclusion. Antiviral ineffectiveness of LPV/RTV against SARS-CoV-2 in the studies included in our review was justified by the necessity to give the drug at a daily amount higher than 800 mg/200 mg; as an in vitro analysis identified antiviral activity of LPV/RTV against SARS-CoV-2 with a half-maximal effective concentration (EC_{50}) of 16.4 µg/mL [25]. However, there is a potential to intoxicate the patient, because high doses of LPV/RTV may lead to delayed ventricular repolarisation (QT prolongation) [7]. Thus, it might be logical to argue that there is a need to determine the effective and safe dose of LPV/RTV against the SARS-CoV-2 virus for better clinical benefit [13].

It is important to consider drug concentrations at the site of infection, and currently, the lack of robust lung penetration data is an important gap that exists for many agents being considered for repurposing. In the case of LPV/RTV, lung penetration is complex and not well understood; however, typically it is the plasma-free fraction that is available to penetrate into tissues. Therefore, given its potency, lung penetration of LPV/RTV would have to be high to provide concentrations in the therapeutic range [26]. The antiviral activity in vivo is estimated by calculating the ratio of unbound drug concentrations achieved in the lung at the administered dose to the in vitro EC50 (R_{LTEC}) [27]. Even though the majority of the observed total LPV/RTV plasma concentrations in COVID-19 patients were above the published EC50 for SARS-CoV-2 [25], boosted LPV/RTV is unlikely to attain sufficient effective levels in the lung to inhibit the virus. Indeed, the largest trials of RECOVERY [23] and SOLIDARITY [24] found LPV/RTV had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients.

There is uncertainty about the optimal approach to treat hospitalized COVID-19 patients. Management approaches are based on limited data and evolves rapidly as clinical data emerge. For patients with non-severe disease, care is primarily supportive, with close monitoring for disease progression. Remdesivir is suggested in hospitalized patients with severe disease (i.e., they have hypoxia) but who are not yet on oxygen [28][29]. For patients who are receiving

supplemental oxygen (including those who are on high-flow oxygen and noninvasive ventilation), low-dose dexamethasone and, if available, remdesivir is/are suggested [30][31]. However, the optimal role of remdesivir remains uncertain, and some guidelines panels (including the WHO) suggest not using it in hospitalized patients because there is no clear evidence that it improves patient-important outcomes for hospitalized patients (e.g., mortality, need for mechanical ventilation). In general, use of LPV/RTV for treatment of SARS-CoV-2 in hospitalized patients is not suggested as several trials have failed to prove efficacy [15][23][24]. Evidence as to whether LPV/RTV is beneficial in outpatients with mild or moderate severity COVID-19 infection is lacking; therefore, use of LPV/RTV is suggested in outpatients only in the context of a clinical trial.

Vaccines to prevent COVID-19 infection are considered the most promising approach for controlling the pandemic. COVID-19 vaccine development is occurring at an unprecedented pace. Several different platforms are being utilized to develop COVID-19 vaccines such as: inactivated virus or live-attenuated virus platforms (traditional methods); recombinant proteins and vector vaccines (newer methods); and RNA and DNA vaccines (methods never previously employed in a licensed vaccine) [32]. Several vaccine candidates have demonstrated immunogenicity without major safety concerns in early-phase human trials [33]. Two mRNA vaccine candidates have also been reported to have approximately 95% vaccine efficacy [34][35]. AstraZeneca's Oxford coronavirus vaccine is 70% effective on average, data shows, with no safety concerns [36]. Importantly, the AstraZeneca vaccine can be distributed and administered within existing healthcare systems, as it can be stored, transported and handled in normal refrigerated conditions for at least six months, the company said. The vaccine will also be cheaper than rival coronavirus vaccines from makers Pfizer and Moderna [36].

Since disease resulting from SARS-CoV infection is driven by both virus and host immune response factors, depending on the stage of the disease progression, early initiation of antiviral therapy, and/or holistic combination therapies will likely be needed to diminish virus replication, immunopathology, and/or promote repair and restoration of pulmonary homeostasis [37]. Until sufficient evidence is available, the WHO has warned against physicians and medical associations recommending or administering unproven treatments to patients with SARS-CoV-2 or people self-medicating with them.

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Keywords

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