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Letter

Fighting COVID-19

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Abstract

The current COVID-19 pandemic caused by the novel coronavirus (SARS-CoV2) poses a threat to global health owing to its high rate of spread and severe forms of respiratory infection. The lack of vaccines and antivirals prevents clinical strategies against the disease, creating an emerging need for the development of safe and effective treatments. Strategies for vaccine development include complete vaccines against viruses, subunits, and nucleic acids, but are still in their early stages. Studies carried out to date on possible SARS-CoV2 drug targets highlight glycoprotein S, Mpro (main protease or protease type 3C), and a member of the transmembrane serine protease II families (TMPRSS2). However, due to the pandemic state, priority is given to marketed drugs. These include chloroquine (CQ), hydroxychloroquine (HCQ), nitazoxanide, remdesivir, Lopinavir/ritonavir (LPV / r), in addition to treatment with convalescent plasma. But, therapeutic specific effects against SARS-CoV2 have not yet been verified. Most of the information obtained about treatment is based on preliminary and limited studies. We conclude that, at this time of emergency, the search for new therapies is more urgent due to the need to save lives. Thus, we point out as interesting targets for future more specific research: glycoprotein S, Mpro, and TMPRSS2.

Keywords: virology, SARS-CoV2, COVID-19, infectious diseases.

Combatendo a COVID-19

Resumo

A pandemia de COVID-19 causada pelo novo Coronavírus (SARS-CoV2) representa uma ameaça à saúde global devido à alta taxa de disseminação e formas graves de infecção respiratória. A falta de vacinas e antivirais específicos dificultam as estratégias clínicas de controle da doença, criando a necessidade urgente do desenvolvimento de tratamentos seguros e eficazes. Com relação as estratégias para o desenvolvimento de vacinas, incluem-se: aquelas com o vírus completo, subunidades e ácidos nucléicos, mas estas ainda estão em estágios iniciais. Já sobre os estudos realizados até o momento buscando novos alvos terapêuticos contra o SARS-CoV2, destacam a glicoproteína S; Mpro (principal protease ou protease tipo 3C) e um membro da família transmembrana serina protease II (TMPRSS2). No entanto, devido ao estado pandêmico, tem sido dada prioridade aos medicamentos comercializados. Estes incluem a cloroquina (CQ); hidroxicloroquina (HCQ); nitazoxanida; remdesivir; Lopinavir / ritonavir (LPV/r); além do tratamento com plasma de pacientes curados. Porém, ainda não há uma estratégia terapêutica contra o SARS-CoV2 totalmente eficaz, e a maioria das informações obtidas sobre o tratamento é baseada em estudos preliminares e limitados. Concluímos então que, neste momento de emergência, a busca por novas terapias é algo urgente devido à necessidade de salvar vidas. Assim finalizamos sugerindo como alvos interessantes para futuras pesquisas específicas: a glicoproteína S, Mpro e o TMPRSS2.

Palavras-chave: virologia, SARS-CoV2, COVID-19, doenças infecciosas.

Dear Editor,

As is known, the current pandemic of COVID-19 caused by the novel coronavirus SARS-CoV-2 poses a threat to global health owing to its high rate of spread causing severe forms of respiratory infection. The lack of vaccines and antivirals precludes clinical strategies against the disease; thus, the development of safe and effective treatments is required to prevent further damage to the population by offering better treatment options, controlling the spread of the disease, and preventing future outbreaks (Fisher and Heymann, 2020; Dong et al., 2020; Heymann

and Shindo, 2020). In this sense, this letter aims to discuss targets for vaccines, but mainly about new possibilities for the treatment of a new virus, SARS-CoV-2.

Strategies for the development of vaccines include whole virus, subunit, and nucleic acid vaccines. The first is the classical model, utilizing live-attenuated or inactive whole virus particles to generate vaccines. A subunit vaccine would rely on eliciting an immune response against the spike (S) glycoprotein of the new coronavirus to prevent its interaction with the angiotensin-converting enzyme 2 (ACE2) receptor. S protein is responsible for promoting entry of the virus into host cells and is the main target of neutralizing antibodies (Abs) upon infection. Nucleic acid vaccines are a promising approach, acting against the RNA genome of SARS-CoV-2, but these vaccines have not yet been licensed in humans (Chen et al., 2020b). Thus, they may be important tools for the future.

The studies published to date on the potential drug targets of SARS-CoV-2 highlight the S glycoprotein, Mpro (main protease or 3C-like protease), and transmembrane serine protease 2(TMPRSS2) (Walls et al., 2020; Xu et al., 2020). It is also important to highlight the action of griffithsin, an algae-derived lectin that binds to the S protein and strongly inhibits HIV, MERS-CoV, SARS-CoV, HCV, and HSV entry (O'Keefe et al., 2010). The potency and delivery systems of this S glycoprotein inhibitor should be reevaluated for the treatment or prevention of COVID-19.

Mpro is seen as an attractive target for drug development due to its essential role in viral replication. This protease is highly conserved among Coronaviridae members (exhibiting approximately 40-44% sequence homology), specifically SARS-CoV (96% similarity with SARS-CoV-2), and acts in the processing of polyproteins and virus maturation. In this context, Nelfinavir may be a potential inhibitor of SARS-CoV-2 Mpro, which could be elucidated by an integrative approach combining homology modeling, molecular docking, and binding free energy calculation (Xu et al., 2020). However, no clinical data have yet been reported on this interaction.

Hoffmann et al. (2020) provided evidence that SARS-CoV-2 can use TMPRSS2 for S protein priming, and camostat mesylate, an inhibitor of TMPRSS2, blocks SARS-CoV-2 infection of lung cells. This compound, or related compounds with potential antiviral activity such as nafamostat, could thus be considered for off-label treatment of SARS-CoV-2-infected patients (Yamamoto et al., 2016).

Due to the nature of the pandemic, priority is being given to FDA-approved drugs or clinical trial candidates in phase III that are close to being commercialized. Among the drugs studied, the antimalarial chloroquine (CQ), its analogue hydroxychloroquine (HCQ), and remdesivir, a broad-spectrum antiviral, have been suggested as potential treatments for COVID-19 (Wang et al., 2020a; Dong et al., 2020). A study of more than 100 patients indicated that CQ phosphate is superior to the control in inhibiting the exacerbation of pneumonia; however, no further details are provided (Gao et al., 2020). Despite poor evidence, CQ has been officially declared as a medical agent for COVID-19 by the National Health Commission of the People's Republic of China, FDA (by EUA), and Indian Council for Medical Research (Lenzer, 2020; Zhou et al., 2020).

The combined therapy of HCQ and azithromycin has been suggested as an alternative treatment, considered to be more effective and less toxic than CQ (Liu et al., 2020). However, the most recent study on patients hospitalized for COVID-19, led by a team from the Clinical Center for Public Health in Shanghai, China, demonstrated that HCQ monotherapy was not effective in treating these patients (Jun et al., 2020). Additionally, a non-randomized study of HCQ reportedly supported efficacy in 20 patients; however, the trial design was poor, and thus the results are unreliable (Gautret et al., 2020).

Another antiparasitic medication under analysis is nitazoxanide, which has demonstrated potent in vitro activity against SARS-CoV-2 in Vero E6 cells, consistent with its activity against MERS-CoV (Rossignol, 2016; Wang et al., 2020a). Unfortunately, it failed to reduce the duration of hospitalization or the time to symptom alleviation in a phase II randomized controlled trial of patients with severe acute respiratory illnesses requiring hospitalization (Gamiño-Arroyo et al., 2019). Several other therapeutic schemes have been evaluated, with different success rates.

Although data from several ongoing randomized controlled trials will soon provide more evidence regarding the safety and efficacy of remdesivir for COVID-19, interesting clinical improvement has been observed in patients hospitalized for severe COVID-19 in a compassionate-use program (Grein et al., 2020).

Another alternative involves lopinavir/ritonavir (LPV/r), a combination protease inhibitor used for the treatment of HIV infection that showed improvement in the clinical-pathological outcomes and cytopathic effect of SARS and MERS (Chu et al., 2004; Chan et al., 2015). Although the first clinical trial of LPV/r for the treatment of COVID-19 did not show superiority over standard care for time to achieve clinical improvement or viral clearance (Cao et al., 2020), the combination of LPV/r, umifenovir (Arbidol), and Shufeng Jiedu Capsule (a traditional Chinese medicine) alleviated pneumonia symptoms in a study of four patients and decreased the viral load to undetectable levels in two of these patients (Wang et al., 2020b). However, a retrospective study revealed no significant difference between the control group and groups treated with LPV/r and Arbidol in symptom improvement or reduction of viral loads (Chen, 2020). The efficacy of this treatment warrants verification in future studies.

Finally, another promising therapy involves convalescent plasma from patients who have recovered from viral infections. This therapy has been successfully performed (Chen et al., 2020a) and may be an effective alternative for the treatment of patients with COVID-19. . The hope in the use of this plasma has been increasing because a recent study shows that patients who had the disease develop IgG antibodies (Long et al., 2020).

Due to the rapid epidemic spread, scientists around the world are exploring potential vaccines and drugs that

can act against COVID-19; however, no therapeutic agents have yet been verified as effective against SARS-CoV-2. Most of the available treatment information is based on preliminary studies and limited trials. Therefore, robust preclinical and clinical studies need to be conducted on infected patients to prove the efficacy and safety of the current candidates and/or to uncover new drugs and vaccines suitable for treatment.

We conclude that in this moment of emergency, research on new therapies is urgent due to the need to save lives. Thus, the use of drugs that are already on the market is understandable, but we point out S glycoprotein, Mpro, and TMPRSS2 as interesting targets for more specific future research.

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