COVID-19: a basic approach to understanding potential treatments

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Abstract

SARS-CoV-2 virus has been identified as the causative agent of the COVID-19 pandemic. Even when no standard treatment is available, antivirals such as remdesivir and other drugs such as chloroquine and ivermectin, which interfere with viral replication, have been assayed. Some strategies aimed at reducing immune mechanisms, such as the use of tocilizumab and natural antioxidants, have also been tested. The use of drugs related to the renin-angiotensin system has been controversial. Pathogenicity mechanisms, as well as controlled treatments, still have to be studied in detail in order to propose a viable therapeutic option that prevents the entry and replication of the virus or enhances the host immune system.

KEY WORDS: Covid-19. Pharmacological treatments. Renin-angiotensin system.

COVID-19: enfoque básico para entender sus tratamientos

Resumen

El virus SARS-CoV-2 ha sido identificado como el agente patológico causante de la pandemia de COVID-19. Aun cuando no se cuenta con un tratamiento estándar, se han probado antivirales como remdesivir y otros fármacos como cloroquina e ivermectina, que interfieren con la replicación del virus. También se han intentado algunas estrategias encaminadas a disminuir los mecanismos inmunitarios, como el uso de tocilizumab y antioxidantes naturales. Los fármacos relacionados con el sistema renina-angiotensina han resultado controversiales. Aún se debe estudiar con detalle los mecanismos de patogenicidad, así como los tratamientos controlados para proponer alguna opción terapéutica viable que evite la entrada y replicación del virus o que aumente los sistemas inmunitarios del huésped.

PALABRAS CLAVE: COVID-19. Tratamientos farmacológicos. Sistema renina-angiotensina.

Possible therapeutic interventions for SARS-CoV-2 infection

A wide variety of drugs have been used in the fight to counteract the emerging disease caused by

SARS-CoV-2; however, a standard treatment is not yet available.

Treatment proposals address different aspects:

- Virus entry into cells.
- Virus replication.

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- Reinforcement of immunity and prevention of exacerbated inflammation.
- Control of complications.

Numerous trials have been conducted looking for treatments or drug combinations to achieve recovery or reduce progression to severe forms of the disease. In this review, some of the most important proposals are described.

Remdesivir

Remdesivir is an adenosine analogue, and therefore it reduces viral RNA production.¹ Its use for COVID-19 treatment is not yet approved, although several experimental studies are undergoing. In *in vitro* studies, remdesivir effectiveness against SARS-CoV-2 was observed. In experimental animals, remdesivir reduced pulmonary hemorrhage and the number of viral RNA copies. Preliminary studies on humans suggest that 70 % of patients treated with this antiviral achieved improvement, including those with assisted ventilation. A non-controlled multicenter analysis used remdesivir, 200 mg on the first day and then 100 mg/day for nine days; out of 53 patients who received the drug, 36 showed clinical improvement (68 %).² In another multicenter, randomized, double-blind, placebo controlled study, 237 patients were included; the use of remdesivir was not associated with clinical improvement in comparison with the control group. In addition, more adverse effects were reported in the group that received the drug.³ The results of these investigations suggest that protocols with a larger number of patients are required in order to assess the benefits the drug might offer in terms of time to clinical improvement.

Ribavirin, lopinavir and ritonavir

Ribavirin is a synthetic guanosine nucleoside that interferes with mRNA synthesis. In turn, lopinavir is a protease inhibitor that when co-administered with low-dose ritonavir significantly improves its pharmacokinetic properties and enhances its activity against HIV-1 protease.^{4,5}

In a study carried out in 75 patients with severe acute respiratory syndrome, a reduction in mortality (2.3 %) and intubation (0 %) rates was observed in patients initially treated with lopinavir/ritonavir 400/100 mg every 12 hours for 14 days.⁶ In another investigation of 199 patients with SARS-CoV-2 infection, 99 patients were administered lopinavir/ritonavir and standard therapy and compared with a control

group that received only standard therapy; the results showed no difference between groups in time to patient improvement.⁷

In another analysis of COVID-19 patients, 400/100 mg of lopinavir/ritonavir were administered every 12 hours to one group, while another received an additional 400 mg of ribavirin every 12 hours and three interferon doses of 8×10^6 IU on alternate days. The results indicated that the triple antiviral therapy was safe and superior to lopinavir/ritonavir monotherapy in terms of disease duration and hospital stay days.⁸ Currently, studies are underway to determine the efficacy of different doses of ribavirin, as monotherapy or in combination with other drugs, in the management of COVID-19.⁹

Azithromycin

Azithromycin is a macrolide antibiotic whose mechanism of action is based on its reversible binding to bacterial ribosome 50s subunit, thus preventing translocation.¹⁰ This drug has also shown anti-inflammatory and immunomodulatory properties, which has generated interest on its use in viral infections. Reports show a decrease in neutrophil counts and interleukins (IL) 8, 6, 1 β , tumor necrosis factor α , eosinophil cationic protein and metalloproteinase 9 concentration.¹¹ These data suggest that azithromycin might decrease the pro-inflammatory cytokine cascade that is characteristic of COVID-19. Azithromycin also creates an unfavorable environment for viral replication.¹² Azithromycin administration is started with 500 mg orally on the first day, followed by 250 mg/day for two to five days, according to medical judgment and patient pre-existing conditions.¹³ Other authors evaluated viral loads in patients with COVID-19 after receiving hydroxychloroquine and azithromycin; they concluded that this drug combination produces viral elimination with higher efficacy.¹⁴ Currently, the National Institute of Allergy and Infectious Diseases of the United States is sponsoring a clinical trial to assess this drug in combination therapy with hydroxychloroquine.¹⁵

Chloroquine and hydroxychloroquine

These drugs are considered to be able to change lysosomal pH and, therefore, to modify the activity of proteases and interfere with viral entry into cells. Chloroquine and hydroxychloroquine are also characterized for reducing pro-inflammatory interleukins, particularly IL-6, and thus their action could also be

beneficial in the “cytokine storm”.¹⁶ Furthermore, both drugs, at low concentrations, were observed to be able to inhibit viral replication and reduce viral load in vitro and in human studies, respectively. However, as a disadvantage, the use of chloroquine and hydroxy-chloroquine has been found to cause cardiotoxic effects, a particularly important effect that must be considered.¹⁷

Ivermectin

In vitro studies of Vero/hSLAM cells infected with SARS-CoV-2 and treated with ivermectin at a concentration of 5 μ M showed an almost absolute reduction of viral RNA; in addition, no toxicity associated with ivermectin was observed at the evaluated concentration.¹⁸

Ivermectin mechanism of action is still unknown; however, it is believed that it inhibits importin α/β 1 and nuclear proteins of the virus and the host.¹² The dose varies according to some criteria and it can be 12 mg in a single oral dose or 12 mg orally for two days. Several countries are using ivermectin in first-line treatments to combat the disease, as, for example, the Dominican Republic, Bolivia, and Peru. However, conducting further studies is considered appropriate in order to further evaluate its effectiveness as antiviral.¹⁹

Tocilizumab

This drug is a humanized monoclonal antibody that antagonizes IL-6 receptor.^{20,21} Currently, numerous clinical trials are underway to assess the use of tocilizumab in the treatment of SARS-CoV-2 infection.²² An investigation carried out in China with 21 patients reported that the addition of 4 to 8 mg/kg of tocilizumab to standard therapy produced clinical improvement, the ground-glass opacity pattern on computed tomography decreased after administration of the drug; 15 out of 20 patients required less supplemental oxygen and one patient did not require it.²³ However, this study was not controlled, and the number of analyzed patients is not enough to formulate further inferences, and more research is therefore required to assess tocilizumab efficacy.

Vitamin C

Vitamin C possesses antioxidant capacity owing to the donation of an electron to the lipid radical, which stops lipid peroxidation self-perpetuating reaction; subsequently, vitamin C is transformed into two molecules,

the ascorbate radical and dehydroascorbate; the latter is transformed back into ascorbate by the action of an oxidoreductase.²⁴ Vitamin C recommended daily dose is 90 and 75 mg/day in men and women, respectively, without special requirements. Viral infections are known to generate large amounts of oxygen free radicals; vitamin C is used to neutralize this oxidative stress.^{25,26} In addition, vitamin C reduces inflammation by stimulating the production of anti-inflammatory cytokines and interferon, and it is therefore attributed a direct antiviral effect,²⁷⁻²⁹ hence its probable therapeutic usefulness in COVID-19 is considered.³⁰

A randomized controlled clinical trial was recently carried out: CITRIS-ALI, in hospitalized patients who were administered a high dose of vitamin C by infusion (50 mg/kg every six hours for 96 hours). Although no significant differences were identified in the Sequential Organ Failure (SOFA) scale score or improvement in inflammation or vascular damage biomarkers (C-reactive protein and thrombomodulin, respectively), patients treated with vitamin C were found to require fewer days of intensive therapy and, in general, hospital stay.^{31,32} High doses of vitamin C behave as pro-oxidants, which is why some studies suggest that small doses may have greater benefit.³³ In COVID-19, the role of vitamin C as an adjuvant treatment is still uncertain.

Vitamin D

Vitamin D is photosynthesized in the skin from 7-dehydrocholesterol.³⁴ In addition to other functions, vitamin D active form (calcitriol) plays an immunomodulatory role, increasing innate immune response and inhibiting adaptive immune response.³⁵ In a retrospective multicenter study of 212 cases, low levels of vitamin D were found in critically-ill COVID-19 patients, with an association with clinical outcome being reported.³⁶ The main cause of vitamin D deficiency is inadequate exposure to sunlight,^{37,38} which has been suggested as a cause of the severity of responses to SARS-CoV-2-associated infection and mortality in Europe, together with inadequate intake of the vitamin.^{39,40} These data suggest that supplementation with vitamin D can be part of the therapeutic and prophylactic intervention in COVID-19.⁴¹

Treatments related to the renin-angiotensin system

The role of drugs that inhibit the renin-angiotensin system, such as angiotensin-converting enzyme

Figure 1. Proposed COVID-19 treatments. Probable sites of action of some drugs experimentally and clinically used against SARS-CoV-2 are shown. Chloroquine and hydroxychloroquine inhibit viral internalization and endocytosis; in addition, they have an immunomodulatory effect on the host. Azithromycin and tocilizumab inhibit IL-6 receptors activation and signaling pathways, which decreases macrophages and neutrophils chemoattraction. Lopinavir and ritonavir inhibit the formation of nonstructural proteins through the process of viral replication in 3-chymotrypsin-like protease. Remdesivir and ribavirin inhibit RNA-dependent RNA polymerase (RdRp) synthesis. In experimental studies, ivermectin inhibits the synthesis of structural proteins that are necessary for viral capsid assembly.

inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) is controversial in the context of the COVID-19 pandemic. On one hand, there is information that shows that continuity of treatment with ACEI or ARB reduces morbidity and mortality in patients with COVID-19.⁴² In a systematic review that included 12 articles with more than 19,000 cases of COVID-19, exposure to ACEIs or ARBs was reported not to be associated with a higher risk of COVID-19 infection or higher risk of serious infection or mortality; on the contrary, exposure to ACEIs or ARBs was associated with a lower risk of mortality when the results were compared with those obtained in patients medicated with other antihypertensives.⁴³ Mehta et al. concluded that there is no significant association between the use of ACEIs or ARBs and COVID-19 test positivity.

Together, all these data support the notion of not discontinuing ACEIs or ARBs in the context of the COVID-19 pandemic.⁴⁴ In addition, several trials are currently underway to assess the effect of the administration of said antagonists for the treatment of patients with COVID-19.⁴²

In contrast, recent cohort studies from Wuhan, China, suggest that the worst outcomes appear to be more common in patients with hypertension and diabetes, possibly due to angiotensin-converting enzyme 2 (ACE2) overexpression in alveolar epithelial cells owing to the treatment with ACEIs or ARBs. In investigations with animals, ARAs and ACEIs increased the expression of ACE2, SARS-CoV-2 access site, which generated concerns about whether these drugs increase COVID-19-associated morbidity and mortality.⁴⁵

It is important to note that a careful search for data in the literature does not support this association.⁴⁶

Soluble ACE2, not associated with the membrane, is enzymatically active and partially inhibits viral entry into target cells. A phase II clinical trial was recently reported in Europe, in which clinical-grade soluble human ACE2 is being tested to block SARS-CoV-2 infection.⁴² In fact, some structural variations of human ACE2 have been described, which is characterized by its low affinity to viral spike protein. The above data open possibilities for ACE2 protective implications on viral entry⁴⁷ (Figure 1).

Conclusions

SARS-CoV-2 coronavirus infection spread all over the world in very few months. By the publication date of this manuscript, there was not yet a globally recommended drug available for treating the disease. Undoubtedly, scientific advances have led to proposing several drugs and vaccines to fight the virus. SARS-CoV-2 transmission in humans brings along a reflection on our coexistence with wildlife, our eating habits, and the care of our health in general.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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