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Medical treatment options for COVID-19

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Abstract

Therapeutic options for coronavirus disease 2019 are desperately needed to respond to the ongoing severe acute respiratory syndrome coronavirus 2 pandemic. Both antiviral drugs and immunomodulators might have their place in the management of coronavirus disease 2019. Unfortunately, no drugs have been approved yet to treat infections with human coronaviruses. As it will take years to develop new therapies for severe acute respiratory syndrome coronavirus 2, the current focus is on the repurposing of drugs that have been approved or are in development for other conditions. Several clinical trials have already been conducted or are currently ongoing to evaluate the efficacy of such drugs. Here, we discuss the potential of these therapies for the treatment of coronavirus disease 2019.

Keywords

SARS-CoV-2, COVID-19, treatment, antiviral drugs, immunomodulators

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Introduction

Approximately 15% of coronavirus disease 2019 (COVID-19) patients will develop severe lung disease. It is thought that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) results in an acute respiratory infection that is cleared in most cases by the immune system after 7 to 14 days.[1] The severe lung pathology that follows in a subset of patients after this acute viral stage is characterised by systemic inflammation reactions. The cytokine storm in these patients seems to be associated with disease severity.[2] Both antiviral agents and immunomodulating drugs might therefore have their place in managing the disease in these patients. Drugs that slow down the replication of SARS-CoV-2 and/or decrease disease symptoms may save the lives of (very) ill patients. In addition, it could reduce the time that is being spent in intensive care units and could thus decrease the pressure on these units by freeing hospital beds. Furthermore, the drugs could be used as a prophylaxis to protect healthcare workers.

Here, we summarise the current knowledge regarding antiviral and immunomodulating treatment strategies against COVID-19.

Antiviral drugs

Unfortunately, no antiviral drug has yet been approved to treat human coronaviruses. As a specific, highly potent antiviral drug for SARS-CoV-2 will take years to develop and to evaluate in clinical studies, the main focus for COVID-19 treatment is now on the repurposing of drugs that have been approved for other diseases. Such drugs have known safety profiles and drug production strategies have been implemented. Unapproved drugs that showed antiviral activity in animal models for SARS-CoV-1 and/or Middle East respiratory syndrome coronavirus (MERS-CoV), two other coronaviruses causing severe disease, are currently also considered as treatment options. However,

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repurposed drugs cannot be expected to be highly potent inhibitors of SARS-CoV-2, as these were not developed specifically against this particular virus.

Clinical trials have already been conducted or are currently ongoing to evaluate the efficacy of several repurposed/experimental drugs for the treatment of COVID-19. On 7 March 2020, the most frequently evaluated antiviral therapies were lopinavir/ritonavir (LPV/r) ($n = 15$), chloroquine ($n = 11$), arbidol ($n = 9$), hydroxychloroquine ($n = 7$), favipiravir ($n = 7$) and remdesivir ($n = 5$).[3] Most of these agents have demonstrated antiviral activity in cell culture against coronaviruses. In addition, the World Health Organization (WHO) very recently announced the launch of a large global trial, called SOLIDARITY. This trial will include thousands of patients of different countries and will evaluate the efficacy of what WHO finds the four most promising therapies at this time: the malaria drugs chloroquine and hydroxychloroquine; remdesivir, an experimental antiviral drug; LPV/r, an HIV drug combination; and LPV/r plus interferon-beta, an immunomodulator.[4]

Chloroquine and hydroxychloroquine. Chloroquine and hydroxychloroquine are anti-malaria drugs that have been widely used to treat malaria patients. Due to the emergence of chloroquine-resistant *Plasmodium* parasites, the use of chloroquine to treat malaria has been more restricted. Hydroxychloroquine is also administered to patients with auto-immune disorders such as lupus and rheumatoid arthritis. Both chloroquine and hydroxychloroquine are considered as safe drugs and the side effects are usually mild and transient. However, it is important to note that the window between therapeutic and toxic doses is narrow. Chloroquine poisoning has been associated with cardiovascular symptoms and can be life-threatening. Self-treatment with chloroquine and hydroxychloroquine is therefore not recommended.

The antiviral activity of chloroquine was already identified in the late 1960s.[5] Both chloroquine and hydroxychloroquine are able to inhibit a broad range of viruses from different virus families in cell culture, including coronaviruses (SARS-CoV-1, MERS-CoV).[6,7] Recently, in vitro antiviral efficacy against SARS-CoV-2 was also demonstrated.[8] For some viruses, antiviral activity was observed in mouse models, including for the human coronavirus OC43[9] and influenza A virus H5N1.[10] However, in a SARS-CoV-1 mouse model, chloroquine was not able to reduce viral titres in the lungs.[11] In patients, no evidence of antiviral activity has yet been observed during acute viral infections.[5]

A number of clinical trials has been conducted in more than 10 hospitals in China to assess the efficacy of chloroquine to treat COVID-19 patients. In a recent publication,[12] it was stated that 'according to the news briefing', 'results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course'. However, no data from these clinical trials have yet been released to support this announcement, making it impossible to draw firm conclusions. In France, 26 COVID-19 patients were treated for 6 days with hydroxychloroquine (200 mg, three times per day).[13] Six of these patients also received azithromycin. Sixteen patients were used as the control group. SARS-CoV-2 RNA was measured in nasopharyngeal swabs daily during the treatment. During the study, six patients from the treated group had to be excluded and were not considered in data analysis. Three patients had to be transferred to intensive care units, one left the hospital because the patient tested negative, one stopped treatment due to side effects and one person died during the treatment. The authors reported clearance in SARS-CoV-2 RNA in the nasopharyngeal swabs in 57% of chloroquine-treated patients compared to 12.5% of untreated patients at day 6 post-inclusion in the study. In addition, a synergistic effect of azithromycin and hydroxychloroquine was suggested, because all patients treated with this combination cleared viral RNA by day 6 post-inclusion. However, as not all patients entered the study at the same stage of the disease, it is difficult to assess whether the clearance in viral RNA was due to the treatment or due to the immune system of the patient. Furthermore, the combination of chloroquine and azithromycin is associated with severe QT prolongation and should thus be considered with care. Before chloroquine can be considered safe and effective as a treatment for COVID-19, more studies are needed.

Remdesivir. Remdesivir (GS-5734) is an experimental drug that was under development for the treatment of Ebola virus-infected patients.[14] Remdesivir is a nucleotide prodrug that inhibits viral RNA replication. The prodrug needs to be activated in the cell into a nucleoside triphosphate which then serves as an alternative substrate for the viral RNA-dependent RNA polymerase. The incorporation of the nucleoside triphosphate in the growing viral RNA chain will result in chain termination and therefore halt viral RNA replication. Despite potent efficacy in Ebola virus animal models, remdesivir was less efficacious in a clinical trial conducted in the Democratic Republic of Congo.[15]

In cell culture, remdesivir has broad-spectrum antiviral activity against several other RNA viruses, including arenaviruses[14] and coronaviruses.[16] It was

previously shown that remdesivir can efficiently inhibit SARS-CoV-1 and MERS-CoV in cell culture, including in human airway epithelial cells.[16] Remdesivir also demonstrated antiviral activity against SARS-CoV-1 and MERS-CoV in an animal model. In the MERS mouse model, remdesivir reduced lung viral loads and severe lung pathology.[17] Very recently, it was shown that remdesivir is also active against SARS-CoV-2 in cells.[8]

A case report described the use of remdesivir in one COVID-19 patient.[18] This patient initially presented with mild symptoms including a cough and low-grade intermittent fevers, without evidence of pneumonia. However, by illness day 9 the patient progressed to pneumonia. As the clinical status of the patient worsened, compassionate administration of remdesivir was pursued. Treatment with intravenous remdesivir was initiated on day 11 of illness. On illness day 12, the clinical condition of the patient improved. Supplementation with exogenous oxygen was stopped. Although encouraging, the apparent success of remdesivir treatment in this one patient does not prove that the drug is effective. Remdesivir is now being evaluated in COVID-19 patients in five clinical studies worldwide: two studies in China, and studies in the United States, Singapore and South Korea. Results of these trials are not available yet.

Lopinavir–ritonavir. Lopinavir is an HIV protease inhibitor that is usually combined with ritonavir to increase its half-life via cytochrome P450 inhibition. Whether HIV protease inhibitors might also inhibit the coronavirus protease remains a question, because the HIV protease belongs to a different protease family from the two coronavirus proteases (aspartic vs. cysteine protease family, respectively).[19] Furthermore, HIV protease inhibitors were specifically designed to fit in a certain pocket of the HIV protease dimer, but this pocket is not present in coronavirus proteases. Antiviral activity of LPV/r against SARS-CoV-1 was reported in cell culture,[20] but conflicting results were reported for MERS-CoV.[7,21] In common marmosets infected with MERS-CoV, LPV/r was able to improve the clinical outcome and reduce viral loads in the lungs.[22] However, in a MERS-CoV mouse model, the prophylactic use of LPV/r in combination with interferon-beta only slightly reduced the viral loads in the lungs without impacting other disease parameters.[17] Therapeutic treatment of LPV/r with interferon-beta improved the pulmonary function but did not reduce virus replication or severe lung pathology. In SARS-CoV-1-infected patients, results of the treatment with LPV/r were inconclusive.[23] In addition, two case reports describing MERS patients receiving LPV/r in combination with ribavirin and interferon-alpha reported conflicting results.[24,25] The preclinical and clinical evidence for the use of LPV/r in COVID-19 patients is thus modest.

A case report from South-Korea described the use of LPV/r in a COVID-19 patient with mild respiratory symptoms.[26] LPV/r was started at day 10 of illness. No clear inhibitory effect on viral RNA was observed in the daily sputum samples. In a randomised, controlled, open-label trial involving hospitalised adult patients with severe COVID-19, 99 patients were treated with LPV/r, while 100 patients received the standard care treatment.[27] No difference in the time to clinical improvement and in mortality was observed between both groups.

Favipiravir. Another molecule that is being evaluated in COVID-19 patients in China is favipiravir. Favipiravir (T-705) is an antiviral drug that has been approved in 2014 in Japan to treat pandemic influenza virus infections. It acts as a prodrug which is converted intracellularly into its ribofuranosyl 5′-triphosphate metabolite (favipiravir-RTP).[28] Interestingly, this molecule is able to inhibit a broad range of other RNA viruses.[29] The exact mode of action that underlies this broad-spectrum anti-RNA virus activity has not been completely unravelled. It is hypothesised that favipiravir-RTP could be misincorporated in a growing viral RNA chain, or that it could act by binding to conserved polymerase domains, thus preventing viral RNA replication. Incorporation of favipiravir-RTP in the nascent viral RNA could result in lethal mutagenesis by ambiguous base-pairing or in chain termination.

Favipiravir was evaluated in clinical trials for influenza virus infections, mainly in Japan, in which the drug was well tolerated. Reported side effects were mild to moderate diarrhoea, asymptomatic increase of transaminases, and uncommonly decreased neutrophil counts. Importantly, favipiravir is contraindicated in women who might be or are pregnant and in lactating women because of its association with embryonic deaths and teratogenicity in animal studies.[29]

Favipiravir has modest antiviral activity against SARS-CoV-2 in cell culture (EC_{50} value of 62 μM).[8] Activity against other coronaviruses in cells or animal models has not been reported. Despite the rather weak scientific base for the use of favipiravir as an anti-coronavirus drug, clinical trials with favipiravir have been conducted in China. In an open-label, non-randomised controlled study, 35 patients with laboratory-confirmed COVID-19 were treated with oral favipiravir (day 1: 1600 mg twice daily; days 2–14: 600 mg twice daily) plus interferon-alpha by aerosol inhalation (5 million U twice daily).[30] In the control group, 45 patients were treated with LPV/r (days 1–14: 400 mg/100 mg twice daily) plus interferon-alpha by aerosol

inhalation. Both treatments were continued until viral clearance was confirmed or until 14 days after the start of treatment. The median time of viral clearance for the patients treated with favipiravir was 4 days, which was significantly shorter than the time for patients in the control group with LPV/r (11 days). The report of this study does not clarify in which type of samples viral clearance was studied. Chest computed tomography scans improved in the favipiravir-treated group (91.4% vs. 62.2% in the LPV/r treated group).

In an open-label, randomised study, 116 COVID-19 pneumonia patients received favipiravir in combination with conventional therapy, whereas 120 patients received arbidol in combination with conventional therapy. Arbidol is an antiviral drug with activity against influenza virus infection that is approved in Russia and China.[31] The primary outcome of this study was the clinical recovery rate at day 7 after start of treatment, which was defined as recovery of fever, respiratory rate, oxygen saturation and cough relief for at least 72 hours. A non-peer-reviewed report on this study describes that in COVID-19 patients with mild symptoms (fever and respiratory symptoms without difficulties in breathing), the clinical recovery rate at day 7 was higher in the favipiravir-treated group when compared to the arbidol-treated group (71.4% vs. 55.9%). Furthermore, the time of cough relief and fever reduction by favipiravir was significantly shorter than that by arbidol. However, for COVID-19 patients with hypertension and/or diabetes, the clinical recovery rate was not significantly different between both groups (54.8% vs. 51.4%). The same picture was observed for critically ill COVID-19 patients. These data suggest that favipiravir might be useful for patients with mild symptoms, but not for severely ill patients.

Immunomodulating biologicals

In a subgroup of COVID-19 patients, a cytokine profile is observed that is similar to the profile in macrophage activation syndrome (MAS).[2] A retrospective analysis in China indicated IL-6 and ferritin as predictors for COVID-19-related mortality, suggesting that hyperinflammation increases the risk of mortality.[32] Anti-cytokine therapies could thus be useful to treat this group of COVID-19 patients that experience such a cytokine-storm syndrome. It must be noted, however, that the selective inhibition of specific cytokines during acute respiratory distress syndrome or sepsis might involve risks, such as reactivation of viral infections and an increased sensitivity for bacterial infections.

IL-6 inhibitors. Tocilizumab (Actemra) is a humanised interleukin-6 (IL-6) receptor antagonist that was approved to treat patients with rheumatoid arthritis. A non-peer reviewed report describes the results of a single-arm Chinese trial in which 21 severe or critical COVID-19 patients received tocilizumab.[33] On the first day after receiving tocilizumab, the body temperature of all patients returned to normal conditions and remained stable for the next days. In addition, the need for supplemental oxygen decreased in 75% of the treated patients. Although promising, the lack of a control group makes it difficult to interpret the true benefit of this therapy. Based on these results, China updated its treatment guidelines and approved the use of tocilizumab to treat COVID-19 patients with serious lung damage and high IL-6 levels.

As published data that support the use of tocilizumab are currently limited, properly designed, randomised trials are essential to understand the true impact of this therapy in COVID-19. Two non-randomised clinical trials are currently ongoing in China, evaluating the efficacy and safety of tocilizumab in larger groups of COVID-19 patients. Furthermore, a phase III study (COVACTA) will enroll hospitalised adults with severe COVID-19 pneumonia globally, starting from April 2020. This study will be a randomised, double-blind, placebo controlled trial. A US-based phase II/III trial will evaluate the efficacy of sarilumab (Kevzara), another IL-6 receptor antagonist, in adults hospitalised with serious complications from COVID-19. In the double-blind phase II trial, the primary endpoint will be reduction of fever and the secondary endpoint the decreased need for supplemental oxygen.

Granulocyte-macrophage colony-stimulating factor. Granulocyte-macrophage colony-stimulating factor (GM-CSF) plays a critical role in the defence against viruses and maintaining a proper function of the immune system. GM-CSF might thus be one of the key cytokines involved in the overreacted inflammatory response observed in COVID-19 pneumonia. A yeast-derived version of GM-CSF, Leukine (sargramostim, rhu-GM-CSF), has been approved for use in five clinical indications; the safety profile of this drug is therefore well known. The efficacy of Leukine for the treatment of COVID-19 patients with respiratory failure will be evaluated in a clinical study in Belgium (SARPAC trial). Leukine will be administered in a nebulised form for direct inhalation or through intravenous administration for patients that are already on a respirator.

Conclusion

With hospitals being overwhelmed with severely ill patients, treatment options for COVID-19 are very much needed. Rapid identification of such therapies

is thus essential, but challenging. Repurposing of existing antiviral and immunomodulating drugs is an important strategy, because the safety profile of these drugs is well known. However, the current outbreak of SARS-CoV-2 has emphasised once again the urgent need to develop broad-spectrum antiviral drugs, not only for coronaviruses, but also for other virus families that may also be the cause of future epidemics/pandemics.

Several clinical trials with COVID-19 patients are evaluating repurposed drugs, but there is no uniformity in timing, duration of treatment and study endpoints. In the currently registered clinical trials, the primary outcome was clinical in 66% of the studies, virological in 23%, radiological in 8% or immunological in 3%.[3] As the pathogenesis of COVID-19 is not yet well understood and associations between clinical status and viral clearance, radiological or immunological evaluations are unclear, the use of clinical outcomes should be encouraged. In the SOLIDARITY trial launched by the WHO, only simple outcomes will be measured that are currently relevant for public health: the day the patient left the hospital or died, the duration of the hospital stay, and whether the patient required oxygen or ventilation.[4]

In this pandemic context, it is essential that clinicians have rapid access to the information from clinical trials. Still, it is important that clinical trials and the reports on their results are of high quality, as these results will guide clinicians in their decision on which drug to use, the dosing and duration of the treatment, and which patients to include and exclude. Clinical trials should thus be designed with care, because robust results are essential. In addition, transparent and complete reporting on these clinical trials is needed to allow independent assessment of the potential benefit for COVID-19 patients. Furthermore, the selection of therapies to be evaluated in clinical studies needs to be based on clear scientific in vitro and preclinical in vivo evidence. We may expect that in the next few weeks carefully performed trials will be reported that will guide doctors around the world to give the best care (both in terms of reducing viral replication and mitigating hyperinflammation) to COVID-19 patients.

Conflict of interest

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