

COMMENT

Treatment strategies to fight the new coronavirus SARS-CoV-2: A challenge for a Rubik's Cube solver

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Abstract. SARS-coronavirus-2 (SARS-CoV-2), the etiologic agent of the new lung disease COVID-19 is closely related to SARS-CoV, and together with MERS-CoV are three new human coronaviruses that emerged in the last 20 years. The COVID-19 outbreak is a rapidly evolving situation with higher transmissibility and infectivity compared with SARS and MERS. Clinical presentations range from asymptomatic or mild symptoms to severe illness. The prevalent cause of mortality is pneumonia that progresses to ARDS. The ongoing pandemic has already resulted in more than 135,000 deaths and an unprecedented burden on national health systems worldwide. Pending the availability of a vaccine, there is a critical need to identify effective treatments and a number of clinical trials have been implemented worldwide. Trials are based on repurposed drugs that are already approved for other infections, have acceptable safety profiles or have performed well in animal studies against the other two deadly coronaviruses. Supportive care remains the mainstay of therapy at present, as it is still unclear how well these data can be extrapolated to SARS-CoV-2. Most of those emerging re-introduced drugs are administered to patients in the context of clinical trials. In this review, we summarize the strategies currently employed in the treatment of COVID-19.

Introduction

On March 18, 2020, the World Health Organization launched the SOLIDARITY trial and soon after an add-on trial, a European

initiative of the Reacting consortium, the DISCOVERY trial was announced (1,2). Currently, there are no approved therapies specific for any human CoV. Trials are based on repurposed drugs that are already approved for other diseases, have acceptable safety profiles or have performed well in animal studies against the other two deadly coronaviruses, which cause SARS and Middle East respiratory syndrome (MERS). SOLIDARITY includes research looking at four possible therapeutics with direct antiviral actions: remdesivir, chloroquine and hydroxychloroquine, lopinavir plus ritonavir, and lopinavir plus ritonavir and interferon-beta while chloroquine will not be included in the DISCOVERY trial. Additionally, the DISCOVERY trial will include a placebo arm with standard of care while the SOLIDARITY trial will not be blinded and patients will know they received a treatment that would cause a placebo effect as stated by Ana Maria Henao Restrepo, a medical officer at the WHO Department of Immunization Vaccines and Biologicals. Additional information regarding lung imaging and blood gases will be monitored in the DISCOVERY trial besides data on hospitalization length and requirement for oxygen or ventilation to be collected by the SOLIDARITY trial (3).

SARS-coronavirus-2 (SARS-CoV-2), the etiologic agent of the new lung disease COVID-19 (4) is closely related to SARS-CoV, and together with MERS-CoV are three new human coronaviruses that emerged in the last 20 years (5). The three viruses are associated with increased risk of acute lung injury (6). As of April 15, 2020 more than 2 million people have been infected worldwide in 200 countries resulting in a death toll that surpasses 135,000 people in this ongoing pandemic (<https://www.worldometers.info/coronavirus/>). SARS-CoV-2 is an enveloped, positive sense, single stranded, non-segmented RNA virus of the betacoronavirus family (7).

Remdesivir

Remdesivir targets virus replication, through inhibition of the viral RNA dependent RNA polymerase (RdRp) required for

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the copying and synthesis of novel viral genomes and viral mRNAs for the expression of viral proteins. Remdesivir incorporation in the nascent viral RNA by the RdRp results in premature chain termination and because of the high conservation of the core RdRp enzyme among coronaviruses. It has a broad-spectrum antiviral efficacy against multiple genetically distinct coronaviruses including the SARS-CoV and MERS-CoV *in vitro* and *in vivo* (8). Furthermore, it has shown prophylactic action against infection of corona viruses in animal models (8). Notably remdesivir potently blocked SARS-CoV-2 infection at low-micromolar concentration and showed high selectivity index in Vero E6 cells, a monkey epithelial cell line ($EC_{50} = 0.77 \mu\text{M}$; $CC_{50} > 100 \mu\text{M}$; $SI > 129.87$) (9). It should be noted that remdesivir resistance is already documented for SARS-CoV and other coronaviruses that lead to reduced viral inhibition (10).

The outcomes in a cohort of patients hospitalized for severe COVID-19 who were treated with remdesivir on a compassionate-use basis were recently reported by Grein *et al* (11). Fifty-three patients received 10-day course of remdesivir, consisting of a loading dose of 200 mg intravenously on day 1, plus 100 mg daily for the following 9 days. Improvement in oxygen-support status was observed in 68% of patients, and overall mortality was 13% over a median follow-up of 18 days although no data on viral dynamics were documented throughout the study. Clinical improvement was less frequent among patients receiving invasive ventilation than among those receiving noninvasive ventilation and among patients aged 70 years or older as compared with patients younger than 50 years.

Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine a less toxic derivative, represent potential broad-spectrum example of inhibiting viral cell entry. Chloroquine is a weak base that becomes entrapped in membrane-enclosed low pH organelles such as endosomes and lysosomes, and inhibits their acidification. Low pH in the endosomes regulates the action of proteases that lead to conformational changes of the virus envelope proteins allowing for the fusion of cellular and viral membranes and the escape of the viral genome into the cytosol. Attachment and entry of SARS-CoV-2 on host cells requires interaction of the spike protein subdomain 1 (S) with angiotensin converting enzyme 2 (ACE2) and its proteolytic cleavage by TMPRSS2 and to a lesser degree by the acid activated cathepsin B/L (12). Although the exact mechanism of SARS-CoV-2 entry is not completely understood and a new study has suggested that pH-dependent fusion of viral and cellular membranes is dispensable for viral genome entry into host cells, chloroquine, similarly to remdesivir, inhibited SARS-CoV-2 infection at low-micromolar concentration and showed high selectivity index in Vero E6 cells ($EC_{50} = 1.13 \mu\text{M}$; $CC_{50} > 100 \mu\text{M}$, $SI > 88.50$) (9).

Chloroquine is also used in the treatment of autoimmune diseases such as SLE and RA (13). Although the precise mechanism of action is not documented, inhibition of endosome acidification also interferes with innate immune response signaling from endosomal TLRs such as TLR 3, 7, 8 and 9, that mainly detect nucleic acid PAMPs and DAMPs, and in this way reduce inflammatory responses. Therefore, chloroquine and hydroxychloroquine may also protect the host from overt

inflammatory responses driven by the activation of immune cells such as macrophages by the increased load of viral RNA or cellular nucleic acids released from infected cells.

Results from clinical trials using chloroquine have provided promising results despite the limitations of these studies and suggest that chloroquine may represent a line of defense in the protection of medical staff and patients with increased risk for severe COVID-19 symptoms. Chen *et al* (14), evaluated the efficacy of hydroxychloroquine (HCQ) in the treatment of 62 patients with mild COVID-19 from February 4 to 28, 2020 at Renmin Hospital of Wuhan University. Patients were randomized either in a control group, receiving standard treatment, or in the HCQ group in which the patients received standard treatment plus HCQ 200 mg/bid between days 1 and 5. The study focused on time to clinical recovery (TTCR), clinical characteristics of patients and pulmonary recovery as it was depicted on chest CT results one day before (day 0) and one day after (day 6). A beneficial effect of HCQ in the treatment of COVID-19 was pointed out, despite the small number of the cases. More specifically, body temperature recovery time and cough remission time were significantly reduced in the HCQ treatment group. Moreover, the study of the chest CT scans revealed larger proportion of patients with improved pneumonia in the HCQ group (80.6%), compared with the control group (54.8%).

Gautret *et al* (15) from France conducted a single arm protocol from early March to March 16. Patients received 600 mg of hydroxychloroquine daily. Azithromycin was added to the treatment regimen as the clinical presentation required and the control group was represented by untreated patients from another center and cases refusing the protocol. Patients' viral load in nasopharyngeal swabs was evaluated on daily basis. Virus clearance at day-6 post-inclusion was the primary endpoint, while virus clearance during the study period, clinical parameters and occurrence of side-effects were considered secondary outcomes.

Regarding the effect of hydroxychloroquine on viral load, the study showed that a greater proportion of patients from the treated group had negative PCR results at days 3-6 post-inclusion, compared with the control group. Interestingly, at day 6 post-inclusion, the percentage of negative PCR patients in the treated group was 70%, while it was 12.5% in the control group ($p=0.001$). The addition of azithromycin in the therapeutic regimen enhanced the beneficial effect of hydroxychloroquine more intensely. Patients treated with hydroxychloroquine and azithromycin were all (100%) clear of virus at day 6 post-inclusion, comparing with 57.1% in the group that was treated with hydroxychloroquine only and 12.5% in the control group ($p<0.001$).

Kaletra

The last two arms of SOLIDARITY and DISCOVERY trials include Kaletra which is a combination of two antiviral drugs - lopinavir and ritonavir - normally used to treat HIV. Lopinavir acts against the viral 3CL protease, responsible for the cleavage of the viral structural proteins from a polypeptide chain in order to produce new virions. Lopinavir has modest antiviral activity against MERS and is significantly less potent than remdesivir (16), however, in combination with ritonavir and the antiviral immunomodulator interferon β it is currently in clinical trials for the treatment of MERS (17). The efficacy and safety of oral

lopinavir-ritonavir for SARS-CoV-2 infection was tested through a randomized controlled trial in China, but found 'no benefit' beyond standard care (18). Kaletra with or without interferon β 1 will be tested in the SOLIDARITY and DISCOVERY trials.

Favipiravir

Favipiravir (brand name Avigan) is a type of RNA-dependent RNA polymerase (RdRp) inhibitor which acts through blocking the replication of RNA viruses and is a potential antiviral agent against SARS-CoV-2 (19). A prospective, multicenter, open-label, randomized superiority trial examined the efficacy of favipiravir (n=120) versus arbidol (n=120) for treating COVID-19 (20). There was no difference in the 7-day clinical recovery rate (primary endpoint) for favipiravir versus arbidol in the overall population (61.21% versus 51.67%; $p=0.14$). However, this difference existed for a subgroup of non-critical patients without hypertension or diabetes (favipiravir 71.43% versus arbidol 55.86%, $p=0.02$) (20). Three registered clinical trials are planned regarding the use of favipiravir against COVID-19 (21-23).

Several promising therapeutic options are emerging such as a protease inhibitor specific for TMPRSS2 cell protease required for virus entry (12), the broad spectrum orally bioavailable β -D-N4-hydroxycytidine (NHC, EIDD-1931) that is incorporated in the viral genome by the RdRp leading to the accumulation of deleterious mutations and viral inactivation (24).

Tocilizumab (Actemra)

The four current regimens in SOLIDARITY and DISCOVERY focus on antiviral drugs rather than treating ARDS symptoms that are actually the cause of the virus morbidity and mortality. Hyperinflammation in coronavirus disease 2019 (COVID-19) could be a driver of severity that may be managed with immunomodulatory therapeutic options (25,26). Low-dose corticosteroid therapy ('shock-reversal'), over no corticosteroid therapy is suggested for adults with COVID-19 and refractory shock. In mechanically ventilated adults with COVID-19 and respiratory failure but without ARDS the routine use of systemic corticosteroids is not suggested. However, in mechanically ventilated adults with COVID-19 and ARDS using systemic corticosteroids is suggested (27-29). Importantly, the use of hydroxychloroquine, with or without the co-administration of azithromycin, may not be beneficial for the treatment of critically ill patients admitted to the ICU (30) and is not recommended (27,31).

Immunomodulatory drugs such as Tocilizumab (Actemra) 'anti-IL6' have been tested during the pandemic, however, great caution in inhibiting host antiviral responses should be taken (26). Tocilizumab (Actemra) is a recombinant humanized anti-human IL-6 receptor monoclonal antibody currently used for rheumatoid arthritis (32). Xu *et al* demonstrated that giving tocilizumab in addition to routine therapy to patients diagnosed as severe or critical COVID-19 is an effective treatment (33). COVACTA is a newly initiated randomized, double-blind, placebo-controlled phase III study to evaluate the safety and efficacy of intravenous Actemra/RoActemra added to standard care in adult patients hospitalized with severe COVID-19 pneumonia compared to placebo plus standard care. The primary and secondary endpoints include

clinical status, mortality, mechanical ventilation and intensive care unit (ICU) variables (34).

Stem cell therapy

Finally, the use of stem cell therapy to treat COVID-19 is currently considered with multiple clinical trials from China registered at www.clinicaltrials.gov (35). In a recently published clinical trial with a limited number of patients, 7 patients (1 critically serious, 4 serious and 2 common) infected with the coronavirus received one dose of stem cell therapy with 3 patients in the control group (3 serious) did not. All patients with stem cell therapy recovered whereas in the control group, one patient died while another patient developed ARDS and only one patient in the control group was stable (36).

Conclusion

Important considerations in the successful testing and use of currently available and future therapies for COVID-19 are the timing of the treatment, the viral load of the patient and markers predictive of lung injury. Antiviral treatment is more efficient as a prophylactic measure and at earlier times during the infection, when virus replication is at its peak. Conversely, immunomodulatory and anti-inflammatory treatments may be more effective later and may be combined with careful monitoring of the patient viral loads.

The emergence of zoonotic human viruses causing pandemics are probably not going to be limited to the SARS-CoV-2 and represent enormous threats to global health. Pandemic preparedness in the future, broad-based vaccines and therapeutics, which are active against the higher risk virus families prone to emergence, are desperately needed, as well as global efforts to minimize their emergence.

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Availability of data and materials

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Authors' contributions

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Not applicable.

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Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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