REVIEW

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# Antiviral Agents

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**ABSTRACT**

Coronavirus disease 2019 (COVID-19) is a respiratory track infection which caused a pandemia after being recognized in Wuhan, China at the end of 2019. While most people with COVID-19 develop mild or uncomplicated illness, approximately 14 % develop severe disase requiring hospitalization and oxygen support and 5 % require intensive care unit admission. Currently, there is no proven reliable and effective antiviral agent for COVID-19 pneumonia however, more than 100 randomised controlled clinical trials are ongoing. This paper will discuss the antiviral treatments in the critically ill patients with COVID-19 pneumonia.

**Keywords:** COVID-19, pneumonia, antiviral agents, critically ill

## Introduction

At the end of 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China, and subsequently spread all around the world. The major morbidity and mortality from COVID-19 is largely due to acute viral pneumonitis that progresses to acute respiratory distress syndrome (ARDS). Although no treatments have been proven to date, several antiviral treatments considered to be effective in COVID-19. This paper will discuss the current information on antiviral treatments in the critically ill patients with COVID-19 pneumonia.

Currently, there is no proven reliable and effective antiviral agent for COVID-19 infection. However, more than 100 randomised controlled clinical trials are ongoing. Although the results of these studies should be waited for strong scientific recommendations, several medications are used worldwide due to the urgency of the clinical condition.

### Chloroquine and Hydroxychloroquine

Chloroquine and Hydroxychloroquine are antimalarial drugs with a long history of clinical use. Previously, chloroquine has been reported to have antiviral activity against influenza, seasonal CoVs and SARS. As for these viruses, cell entry and replication of SARS-CoV2 depends on ph dependent internalization by endocytosis and lysosomal fusion. Experimental reports indicated antiviral activity of chloroquine derivates against SARS-CoV2 in vitro. Based on this, the drug was rapidly introduced into clinical use and some preliminary reports suggested improved viral clearance and better clinical outcomes in a 10 day course of hydroxychloroquine treatment. On the other hand, some other reports failed to show any benefit. Immunomodulatory effects of hydroxychloroquine are well established and may enhance its therapeutic effect in COVID-19 complicated cytokine storm. Finally, hydroxychloroquine has antithrombotic effects which may be beneficial in COVID-19. Although the clinical efficacy has not been proven in any randomised controlled trial yet, the use seems to be safe when administered at correct dosing and under close monitorization. However the therapeutic range is narrow and side effects including conduction defects, cardiomyopathy, retinopathy and hypoglycaemia should be kept in mind.

### Lopinavir/Ritonavir

This combined protease inhibitor, which has primarily been used for HIV infection, has in vitro activity against the SARS-CoV when used with

ribavirin. Diarrhea, nausea and asthenia were the most frequently reported adverse effects. It has also significant interactions with a number of drugs. In a study of MERS-CoV infection, Kim *et al* showed the favorable effect of LPV/RTV with ribavirin and IFN-alpha2a combination. However, another randomised controlled trial which was performed in 199 COVID-19 patients, LPV/RTV (400/100 mg) two times a day failed to show any effect on clinical remission or 28-days mortality with an increase in side effect profile. Thus, current guideline does not recommend routine use of this agent in COVID-19. However, the only randomised controlled trial is being discussed because of not blinded, including limited patient number and with the total number of 44 mortality cases. LPV/RTV is one of the arms in a planned WHO core treatment protocol for hospitalized patients with COVID-19, and in the REMAP-CAP (Randomised Embedded Multifactorial Adaptive Platform Trial for Community Acquired Pneumonia) trial (NCT02735707). The results of ongoing trials will help increase the prediction of estimates and the certainty of scientific evidence. The latest Ministry of Health Guidelines published in 14 th April 2020 suggest the use of LPV/RTV in pregnant with documented COVID-19 infection.

### Umifenovir (Arbidol)

Umifenovir (branded as Arbidol), a derivate of indole carboxylic acids has shown efficacy in the treatment of Influenza A, B, Ebola Human herpes virus 8 and Hepatitis C. Its major mechanism of action is to block the virus-cell membrane fusion and virus-endosime fusion through incorporation into cell membranes. It has shown very promising activity against SARS-CoV2 in vitro. It has no significant side effect except possible allergic reaction of rash. According to a randomised open labelled multicentre trial, it showed less efficacy compared to Favipiravir. There are two randomised open label trials ongoing in China which investigates the efficacy and safety of Umifenovir against COVID-19. A retrospective cohort study has reported that combination of umifenovir and LPV/RTV has improved negative conversion rate and chest CT scan results compared with only LPV/RTV group.

### Remdesivir

Remdesivir is a adenosine analogue pro drug which is a strong inhibitor of viral RNA polymerase. It was considered as a promising drug with WHO with its effect on RNA viruses. Possible side effects include increase in liver function tests, nausea and vomiting. According to in vitro clinical trials it showed a higher anti viral activity than LPV/RTV with IFN1b. In addition to promising results on SARS-CoV and MERS-CoV, there are published case reports which shows effective inhibition in COVID-19. Currently there are no published trials in COVID-19 however results of several clinical Phase II and Phase III investigations are warranted (NCT04257656, NCT 04252664, NCT 04280705). Although intravenous form appears to adequately tolerated, a RCT documented it's less effectivity in EBOLA virus disease compared to other antibody treatments. Recently, the results of compassionate use of remdesivir were published. This trial was performed by Gilead Sciences on 61 critically ill COVID-19 patients. The patients were given intravenous remdesivir at a dose of 200 mg on the first day followed by 100 mg for a total of 10 days. Clinical improvement in terms of oxygen requirements was observed in 68 % of the study group. As well many of the mechanically ventilated patients were successfully extubated. However, it's difficult to extrapolating these results since the study did not include a control group. As a result, it's too early to conclude the direct antiviral effect of remdesivir but it seems to be a promising therapeutic agent in COVID-19.

### Nelfinavir

Nelfivavir is a selective HIV protease inhibitor. It has been predicted a potential treatment option with strongly inhibiting effect on SARS-CoV replication.

### Favipiravir (Avigan)

Favipiravir is an RNA polymerase inhibitor which blocks the viral replication. Favorable effects have been reported in Influenzae, Ebola and other RNA viruses. According to a in vitro research, it has been shown efficacy on SARS-CoV2 with high concentrations. A randomized controlled trial which compared the efficacy of Favipiravir 1600 mg x2 on the first day followed by 600 mg x2 for 9 days showed higher recovery rate (71%) than Umifenovir (55%) and improvement in the duration of symptoms. It has several advantages with lower side effect profile and drug-drug interactions however the current literature on COVID-19 infection is limited. There are several ongoing trials evaluating the efficacy and safety of Favipiravir. A preliminary clinical trial on Favipiravir which was conducted in China indicated better results for Favipiravir compared with LPV/RTV with lesser side effects. Another study from China showed cleared viral load in four days compared to standard care which cleasrence was obtained in 11 days. Today, according to National Guidelines of Ministry of Health, it has been recommended for possible or documented COVID-19 patients with severe pneumonia with 1600 mg two times a day loading dose, followed by 600 mg doses two times a day as a maintenance therapy.

### Type 1 Interferons (IFN-1)

Type 1 interferons designate a group of cytokines comprising α, β, ε, κ and ω subtypes which are secreted by various cell types. They are among the first cytokines produced during a viral infection and play a ey role in antiviral immunity. IFN-1 treatment has been studied against MERS-CoV and SARS-CoV in a number of studies as either alone or with combination therapy and the results were inconclusive. IFN β1 appears to be the most relevant interferon especially when used at the early phase. In another study, IFNα2b was showed to reduce the infection rate of COVID-19. SARS-CoV2 induces an excessive IFN-1 mediated antiviral response which leads tissue damage. According to limited studies, IFN-1 treatment may be effective at the early phases of infection. In the late phases, it is even possible that anti IFN drugs should be used to mitigate the pathology. In China, the Guidelines for the treatment of COVID-19 recommend to administer 5 million U of IFN α by vapour inhalation twice a day in combination with ribavirin. Clinical trials have been registered to evaluate the efficacy of IFN α and β and the results should be waited for a more accurate conclusion.

## Conclusion

In critically ill adults with COVID-19, there is insufficient evidence to make a recommendation on the use of antiviral agents. According to current practice, we suggest early use of favipiravir in the critically ill adult patient with severe pneumonia due to the lower potential side effects with the light of our National Guidelines.

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