LITERATURE REVIEW

Current Antiviral Options for Therapeutic Management Of SARS-CoV-2 Infection

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Abstract

Introduction: The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to an urgent need for effective antiviral treatments. This paper provides an overview of current antiviral options for therapeutic management of SARS-CoV-2 infection, focusing on their mechanism of action, clinical efficacy and considerations for specific populations.

Methods: A literature review of several antiviral drugs have been evaluated for their effectiveness. Notable options include ritonavir-boosted nirmatrelvir, remdesivir, molnupiravir, favipiravir, and chloroquine/hydroxychloroquine.

Results: Ritonavir-boosted nirmatrelvir has shown promising results in reducing the risk of hospitalisation or death when administered within 5 days of symptom onset. Remdesivir has demonstrated efficacy in reducing hospitalisation rates and improving clinical outcomes in certain patient populations. Molnupiravir, has shown a reduction in rate of hospitalisation, although caution is advised regarding its use in pregnancy. Favipiravir and chloroquine/hydroxychloroquine have shown varied efficacy and are not currently recommended by organisational guidelines. Considerations for special patient populations, such as pregnant individuals, are discussed. While antiviral therapies may offer potential benefits, the evidence for their use in pregnant individuals is limited, emphasising the need for a case-by-case multidisciplinary approach.

Discussion: While antiviral treatments play a crucial role in managing SARS-CoV-2 infection, more research is needed to fully understand their efficacy and safety profiles, particularly in specific patient populations. Vaccination remains the most effective method for preventing severe COVID-19 presentations. .

Keywords: COVID-19, SARS-CoV-2, antivirals

Introduction

The COVID-19 outbreak was declared a pandemic on March 11th 2020[1]. The rapidly transmitting and deadly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had increased the number of cases by 13-fold in the preceding two weeks1. To date, there have been over 774 million cases, and 7 million deaths, with new cases continuing to be reported[2, 3]. The most common symptoms of COVID-19 include fever, dry cough, dyspnoea, chest pain, fatigue, and myalgia[4].The less commonly reported symptoms like diarrhoea, nausea, vomiting, headache and dizziness[4]. The majority of infections are asymptomatic or with mild symptoms.

However, people with one or multiple health conditions are at a higher risk for severe COVID-19. A metanalysis found that hospitalised patients with comorbidity have a 20.3% chance of requiring intensive care, putting a huge strain on the health care system at the peaks of the pandemic[5].

Treatment of COVID-19

The evidence for antivirals in treatment of COVID-19 is severely limited[6]. Trials were carried out in unvaccinated individuals and prior to the new variant of concern, Omicron. The strongest evidence for treatment of COVID-19 is: venous thromboembolism prophylaxis, corticosteroids and in rapidly deteriorating patients, the use of tocilizumab[6]. In addition, it is recommended that anti-virals only be used in patients with high risk for severe disease[6]. No one treatment is favoured over the other, but the decision is made on the basis of clinical context, such as the patient's renal function and medication interactions[6].

COVID-19 Viral Life Cycle

Rapid assessment began of current antiviral drugs that may be effective in treating COVID-19. A virus can attach to a host cell, penetrate it and once inside the cell, carry out further steps (uncoating, reverse transcription, transcription, translation) of replication before being released and infecting other host cells[7]. Antivirals target the virus lifecycle and can prevent the virus from entering the host cell, replicating, packaging and releasing. There are over 80 antivirals available; the majority used to treat HIV infections and the others for influenzae A and B, cytomegalovirus, hepatitis A and C, and herpes simplex virus[7]. The SARS-CoV-2 lifecycle starts with the attachment to the host cell via co-receptor binding and membrane fusion involving the S spike protein, the host cell's angiotensin-converting enzyme 2 (ACE2) receptor,

and the cell surface serine protease TMPRSS2[7, 8]. This allows the virus to be enter the host cell by endocytosis or by plasma membrane fusion. The S spike protein has also been found to neutralise antibodies, making it easier for the virus to bind to the host receptors[9]. Viral fusion inhibitors can be used to inhibit this step[7].

Once in the cytoplasm, the virus uncoats and the SARS-CoV-2 RNA is released. Host ribosomes translate the RNA open reading frames (ORF) ORF1a and ORF1b into polyprotein pp1a and pp1b[8, 10]. These polyproteins help in hijacking the host ribosome, which is necessary for viral replication. The polyproteins undergo cleavage by proteases, such as main protease (MPRO), yielding non-structural proteins needed for viral replication and transcription[8, 10]. Thus, inhibiting proteases is a potential strategy to treat SARS-CoV-2[7].

The exact replication of SARS-CoV-2 is not completely understood, but it can be explained using the SARS-CoV model[7]. The non-structural protein (nsp12) forms an RNA-dependent RNA polymerase (RdRp) producing a negative-sense RNA strand, complimentary to the positive-RNA strand template. The negative-sense strand is used to synthesise new positive-sense RNA strands11. It is at this step that reverse transcriptase inhibitors can be used[7].

After replication, post-translational modifications occur in the endoplasmic reticulum-Golgi apparatus compartment. Assembly and budding of the enveloped virus occur in the endoplasmic reticulum before passing through the Golgi apparatus. Here, the mature virus is released in vesicles that leave the cells to infect other cells[7].

Anti-viral Drugs

Ritonavir-boosted nirmatrelvir (Paxlovid)

Ritonavir-boosted nirmatrelvir (Paxlovid) is a protease inhibitor against the protease MPRO[12, 13]. It is orally available and has been shown to be effective against all coronaviruses that infect humans[12]. Ritonavir is a CYP450 3A4 inhibitor and is therefore packaged with nirmatrelvir to increase the latter's concentration to therapeutic ranges. All of patients' medications should be reviewed prior to prescribing Paxlovid due to its CYP450 inhibition effect[6, 12, 13]. For example, it may reduce the efficacy of combined oral contraceptives; therefore, the patient should be advised to use an alternative method of contraception. It is recommended by the Health Service Executive (HSE) that Paxlovid be used in non-hospitalised or hospitalised patients[6]. They must be at least 18 years of age, have no oxygen requirement, have an oxygen saturation greater than 94% and a respiration rate less than 20 breaths per minute[14]. It should be started within five days of symptom onset in a patient with a confirmed COVID-19 polymerase chain reaction test and continued for five days[13, 14].

In the EPIC-HR trial, it was found that Paxlovid reduced the risk of hospitalisation or death by 88% compared to a placebo group[14, 15]. Its high efficacy, paired with it being the only oral antiviral available for treatment of COVID-19, poses a strong argument for Paxlovid to be considered in patients with a high risk of significant medication interactions, and initiates a discussion as to whether the interacting medications can be adjusted or substituted to safer alternatives. Furthermore, it is important to note that the EPIC-HR trial excluded pregnant and lactating individuals, despite ritonavir being used considerably in pregnant individuals with HIV[14, 15]. According HSE guidelines, Paxlovid can be used in pregnant individuals on a case-by-case-basis, if the benefits outweigh the risks[6].

Other considerations are those patients with renal impairment. The normal dose is 300mg of nirmatrelvir and 100mg of ritonavir taken together every 12 hours for five days[6]. For those with an eGFR <60mL/min, the dose should be reduced by half, 150mg of Nirmatrelvir and 50mg of Ritonavir every 12 hours for five days. In those with an eGFR <30mL/min, Paxlovid is not recommended[6].

Remdesivir

Remdesivir is a nucleotide reverse transcriptase inhibitor; the nucleotide analogue inhibits RdRp in the majority of single stranded RNA viruses, such as the coronaviruses[7]. A three-day intravenous. course of treatment is recommended for unvaccinated patients with risk of progressing to severe COVID-19 or the immunocompromised regardless of vaccination status[6]. The patients must also be presenting within eight days of symptom onset, have a confirmed COVID-19 PCR, be over 18 years old and not requiring oxygen therapy[6]. The PINETREE trial[16] showed that a 3-day treatment of intravenous remdesivir resulted in an 87% reduction in risk of hospitalisation or death compared to the placebo[11].

A five-day course of remdesivir may be advised in patients that are on oxygen therapy, and meeting all other inclusion criteria, however, there is limited evidence of efficacy[6]. It is recommended that a loading dose of 200mg be administered on day 1, followed by 100mg on day 2 and 3[6, 11]. Remdesivir is not recommended for treatment of children under 12 years of age, nor in patients with an eGFR <30mL/min[6]. It is also contraindicated in patients with alanine aminotransferase greater than five times the upper limit of normal. as clinical trials observed elevated transaminases with remdesivir treatment[6].

Molnupiravir

Molnupiravir is a ribonucleoside. When incorporated into the host DNA, it induces lethal mutations[11]. 800mg of molnupiravir orally twice daily for five days is recommended by the National Institute of Health, for those greater than 18 years of age but only for when Paxlovid and Remdesivir are not available or clinically appropriate[11].

The MOVe-OUT study found that molnupiravir reduced the rate of hospitalisation by 30%. The trial consisted of randomising 1433 participants, of which 716 received the drug, and the remainder receiving the placebo[17]. The participants were within five days of symptoms onset, unvaccinated with lab-confirmed COVID-19, with mild-to-moderate symptoms, and at least one risk factor for severe COVID-19[17].

Molnupiravir is not recommended for use in pregnancy due to the foetal toxicity reported in animal

studies[11]. If other therapies are not available than molnupiravir can be used if the patient is beyond the 10 weeks of gestation. However, it is imperative that the patient is fully informed of the risks, and advised of the option to participate in the surveillance programme[11]. For individuals that are lactating, there is limited evidence that molnupiravir may cause adverse effects in infants[11]. It is recommended by the FDA that lactating people stop breast feeding while undergoing treatment until 4 days after their last dose[11].

Favipiravir

Favipiravir is a guanine nucleotide analogue and acts as an RdRp inhibitor[7]. In its activated phosphoribosylated form, favipiravir-RTP, it inhibits RdRp and arrests RNA synthesis. It was initially developed for influenza; and was approved in Japan in 2014 for resistant influenza infection with several other countries following suit[18]. Due to its wide spectrum of activity, favipiravir is a candidate for COVID-19 treatment. There is limited and varying evidence on its efficacy, which has deterred said drug from being recommended by organisational guidelines[19]. A systematic review and meta-analysis of clinical trials of favipiravir for treatment of COVID-19 concluded that the antiviral is associated with significant clinical improvement in most patients. They also concluded that the treatment conferred no serious side effects but also had no significant effect on mortality[20]. The study also noted limitations to the clinical trials, such as varying doses and duration of treatment, small sample sizes, and efficacy due to patient multi-drug pharmacy[20]. In all, the mixed results and low power trial data are indicative that more clinical trials with larger sample sizes need to be carried out[20].

Chloroquine/Hydroxychloroquine

Chloroquine and hydroxychloroquine are used to treat malaria as well as autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis. They have shown to increase the endosomal pH and inhibit SARS-CoV-2 cell fusion with the host cell membrane[21]. Chloroquine also inhibits the glycosylation of the ACE2 receptor, which may interfere with the fusion of SARS-CoV-2[22]. Chloroquine/hydroxychloroquine have been shown to have immunomodulatory effects hence their use in autoimmune diseases, and it is hypothesised that this may potentiate the effects of COVID-19 infection as well. Although these two medications demonstrate antiviral activity, neither hydroxychloroquine nor hydroxychloroquine plus azithromycin, demonstrated a reduction in the viral load of the upper or lower respiratory tract in non-human primates[11, 23].

In the UK RECOVERY trial, 1561 patients were randomly assigned to receive hydroxychloroquine[24]. In the hydroxychloroquine group, they were less likely (59.6%) to be discharged from the hospital alive within 28 days compared to the usual-care group (62.9%). Furthermore, patients in the hydroxychloroquine group that were not undergoing mechanical ventilation at baseline had a higher frequency of invasive mechanical ventilation or death[24]. In the WHO Solidarity trial, an international randomised controlled trial, hydroxychloroquine was given to hospitalised patients and withdrawn from patients due to its low efficacy; there was no difference in mortality when compared to the control group[25]. In a systematic review and meta-analysis of 51 studies (n = 61,221; nine randomised controlled trials; 42 observational studies), there was no significant reduction in mortality, length of hospital stay, time to fever resolution, incidence of mechanical ventilation or time to a negative SARS-CoV-2 PCR test with treatment with hydroxychloroquine with or without azithromycin[26]. Thus, the NIH and the HSE do not recommend chloroquine/hydroxychloroquine alone or in combination with azithromycin for the treatment of SARS-CoV-2[6].

Pregnant individuals

While most pregnant individuals infected with COVID-19 present asymptomatically or with mild-to-moderate disease, there is data suggesting that SARS-CoV-2 infection in pregnant individuals may be at increased risk of severe disease, as well as higher rates of mortality, morbidity, ICU admissions and need for ventilation[6]. Vaccinations remain the most effective method in preventing severe COVID-19 disease in pregnant individuals[6]. They present similarly to non-pregnant individuals and thus, management is the same as per national guidance. With pharmacological treatment, the potential risks of COVID-19 infection should out-weigh the unknown risk of the drug on the pregnant individual or foetus.

The evidence of antivirals for treatment of COVID-19 is very limited. There is currently no evidence for use of nirmatrelvir in pregnancy but that the patients should be reviewed on a case-by-case basis[6]. In nonclinical reproductive toxicity studies, intravenous remdesivir did not show any adverse effects on embryofoetal development in pregnant rats and rabbits, at four times the recommended human dose[27]. Furthermore, an RCT of remdesivir in treatment of EBOLA included six pregnant women with no adverse effects on the pregnancy reported[28]. With that being said, there is still limited evidence on antivirals for treatment of COVID-19 in pregnant individuals, and thus a case-by-case multidisciplinary approach is necessary[6].

Conclusion

Whilst individuals infected with SARS-CoV-2 are mostly asymptomatic, it can cause serious disease and mortality[6]. Thus, antiviral therapies are being investigated for the treatment of SARS-CoV-2. Antivirals target various steps and enzymes of viral replication like fusion, proteases, RNA-dependent RNA polymerases, and reverse transcriptase. Viral replication may be particularly active early in the infection course; thus, antiviral therapy may have the best effect before the illness progresses to the inflammatory late stage[6].

The HSE recommends Paxlovid, and remdesivir for treatment of COVID-19 in the early stages of infection. Paxlovid is administered orally for five days within five days of symptom onset and after medication review

for interactions. Remdesivir, an intravenous drug, should be given for three days and started within seven days of symptom onset in patients with a confirmed COVID-19 PCR test. For those requiring supplemental oxygen therapy, a five-day course of remdesivir may be considered, using a multidisciplinary approach[6].

The NIH also recommends the use of Paxlovid and remdesivir, but additionally recommends molnupiravir, if the former two are unavailable or clinically inappropriate11. Molnupiravir should be given per oral twice daily for 5 days. However, it should be cautioned when used in pregnancy because limited evidence demonstrated foetal toxicity in animal studies[11].

There are also drugs that have yet to be approved by organisations but that have the potential to treat COVID-19. For example, favipiravir is a candidate but there is limited and varying evidence of its efficacy[7]. Thus, more research is needed into the use of favipiravir for the treatment of SARS-CoV-2.

Both the HSE and the NIH recommend against the use of hydroxychloroquine with or without azithromycin[6,11]. A systematic review found that papers reported no significant reduction in mortality, length of hospital stay, time to fever resolve, incidence of mechanical ventilation, and time to a negative SARS-CoV-2 PCR test[26]. Furthermore, the UK RECOVERY trial found that the hydroxychloroquine patient group were less likely (59.6%) to be discharged from the hospital alive within 28 days, compared to the usual-care group (62.9%)[24].

As per HSE guidelines, treatment of pregnant individuals infected with COVID-19 should receive the same treatment is non-pregnant individuals. There is still limited evidence on antivirals for treatment of COVID-19 in pregnant individuals, and thus a case-by-case, multidisciplinary approach is necessary[6].

The strongest evidence for treatment of COVID-19 is venous thromboembolism prophylaxis, corticosteroids and in rapidly deteriorating patients, the use of tocilizumab[6]. The best prevention of severe infection remains to be vaccination. Currently, the HSE only recommends the antivirals Paxlovid and remdesivir for early treatment in those unvaccinated or immunocompromised with risk of severe disease progression and not requiring supplemental oxygen[6]. More research into the efficacy of antivirals for treatment of COVID-19 is needed, including special patient groups such as pregnant and lactating individuals. ◄

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Declarations

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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