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Antivirals for COVID-19

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ABSTRACT

Drugs targeting RNA respiratory viruses have resulted in few effective therapies, highlighting challenges for antivirals to treat COVID-19. Several antivirals are being investigated for symptomatic COVID-19 but no definitive data support their clinical use. Remdesivir appears to result in favorable outcomes with shortened time to recovery and a modest decrease in mortality for hospitalized patients in compassionate use series and some randomized controlled trials. Currently, remdesivir is available only from the US government via an emergency use authorization process. A randomized controlled trial of lopinavir/ritonavir demonstrated no apparent clinical or virologic benefit and drug-drug interactions and side effects further limit its utility. Antivirals to treat influenza (oseltamivir) have limited activity against SARS-CoV-2, but favipiravir and umifenovir, two influenza antivirals available internationally, may have distinct viral targets and require further investigation. Antivirals with evidence of clinical activity must be studied as treatment and prophylaxis for those at high risk for severe COVID-19.

INTRODUCTION

Since COVID-19 emerged in Wuhan, China, over 33 million cases have been confirmed worldwide with a mortality of 3.2%.[1] The majority of infected individuals achieve full recovery, many with few symptoms. For those with more severe illness or high risk for mortality or both, therapeutic strategies have emerged to combat severe acute respiratory syndrome coronavirus (SARS-CoV-2) directly with antivirals and indirectly with immune modulation. In this discussion of proposed antiviral therapies that may hold some promise against SARS-CoV-2, it should be recognized that antiviral drug development against other RNA respiratory viruses has resulted in very few effective therapies. This is primarily due to poorly characterized RNA polymerases and weak clinical activity of nucleoside analogs (ribavirin for respiratory syncytial virus [RSV] and parainfluenza). For the developed non-nucleoside drugs (neuraminidase inhibitors and adamantanes for influenza) clinical challenges include short therapeutic windows, limited effects on the severely ill, and drug resistance. While the following antivirals are of interest for treating symptomatic COVID-19, they may suffer the same challenges. Those drugs with evidence of clinical activity may also warrant investigation as prevention in high risk populations.

REMDESIVIR

Remdesivir (GS-5734) is an adenosine analog antiviral drug that inhibits viral RNA polymerase and has demonstrated in vitro activity against various viruses including Ebola, SARS-CoV, and Middle Eastern respiratory syndrome (MERS-CoV). More recently, remdesivir has demonstrated potent activity against SARS-CoV-2 in in vitro and animal model studies, and holds some promise for treatment of COVID-19.[2,3] Early data from April 2020 suggested mixed results on the utility of remdesivir as a therapeutic option. A case series describing the compassionate use of remdesivir in 61 adult hospitalized patients with COVID-19 demonstrated that 68% of patients experienced an improvement in the need for oxygen support over a median 18 day follow-up period, while 15% of patients clinically worsened. Clinical improvement was observed in 84% of patients, but was less frequent among older patients (70 or older vs less than 50), and in patients who were on invasive ventilation compared with patients on noninvasive ventilator support. Mortality occurred in 13% of patients, with older patients (70 or older) and patients with higher base-

line serum creatinine demonstrating a higher risk. Adverse events were reported by 60% of patients, most commonly increased hepatic transaminases (23%), diarrhea (9%), rash (8%), renal impairment (8%) and hypotension (8%).[4] The lack of a comparator control arm is a significant limitation to the interpretation of the data presented in this compassionate use experience.

Subsequently, a randomized placebo-controlled trial of 236 adult hospitalized patients with COVID-19 in Wuhan, China published on April 29, 2020, demonstrated no significant difference in time to clinical improvement (21 days for remdesivir vs 23 days for placebo) or 28-day mortality (14% for remdesivir vs 13% for placebo). In a subgroup of patients initiated on treatment early (ie, within 10 days of symptom onset), time to clinical improvement was 18 days for remdesivir vs 23 days for placebo and 28-day mortality was 11% for remdesivir vs 15% for placebo, although the differences were not statistically significant. Of note, enrollment in this trial was terminated early due to achievement of infection control in China, thus the sample size may represent a limitation of this study.[5]

On May 1, 2020, the US Food & Drug Administration (FDA) issued an emergency use authorization (EUA) for remdesivir for the treatment of patients hospitalized with COVID-19 based on preliminary results from the National Institutes of Health (NIH) funded Adaptive COVID-19 Treatment Trial (ACTT-1), which were subsequently published on May 22, 2020.[6,7] ACTT-1 was a multinational randomized, placebo-controlled trial of 1,063 patients hospitalized with SARS-CoV-2, of whom 85% required some degree of oxygen support (40% of patients on supplemental oxygen, 19% on high flow or non-invasive ventilation, and 26% on mechanical ventilation or extracorporeal membrane oxygenation [ECMO]).

Compared with placebo, remdesivir shortened the median time to recovery from 15 days to 11 days, with a more significant likelihood of clinical improvement in patients requiring supplemental oxygen. Although the preliminary 14-day mortality benefit of remdesivir was not statistically significant (7.1% with remdesivir vs 11.9% with placebo; hazards ratio [HR] for death 0.7; 95% confidence interval [CI] 0.47 to 1.04), full analysis of the 28-day follow-up data is still pending.[7]

Shortly following the preliminary results of ACTT-1, an industry sponsored phase 3, open label, randomized trial investigating remdesivir 5-day vs 10-day durations in 397 patients with moderate COVID-19 pneumonia was published.[8,9] This study demonstrated no difference in rates of clinical improvement at 14 days or time to clinical improvement between the 2 duration strategies. Moreover, patients receiving the 5-day course noted fewer serious adverse events. Importantly, this study excluded patients on mechanical ventilation, ECMO or with organ dysfunction.[9]

Based on the available data, both NIH and the Infectious Diseases Society of America guidelines favor the use of remdesivir in hospitalized patients with severe COVID-19 requiring oxygen supplementation. A 5-day duration is recommended for patients not requiring mechanical ventilation or ECMO, with considerations for extending to 10 days if no clinical improvement observed. Given that currently remdesivir is not yet FDA approved and only available in the US via EUA allocations, guidelines suggest prioritizing remdesivir use in hospitalized patients requiring supplemental oxygen but not on mechanical ventilation or ECMO.[10,11] Additional comparative data is required for earlier remdesivir treatment in the highest risk patient populations.

◼ LOPINAVIR/RITONAVIR (KALETRA)

Lopinavir/ritonavir is a combination antiretroviral drug comprising 2 protease inhibitors. Lopinavir, the primary agent, acts through viral protease inhibition and ritonavir inhibits CYP3A4-mediated metabolism of lopinavir thus increasing its plasma concentrations. Currently approved by the FDA for the treatment of HIV, lopinavir/ritonavir was studied as an antiviral agent in both the SARS and MERS outbreaks due to demonstrable in vitro activity against both coronaviruses.[12,13] In SARS, patients who received lopinavir/ritonavir (often in combination with ribavirin and corticosteroids) compared with historical controls had lower mortality rates, lower mechanical ventilation requirements, required less rescue corticosteroid treatment, and had lower viral loads after treatment.[13,14]

In light of these findings in SARS, lopinavir/ritonavir was evaluated in patients with COVID-19. Of note, there are no in vitro studies of lopinavir/ritonavir against SARS-CoV-2. In March 2020, a randomized, controlled, open-label trial comparing lopinavir/ritonavir (400 mg and 100 mg, respectively) twice daily for 14 days vs standard care in 199 hospitalized patients with COVID-19 at a single hospital in China demonstrated no statistically significant difference

TABLE 1
Antiviral agents under investigation for COVID-19

Drug	Mechanism of action	FDA-approved indication(s)	Dosage	Adverse reactions/contraindications	Comments
Remdesivir	Adenosine analog RNA polymerase inhibitor	Not currently approved	200 mg IV on day 1, then 100 mg IV daily × 9 additional days	Safety not fully established	Currently undergoing several phase III clinical trials in the US for COVID-19
Lopinavir/ ritonavir (Kaletra)	Protease inhibitor	HIV	HIV: varies based on concomitant medications, typically lopinavir/ritonavir 400 mg/100 mg twice daily	**Adverse reactions**: QTc prolongation, weight gain, fat redistribution, hepatotoxicity, increased cholesterol, hyperglycemia, pancreatitis, skin rash, gastrointestinal effects **Caution/avoid use**: Lopinavir and ritonavir are strong CYP3A4 inhibitors and thus may have many drug interactions	Clinical trials ongoing in the US and internationally
Oseltamivir (Tamiflu)	Neuraminidase inhibitor	Influenza A/B for treatment or prophylaxis	Influenza: 75 mg twice daily Influenza prophylaxis: 75 mg once daily Adjust doses for renal function	**Adverse reactions**: Vomiting, nausea, headache	Two randomized clinical trials currently ongoing in China
Favipiravir (Avigan)	Purine nucleotide RNA polymerase inhibitor	Not currently approved	Varies based on clinical trial	Safety not fully established	Currently undergoing clinical trial evaluation for COVID-19 in China and US
Umifenovir (Arbidol)	Viral envelope membrane fusion inhibitor via S-protein/ ACE2 interaction	Not currently approved	Varies based on clinical trial	Safety not fully established	Pending further clinical trial evaluation for COVID-19

ACE2 = angiotensin-converting enzyme 2 gene; FDA = US Food & Drug Administration; HIV = human immunodeficiency virus; IV = intravenous; QTc = corrected QT interval; RNA = ribonucleic acid; US = United States

in the primary outcome of time to clinical improvement (HR 1.39; 95% CI 1.00 to 1.91).[15] Furthermore, mortality rates were not significantly different in the cohort of patients who received lopinavir/ritonavir (19.2% vs 25.0%; 95% CI –17.3 to 5.7). There was no difference between groups for detection of viral RNA over time. Based on these findings, the authors concluded that no benefit was observed with lopinavir/ritonavir treatment in COVID-19 beyond standard care.

Moreover, lopinavir/ritonavir is associated with many adverse reactions (**Table 1**) and drug interactions due to the strong inhibition of CYP3A4. In fact, 48% of patients who received lopinavir/rito-navir for COVID-19 experienced adverse reactions, most commonly gastrointestinal effects. Of these, 19 events were noted to be serious, and 13 patients discontinued the drug due to adverse reactions.[15] Overall, based on the lack of supportive data for its use in COVID-19, its adverse effect profile and significant drug interactions, lopinavir/ritonavir for COVID-19 should be reserved for use only in the context of a clinical trial.[10]

■ OTHER ANTIVIRAL AGENTS
Various other antiretrovirals such as darunavir-based regimens have also been purported to have in vitro activity against SARS-CoV-2. However, there are no

human clinical data on the utility of these agents in the management of COVID-19.[16] Johnson & Johnson, the makers of darunavir/cobicistat (Prezcobix) and darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza), recently published a statement on the lack of evidence to support the use of darunavir-based treatments for SARS-CoV-2.[17] Furthermore, 1 of 3 randomized, open label clinical trials evaluating darunavir/cobicistat for COVID-19 recently concluded that the agent was not effective at achieving viral clearance at day 7 post-randomization compared with standard care.[10] The neuraminidase inhibitor antiviral oseltamivir was used empirically in several patients during the COVID-19 outbreak in China due to the overlap with peak influenza season. However, oseltamivir has no documented in vitro activity against SARS-CoV-2 and is not expected to play a role in the management of COVID-19.[16]

Umifenovir (Arbidol), a viral envelope membrane fusion inhibitor, is an influenza antiviral agent available in Russia and China with suggested in vitro activity against SARS. An observational study from China of 67 patients with COVID-19 demonstrated lower mortality rates and higher discharge rates among 36 patients treated with umifenovir versus the umifenovir-untreated group.[18] Conversely, in another retrospective study from China of 81 hospitalized (not in an intensive care unit) patients, umifenovir failed to demonstrate a reduction in the proportion of patients testing negative for SARS-CoV-2 within 1 week of admission (73% umifenovir vs 78% control, $P = 0.19$), or hospital length of stay compared with standard of care.[19] Of note, patients in the umifenovir group had higher baseline chest computed tomographic scan scores based on an ordinal scoring tool. Although median time from *admission* to first negative test was longer in the umifenovir group (6 days vs 3 days, $P < 0.05$), the median time from *onset of disease* to first negative test was comparable with the control group (18 days vs 16 days, $P > 0.05$). Randomized controlled trials of the utility of umifenovir in COVID-19 are still lacking. Similarly, favipiravir (Avigan), a purine nucleotide RNA polymerase inhibitor that is available in Japan for treatment of influenza, has also demonstrated in vitro activity against SARS-CoV-2.[2,16] In a randomized study comparing favipiravir with umifenovir in 240 patients with moderate and severe COVID-19, favipiravir demonstrated higher clinical recovery rates at day 7 in moderate illness but failed to demonstrate any difference in severe illness.[20] Ongoing clinical trials evaluating these and other antiviral agents for COVID-19 are described in **Table 1**.

■ TAKE HOME POINTS

- Historically, drug development targeting RNA respiratory viruses has resulted in very few effective therapies, highlighting challenges for antivirals to treat COVID-19.
- While several antivirals are being investigated for those with symptomatic COVID-19, there are no definitive data to support their clinical use and existing data do not suggest robust impacts.
- Remdesivir, with good in vitro activity against SARS-CoV-2, appeared to result in favorable outcomes for a majority of hospitalized patients in a compassionate use series. Early data from a recent NIH-sponsored randomized clinical trial suggest shortened time to recovery and a modest decrease in mortality for some patient group. At this time, remdesivir is available only from the US government via an EUA.
- Enthusiasm is tempered for lopinavir/ritonavir after a single randomized, controlled clinical trial demonstrating no apparent clinical or virologic benefit. Its use is further limited by important drug-drug interactions and side effects.
- Antivirals to treat influenza (oseltamivir) have limited mechanistic activity against SARS-CoV-2, but favipiravir and umifenovir, influenza antivirals available internationally, have distinct viral targets and require further investigation.
- The scope of the pandemic requires that antivirals with evidence of clinical activity be studied both as treatment and prophylaxis for those at high risk for severe COVID-19.

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