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Antivirals for COVID-19

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ABSTRACT

Drugs targeting RNA respiratory viruses has 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, with good in vitro activity against SARS-CoV2, appeared to result in favorable outcomes for hospitalized patients in a compassionate use series with shortened time to recovery and a modest decrease in mortality. Currently, remdesivir is available in phase III clinical trials, the compassionate use program, and eventually through the emergency use authorization. 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, influenza antivirals available internationally, 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 3 million cases have been confirmed worldwide with a mortality of 7%.[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] A recent 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 baseline serum creatinine demonstrating a higher risk. Adverse events were reported by 60% of patients, most commonly increased hepatic transaminases

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(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.

On April 29, 2020, the National Institutes of Health released a statement regarding promising preliminary data from the ongoing randomized Adaptive COVID-19 Treatment Trial involving 1,063 patients. According to the interim analysis, preliminary data suggest that remdesivir conferred a 31% faster median time to recovery compared with placebo of 11 days in the remdesivir group vs 15 days in the placebo group ($P < 0.001$) and mortality of 8% in the remdesivir group vs 11.6% in the placebo group ($P = 0.059$).[5] On the same day, the maker of remdesivir (Gilead Sciences, Inc.) also released a statement regarding their open-label phase III SIMPLE trial that demonstrated similar rates of clinical improvement with a 5-day treatment course of remdesivir therapy compared with a 10-day treatment course.[6] Both studies are pending complete data analysis and peer review. Finally, a randomized placebo-controlled trial of 236 adult hospitalized patients with COVID-19 in Wuhan, China, was also published on April 29, 2020. Contrary to the press releases for the aforementioned studies, this study 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.[7]

Remdesivir is currently still undergoing rigorous evaluation in multiple phase III randomized clinical trials as a possible treatment option for COVID-19. 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. Logistics on medication access through the EUA are still in process between Gilead and the United States government. Currently, remdesivir is only available in the US through one of the clinical trials, a compassionate use program reserved for pediatric and pregnant hospitalized patients, and eventually through the EUA.

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.[8,9] 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.[9,10]

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 in the primary outcome of time to clinical improvement (hazard ration [HR] 1.39; 95% confidence interval [CI] 1.00 to 1.91).[11] 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/ritonavir 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.[11] 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.[12]

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

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.[13] 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.[14] 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.[12] 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.[13]

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.[15] 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.[16] 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.[2,13] 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.[17] Ongoing clinical trials evaluating these and other antiviral agents for COVID-19 are described in **Table 1**.

REFERENCES

1. **Johns Hopkins University & Medicine.** Coronavirus resource center. https://coronavirus.jhu.edu/. Accessed May 6, 2020.
2. **Wang N, Cao R, Zhang L, et al.** Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30(3):269–271. doi:10.1038/s41422-020-0282-0
3. **Cao YC, Deng QX, Dai SX.** Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: an evaluation of the evidence. Travel Med Infect Dis 2020; Apr 2. doi:10.1016/j.tmaid.2020.101647
4. **Grein J, Ohmagari N, Shin D, et al.** Compassionate use of remdesivir for patients with severe COVID-19. N Engl J Med 2020; Apr 10. doi:10.1056/NEJMoa2007016
5. **National Institute of Health (NIH).** NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19. Accessed May 6, 2020.
6. **Gilead Sciences, Inc.** Gilead announces results from phase 3 trial of investigational antiviral remdesivir in patients with severe COVID-19. https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19. Accessed May 6, 2020.
7. **Wang Y, Zhang D, Du G, et al.** Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicenter trial. Lancet 2020; Apr 29. doi:10.1016/S0140-6736(20)31022-9
8. **de Wilde AH, Jochmans D, Posthuma CC, et al.** Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother 2014; 58(8):4875–4884. doi:10.1128/AAC.03011-14
9. **Chu CM, Cheng VC, Hung IF, et al; HKU/UCH SARS Study Group.** Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004; 59(3):252–256. doi:10.1136/thorax.2003.012658
10. **Chan KS, Lai ST, Chu CM, et al.** Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicenter retrospective matched cohort study. Hong Kong Med J 2003; 9(6):399–406. pmid:14660806
11. **Cao B, Wang Y, Wen D, et al.** A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020; Mar 18. doi:10.1056/NEJMoa2001282
12. **Bhimraj A, Morgan RL, Shumaker AH, et al.** Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis 2020; Apr 27. doi:10.1093/cid/ciaa478
13. **Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB.** Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA 2020; Apr 13. doi:10.1001/jama.2020.6019
14. **Johnson & Johnson Services, Inc.** Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2. https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus. Accessed May 6, 2020.
15. **Wang Z, Yang B, Li Q, Wen L, Zhang R.** Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020; Mar 16. doi:10.1093/cid/ciaa272
16. **Lian N, Xie H, Lin S, Huang J, Zhao 1, Lin Q.** Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. Clin Microbiol Infect 2020; Apr 25. doi:10.1016/j.cmi.2020.04.026
17. **Chen C, Zhang Y, Huang J, et al.** Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv 2020; April 15. doi:10.1101/2020.03.17.20037432