COVID-19 Drug Therapy — Potential Options

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According to the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA), there are currently no medications or vaccines proven to be effective for the treatment or prevention of the 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (1) (2) (3)

In the absence of an established treatment regimen, the China International Exchange and Promotive Association for Medical and Health Care (CPAM) issued a novel 2019 coronavirus disease (COVID-19) guideline in February 2020 with recommendations on methodology, epidemiological characteristics, disease screening and prevention, diagnosis, treatment and control, nosocomial infection prevention and control, and disease nursing. For direct antiviral treatment of SARS-CoV-2, CPAM recommends use of lopinavir; ritonavir [2 capsule (dose undefined) by mouth twice daily] in combination with nebulized alfa-interferon (5 million units in Sterile Water for Injection inhaled twice daily). CPAM has based this recommendation on weak evidence from retrospective cohort, historically controlled studies, case reports, and case series that suggest clinical benefit of lopinavir; ritonavir in the treatment of other coronavirus infection [i.e., 2002 SARS-CoV and 2012 Middle East respiratory syndrome coronavirus (MERS-CoV)]. (4) (8) (7)

In addition to CPAM, a group of Korean physicians with experience in treating SARS-CoV-2 infected patients have developed recommendations for the treatment of COVID-19. According to these physicians, antiviral medications are not recommended for use in young, healthy patients with mild symptoms and no underlying comorbid conditions. However, treatment with lopinavir 400 mg; ritonavir 100 mg (2 tablets by mouth twice daily) or chloroquine (500 mg by mouth twice daily) should be considered for use in older patients or patients with under underlying conditions and serious symptoms. If chloroquine is unavailable, they recommend considering use of hydroxychloroquine (400 mg by mouth once daily). Use of ribavirin and interferon were not recommended as first-line treatments because of the risk for side effects; however, use of these medications may be considered if treatment with lopinavir; ritonavir, chloroquine, or hydroxychloroquine are ineffective. (12) (13)

Potential future treatment options include:

- Remdesivir (GS-5734), an investigational nucleoside analogue:
    - Remdesivir has been administered to several hundred patients with confirmed, severe SARS-CoV-2 infections in the United States, Europe, and Japan through Expanded Access or Compassionate Use programs. (9) Compassionate Use requests must be submitted to the drug manufacturer (Gilead Science, Inc.) by the treating physician.
    - A clinical trial evaluating the efficacy of remdesivir in patients infected with SARS-CoV-2 is currently being conducted in China. Data from this trial are expected by April 2020. (9)
    - In preclinical trials, remdesivir has demonstrated significant activity against coronavirus and a high genetic barrier to resistance. (10) (14)

        - *In vitro* data found remdesivir exerts potent antiviral activity against a clinical isolate of SARS-CoV-2; [half-maximal effective concentration (EC50) = 0.77 mcgM, half-cytotoxic concentration (CC50) > 100 mcgM , selective index (SI) > 129.87].
        - Data suggest remdesivir (GS-5735) inhibits activity of 2002 SARS-CoV, MERS-CoV, and bat CoV strains that have the ability to replicate in human epithelial cells and mediate entry via human CoV receptors.
        - Remdesivir has shown prophylactic and therapeutic efficacy against 2002 SARS-CoV in a mouse model.
        - Resistance mutations have not been identified.
- Sofosbuvir in combination with ribavirin:
    - Data from a molecular docking experiment using the SARS-CoV-2 RNA dependent RNA polymerase (RdRp) model identified tight binding of sofosbuvir and ribavirin to the coronavirus RdRp, thereby suggesting possible efficacy of sofosbuvir and ribavirin in treating the COVID-19 infection. (11)

Further data will continue to emerge regarding antiviral therapy for SARS-CoV-2 as clinical data are reported.

Therapies evaluated in human clinical trials during previous coronavirus outbreaks (2002 SARS-CoV and MERS-CoV)

- Lopinavir; ritonavir in conjunction with ribavirin and corticosteroids (4):
    - Open-label trial involving newly diagnosed 2002 SARS-CoV patients who had not developed acute respiratory distress syndrome (ARDS)
    - Treatment with lopinavir; ritonavir plus ribavirin and corticosteroids (n = 41) compared with an historical control group treated with ribavirin and corticosteroids (n = 111)
    - Primary outcome: composite adverse outcome described as severe hypoxemia or death at day 21
        - Historical controls: 22.5% met criteria for hypoxemia, 6.3% died
        - Treatment group: 2.4% met criteria for hypoxemia, no deaths were reported
        - 21-day adverse outcome rate: 28.8% for historical controls and 2.4% for treatment group (26.4%, 95% CI: 16.8 to 36, $p < 0.001$)
- Interferon alfacon-1 in conjunction with corticosteroids (5):
    - Open-label trial comparing the therapeutic benefit and tolerability of interferon alfacon-1 plus corticosteroids in 9 patients with probable 2002 SARS-CoV to treatment with corticosteroids alone (n = 13)
    - Primary outcome: clinical parameters, including oxygen saturation/requirements, laboratory results, and serial chest radiograph results
        - The interferon alfacon-1 treatment group had shorter time to 50% resolution of pulmonary radiograph abnormalities (median time, 4 days vs. 9 days, $p = 0.001$), better oxygen saturation ($p = 0.02$), shorter duration of supplemental oxygen (median time, 10 days vs. 16 days, $p = 0.02$), less increase in creatine kinase ($p = 0.03$), and trended towards faster resolution of lactate dehydrogenase.

        - Resolution of fevers and lymphopenia were similar between the two groups.
- Ribavirin in conjunction with corticosteroids (n = 75) (6)
    - Prospective observational study of 2002 SARS-CoV infected patients who received treatment with ribavirin (14 days) and corticosteroids (21 days); clinical outcomes were followed for 3 weeks.
    - After initial improvement of fever and pneumonia, 85% of patients developed recurrent fever after 8.9 days, 73% had watery diarrhea after 7.5 days, 80% had radiological worsening after 7.4 days, and 45% had worsening respiratory symptoms after 8.6 days. In 45% of patients, improvement of initial pulmonary lesions was associated with appearance of new radiographic lesions at other sites.
    - After three weeks, 12% developed spontaneous pneumomediastinum and 20% developed acute respiratory distress syndrome (ARDS).

Of note, the WHO currently recommends against routine use of corticosteroids in patients with SARS-CoV-2, as available data suggest corticosteroids are associated with no survival benefit and possible harm. (1) CPAM states that use of corticosteroids is controversial and should therefore be use with caution. (7)

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