A Summary Overview of the Pharmacotherapy for COVID-19

Here is a review of talked-about possible treatments—some of which come with caveats, insufficient evidence, and/or non-recommendations.

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The World Health Organization (WHO) reported in early March 2020 that there is no current evidence to recommend any specific anti-COVID-19 supportive or antiviral treatment for patients with confirmed COVID-19.[6] Further, at this time the WHO also reported there are many ongoing clinical trials, and data is emerging frequently. On April 29, 2020, Dr Anthony Fauci, a top US public health official, called the early results from a clinical investigation comparing the use of either remdesivir or a placebo was"quite good news". Lastly the WHO report the use of additional investigational anti-COVID-19 therapeutics should be done under approved, randomized, controlled trials whenever feasible.[6]

The following is a current review of many of the medicines being tested for efficacy against this often-deadly virus.

Monotherapy

A. Aminoquinolone (antimalarial)

Chloroquine's potential mechanism of action is that it increases endosomal pH required for virus cell fusion as well as interferes with glycosylation of cellular receptors for SARS-CoV-2. Further, in vitro studies have demonstrated chloroquine functioned at entry and post entry stages of SARSCoV-2.[1] Chloroquine has immune-modulating activity that may synergistically enhance antiviral effect in vivo. **According to guidelines published by the Society of Critical Care Medicine: "There is insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine."[2]**

Hydroxychloroquine's potential mechanism of action is that it increases endosomal pH required for virus/cell fusion and it interferes with glycosylation of cellular receptors for SARS-CoV-2. Although it shares the same mechanism of action as chloroquine, hydroxychloroquine is noted to be a less toxic derivative of chloroquine. In vitro studies reveal hydroxychloroquine has more potent antiviral activity based on consistently smaller half maximal effective concentration when compared with chloroquine.[2] Results from physiologically-based pharmacokinetic models suggest the recommended dose is a loading dose of 400 mg by mouth twice daily followed by a maintenance dose of 200 mg by mouth twice daily for four days.[3] The Italian guidelines specifically state that they are "against the possible use of chloroquine/ hydroxychloroquine in prophylaxis for COVID-19. **At the time of writing this article, there is no evidence of efficacy of this drug in the prevention of disease COVID-19; therefore, this strategy is not recommended."[2,4,5]**

There is NO evidence of the efficacy of Chloroquine in the prevention of COVID-19.

B. Interleukin-6 (IL-6) receptor antagonists

Tocilizumab's potential mechanism is that it binds to soluble and membrane bound IL-6 receptors and inhibits IL-6 mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine that may play a key role in driving the inflammatory immune response that causes acute respiratory distress syndrome (ARDS) in patients with COVID-19. The effectiveness of tocilizumab needs to be established in a controlled clinical trial. **There is insufficient evidence to issue a recommendation on the use of tocilizumab in critically ill adults with COVID-19.[2]**

C. Antivirals (protease inhibitors)

Lopinavir/ritonavir (LPV/RTV) potentially targets SARS-CoV-2 protease

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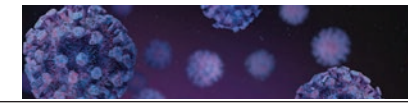

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activity. It must be considered that HIV protease belongs to the aspartic protease family, whereas the two coronavirus proteases are from the cysteine protease family. HIV protease inhibitors are specifically optimized to fit the C2 symmetry in the catalytic site of the HIV protease dimer, but the C2 symmetric pocket is absent in coronavirus proteases. **The Society of Critical Care Medicine suggests against routine use of LPV/RTV because of weak low quality of evidence.**[2]

Johnson and Johnson in their online statement suggests that Darunavir's (an antiretroviral medication) structural analyses show very few interactions of darunavir with the active site of the SARS-CoV-2 protease."[7] **Further, early unpublished results suggest that it is unlikely that darunavir will have significant activity against SARS-CoV-2 when administered at the approved dose for HIV-1 infection.**[7]

D. Antivirals (nucleoside analogs)

Ribavirin's potential mechanism of action is that it inhibits the replication of RNA and DNA of viruses. Based on sequencing analysis, modeling, and molecular docking, ribavirin can tightly bind to SARS-CoV-2 RNA-dependent RNA polymerase, a crucial enzyme in the life cycle of coronavirus.[8] Ribavirin has been recommended in combination with interferon or LPV/RTV at a dose of 500 mg intravenous given twice or three times daily, not to exceed 10 days.

E. Antiviral (neuraminidase inhibitors)

Oseltamivir acts at the stage of viral replication by inhibiting the function of viral neuraminidases. This prevents its reproduction by budding from Coronaviruses which do not utilize neuraminidase for the budding stage of reproduction. **Due to the limitations of the study design and use of multiple medications, the effectiveness of oseltamivir for treatment of COVID-19 infection is unknown.**

F. Antiviral (Miscellaneous)

*Ganciclovir inhibits binding of deoxyguanosine triphophate to DNA polymerase resulting in inhibition of viral DNA synthesis. **Ganciclovir should be avoided for SARS-CoV-2.**

*Remdesivir is a broad-spectrum antiviral medication that inhibits RNA synthesis

Developed by the American biopharmaceutical company Gilead Sciences.[9] Remdesivir was originally developed to treat Ebola virus disease and Marburg virus disease but was ineffective for these viral infections. Proposed dosing regimen for remdesivir is that it is given IV at a dose in clinical trials as 200 mg as a single dose on day 1, followed by 100 mg once daily for a total duration of 5 to 10 days. Data and results were reported from a large clinical worldwide investigation comparing remdesivir and Placebo control study that indicates it may be the first clear signal that a drug can effectively be used to treat COVID-19.[9] These early results, emerged from a large clinical trial sponsored by the National Institute of Allergy and Infectious Diseases, appears to position remdesivir as the standard therapy for hospitalized COVID-19 patients going forward.[9]

In the trial, patients who received remdesivir recovered 31% faster than those who received a placebo, a finding of superiority that could not be attributed to chance, researchers reported. Specifically, half of the patients who were randomly selected to be treated with remdesivir were considered completely recovered within 11 days, and half of those patients took longer. By comparison, it took 15 days or less for half of those who received the placebo to recover.[9]

Further, the results suggested that patients who were given remdesivir were more likely to survive COVID-19 than were those who got the placebo. But the difference in rates of fatalities were found to be 8% for the group that took the drug versus 11.6% for the patients who received the placebo group.[9] On May 1, 2020 remdesivir wins FDA's authorization for wider use in COVID-19 treatment.

G. Biological Response Modulators

Interferon α-2b, Interferon α-1B, and interferon β all inhibit the replication of SARS-CoV-2 in cell culture. The relative effectiveness of different IFNs against SARS-CoV-2 is unknown.[2] As previously states tocilizumab binds to soluble and membrane bound interleukin 6 (IL-6) receptors and inhibits IL-6 mediated signaling through these receptors. Interleukin 6 (IL-6) is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. The effectiveness of tocilizumab needs to be established in a controlled clinical trial.[10] Being a prophylactic rather than therapeutic agent, IFNs may have their highest utility in the prophylaxis or early post-exposure management of SARS.[11]

Concerns regarding drug-drug interactions, particularly QT prolongation with combination use of hydroxychloroquine and azithromycin have been raised.

Combination Therapies

A. Azithromycin and Hydroxychloroquine

Azithromycin's potential mechanism of action is unknown, perhaps maybe theorized as possibly anti-inflammatory. **Concerns regarding drug-drug interactions, particularly QT prolongation with combination use of hydroxychloroquine and azithromycin have been raised.**[12]

B. Interferon–α2b (IFN-α2b) and ribavirin

IFN α-2b and ribavirin concentrations required for viral inhibition must be achievable in humans in order to be relevant for clinical use. At present, there are no data on the serum concentrations required for treatment of COVID-19 patients.[13]

C. Oseltamivir, Ganciclovir, and Lopinavir/Ritonavir

Oseltamivir, Ganciclovir, and

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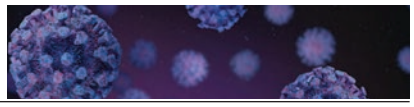

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Lopinavir/ritonavir was used in January 2020 to treat 99 patients with COVID-19 pneumonia that included 4 patients being mechanically ventilated and 13 patients who were described as having noninvasive ventilation.[14] Medication regimen were described as ranging between 3 and 14 days. Drug treatment dosages were described as oseltamivir 75 mg by mouth twice daily, ganciclovir 250 mg intravenously every 12 hours and Lopinavir/Ritonavir 500 mg by mouth twice daily.[14] On January 25, 2020, 31 patients were discharged, 11 patient deaths were reported and the rest remained hospitalized.[14] Without a comparator group, an intervention impact on outcomes cannot be assessed and it is recommend that further investigations are needed to validate a positive outcome from this three drug combination.

The World health organization does not recommend the routine use of systemic corticosteroids for treatment of viral pneumonia outside of clinical trials due to prior studies in patients with closely related viruses (SARSCoV and MERS-CoV) showing a lack of effectiveness and possible harm. Clinicians considering corticosteroids for a patient with COVID-19 and with sepsis must balance the potential small reduction in mortality with the potential for prolonged shedding of coronavirus.[6]

There is interest in the potential role of ACE-inhibitors and angiotensin receptor blockers (ARBs) in the pathophysiology of this disease since the SARS-CoV-2 virus binds to the ACE2 receptor for cellular entry. **However, current guidance from cardiology organizations (i.e., ACC/AHA/HFSA) state that there is not enough evidence to recommend for or against these medications in the setting of the COVID-19 pandemic.[6]**

The FDA is aware of news reports stating that the use of non-steroidal anti-inflammatory drugs (NSAIDs) could worsen coronavirus disease (COVID-19). However, there is no scientific evidence to support these claims to date. The agency is investigating this issue and currently does not have any specific recommendations to withhold NSAID therapy in these patients. The European Medicines Agency has also issued guidance that there is not enough data to recommend avoiding NSAIDs in COVID patients.[6]

Respiratory Treatments

Inhaled medications can be delivered either by metered dose inhalers (MDIs) or by nebulization; when delivered by nebulization, these can be aerosol generating. For COVID positive patients or those suspected of having COVID, the use of MDIs is preferred when/if available.[6] **PM**

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References

[1] Wang M, 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.

[2] Alhazzani W, Moller MH, Arabi YM, et al. Surviving sepsis campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Society of Critical Care Medicine web site. https://sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=enUS&_zs=ugFQi1&_zl=j1cc6. Accessed March 26, 2020.

[3] Yao X, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [published online ahead of print March 9, 2020]. Clin Infect Dis. doi: 10.1093/cid/ciaa23

[4] Coregiani A, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19 [published online March 10, 2020]. Crit Care. doi: 10.1016/j.jcrc.2020.03.005.

[5] Handbook for the care of people with disease-COVID 19, edition 2.0. Italian Society of Infectious and Tropical Diseases (Lombardia). Updated March 13, 2020.

[6] COVID-19 Pharmacotherapy Treatment Guidance March 23, 2020. Trinity health https://www.trinity-health.org/workfiles/covid-19/covid-treatment-guide.pdf accessed March 26,2020.

[7] Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2. Johnson & Johnson web site. HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. Published March 17, 2020. Accessed March 26, 2020.

[8] Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19 [online ahead of print February 28, 2020]. Life Sci. 248:117477. doi: 10.1016/j.lfs.2020.117477.

[9] Healy M. Coronavirus treatment: Remdesivir clinical trial success may be a turning point. Los Angeles The Associated Press Apr 30, 2020. https://www.syracuse.com/coronavirus/2020/04/coronavirus-treatment-remdesivir-clinical-trial-success-may-be-a-turning-point.html Accessed May 1, 2020.

[10] Novel coronavirus pneumonia diagnosis and treatment plan (Provisional 7th edition). China Law Translate web site. https://www.chinalawtranslate.com/en/coronavirus-treatment-plan-7/. Accessed March 26, 2020.

[11] De Clercq E. Potential antivirals and antiviral strategies against SARS coronavirus infections. Expert Rev Anti Infect Ther. 2006;4(2):291-302.

[12] Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial [online ahead of print March 20, 2020]. Int J Antimicrob Agents. doi.org/10.1016/j.ijantimicag.2020.105949.

[13] Falzarano D, DeWit E, Martellaro C. Inhibition of novel B coronavirus replication by a combination of interferon-α2b and ribavirin. Nature. 2013. 3:1686.

[14] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223): 507-513.

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