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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Commentary

Investigational Therapies in the Treatment of COVID-19 Infection

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Received: April 19 2020; **Published:** May 11, 2020

According to the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO), there are, as yet, no vaccines or definitive medications which have been proven to be effective in the treatment of COVID-19 [1].

Many medications are being tested through clinical trials and via compassionate use protocols based on *in vitro* activity against COVID-19, and on the few clinical experiences in patients who had COVID-19 infection.

Drugs being used and tested in the treatment of COVID-19 include:

Chloroquine: It is an antimalarial agent which is shown to have *in vitro* activity against COVID-19. It may also be having immunomodulating properties which could help in the treatment of this infection.

Chloroquine causes inhibition of viral enzymes and of processes such as viral DNA and RNA polymerase, new viral particle transport, viral protein glycosylation, virus assembly and virus release. Chloroquine also causes ACE-2 cellular receptor inhibition [2].

Another important mechanism believed to be effective against the COVID-19 virus is that chloroquine causes acidification at the surface of the cell membrane, thereby inhibiting fusion of the virus with cells in the lung parenchyma.

Chloroquine is also believed to have immunomodulating effects on cytokine release, thereby reducing lung damage.

Clinical experience: Has shown some activity against COVID-19. It could have positive effects in decelerating exacerbation of pneumonia in these patients [2]. Further clinical data is being analyzed regarding its efficacy in COVID-19 infected patients.

Side effects: There is a potential risk of cardiac arrythmias, drug interactions and retinal damage (with long-term use). May need significant caution in patients with G6PD deficiency and diabetes mellitus.

Hydroxychloroquine: Is an antimalarial agent which is shown to have *in vitro* activity against COVID-19. It may also be having immunomodulating properties [2] which could positively benefit patients with COVID-19 infection. Hydroxychloroquine causes inhibition of viral enzymes and of processes such as viral DNA and RNA polymerase, new viral particle transport, viral protein glycosylation, virus assembly and virus release. Hydroxychloroquine also causes ACE-2 cellular receptor inhibition [2] and immunomodulation of cytokine release.

Clinical evidence: Has shown activity against COVID-19. Pre-clinical data has shown a higher *in vitro* antiviral effect as compared to chloroquine. In some cohort of patients, hydroxychloroquine has had positive effects in decelerating exacerbation of pneumonia. However, further clinical data is being analyzed regarding its efficacy in COVID-19 infected patients.

Side effects: There is a potential risk of cardiac arrythmias, drug interactions and retinal damage (with long-term use). May need significant caution in patients with G6PD deficiency and diabetes mellitus.

Remdesivir: Is a nucleoside analog which is believed to have broad-spectrum antiviral action with significant *in vitro* activity against coronaviruses. Remdesivir is a monophosphoramidate prodrug of remdesivir-triphosphate (RDV-TP), an adenosine analog that acts as an inhibitor of RNA-dependent RNA polymerases (RdRps). The RDV-TP competes with adenosine-triphosphate for incorporation into nascent viral RNA chains. Once the RDV-TP incorporates into the viral RNA at position i, RDV-TP terminates RNA synthesis at position i+3. Remdesivir also appears to evade proofreading by viral exoribonuclease, which further helps in eradicating the virus.

Clinical use: Remdesivir has been administered to hundreds of patients with severe COVID-19 infection, in Japan, Europe and the United States. Preliminary results have shown significant activity against the virus, and also a high genetic barrier to resistance.

Lopinavir, ritonavir: These belong to the class of HIV Protease inhibitors.

In vitro studies have shown a potential activity against the coronavirus.

Action: Ritonavir and Lopinavir both bind to M_{pro} which is a key enzyme necessary for coronavirus replication, thereby suppressing coronavirus activity.

However, no difference has yet been observed in the duration of viral shedding after treatment with ritonavir and lopinavir [3] and routine use of these two drugs has not yet been recommended.

Tocilizumab: It is an interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody. It therefore helps in significantly reducing the "cytokine storm" which is responsible for the severe lung injuries in COVID-19 patients [4]. This drug could therefore serve as an adjunct therapy in the treatment of COVID-19 patients but more clinical trials still need to be conducted before this can be conclusively proved.

However, preliminary studies have shown a significant improvement in clinical symptoms and signs, CT chest scan opacities, lymphocyte percentage and C-reactive protein levels.

Side effects: Gastrointestinal perforation, hepatotoxicity, neutropenia, thrombocytopenia and local infusion-related reactions are a concern.

Azithromycin: It is a macrolide antibacterial agent which may prevent bacterial superinfection in COVID-19 patients. It is also believed to have immunomodulating properties in pulmonary inflammatory disorders [5]. Macrolides may downgrade inflammatory responses and reduce excessive cytokine production which is commonly seen in viral infections of the respiratory tract. It is as yet unknown whether macrolides have a direct action on viral clearance. The immunomodulating effects may include reducing chemotaxis of neutrophils to the lungs by inhibiting cytokines (IL-8), decreased production of reactive oxygen species, accelerating neutrophil apoptosis and blocking the activation of nuclear transcription factors.

Hence, Azithromycin may be of potential benefit as an adjunct therapy in COVID-19 infection.

Further clinical trials need to be conducted to effectively and conclusively state which drugs and treatment regimes are most effective and safe in the treatment of COVID-19 infection.

Bibliography

1. World Health Organization. "Clinical Management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected".

2. Gao J., *et al*. "Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies". *BioScience Trends* 14.1 (2020): 72-73.

3. Yao TT., *et al*. "A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease treatment option". *Journal of Medical Virology* (2020).

4. Xu X., *et al*. "Effective treatment of severe COVID-19patients with tocilizumab". China Xiv (2020).

5. Gautret P., *et al*. "Hydroxychloroquine and Azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial". *International Journal of Antimicrobial Agents* (2020).

Volume 9 Issue 6 June 2020