

Review on Use of Hydroxychloroquine and Azithromycin in the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

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Abstract: *Coronavirus pandemic is currently a global public health emergency. No effective prophylactic or post-exposure therapy is currently available for COVID-19, although some have been tried. One of such drug is combination of Hydroxychloroquine and Azithromycin. Recent publication shows that Hydroxychloroquine sulphate treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by Azithromycin. However, there is limited information about the use of them in COVID-19.*

Keywords: COVID-19, prophylactic, post-exposure, Hydroxychloroquine Sulphate, Azithromycin, viral load

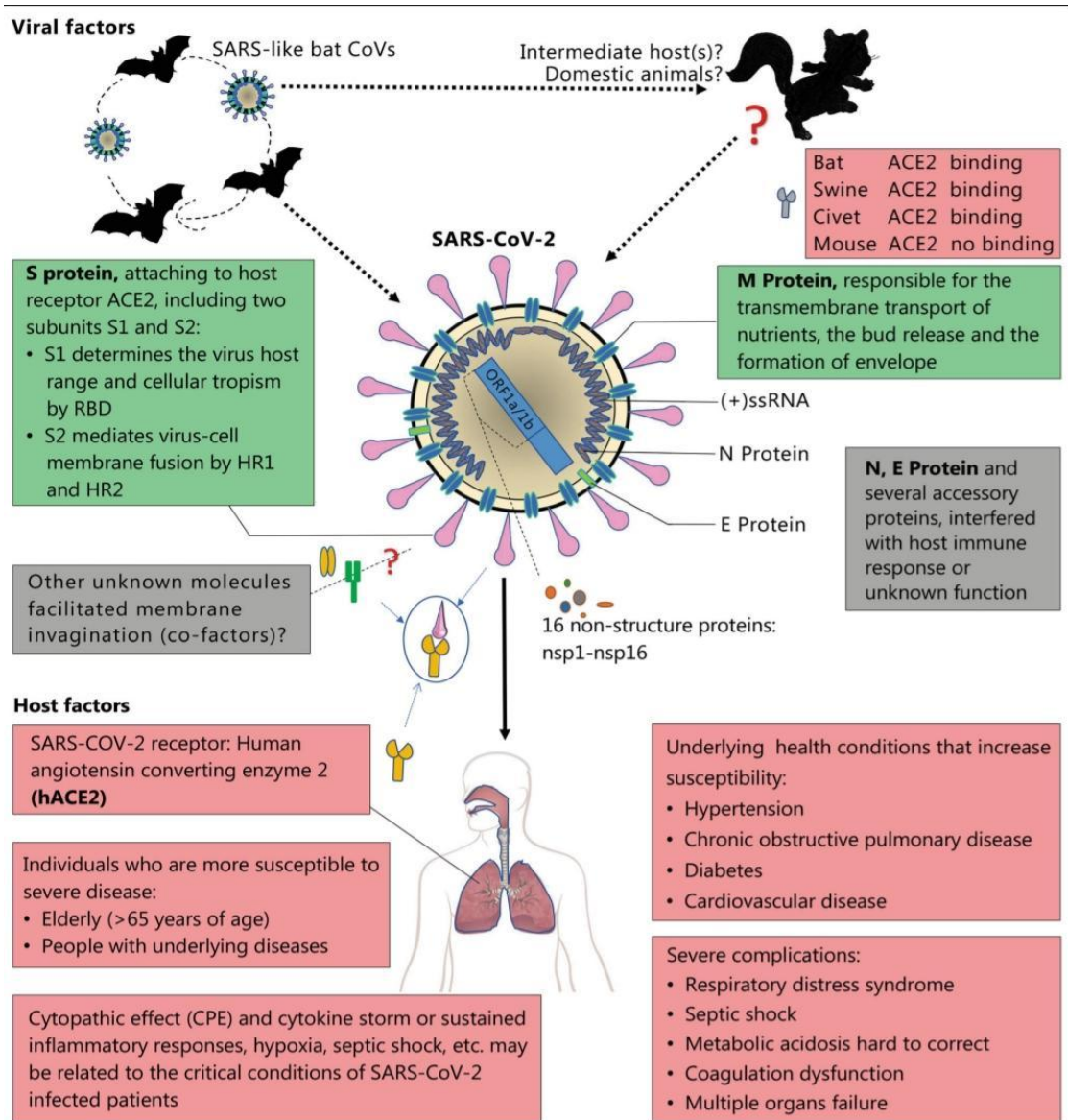
1. Introduction

An outbreak of Novel Coronavirus (2019-nCoV) officially known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 or COVID-19) was reported in Wuhan, China, in December 2019, which spread to the rest of China and many other countries across the globe. On 12th March 2020 the World Health Organization (WHO) declared this disease as pandemic. At present, no pharmacological agent has been approved by regulatory agencies for the treatment of SARS-CoV-2 infection. Among candidate drugs to treat COVID-19, repositioning of old drugs for use as antiviral treatment is an interesting strategy because knowledge on safety profile, side effects, posology and drug interactions are well known^(1, 2). Hydroxychloroquine Sulphate and Azithromycin are one of such drugs which shows promise for the treatment of COVID-19. Two studies have demonstrated that hydroxychloroquine sulfate inhibits SARS-CoV-2 [8-10] in vitro. In addition, and in parallel to this study, we evaluated in vitro the combination of Hydroxychloroquine and Azithromycin on SARS-CoV-2 infected cells, and showed that there was a considerable synergy of these two products when they were used at doses

which mimic the concentrations likely to be obtained in humans

1.1 COVID-19 (Novel Coronavirus 2019)

The SARS-CoV-2 is a β -coronavirus, which is enveloped non-segmented positive-sense RNA virus (subgenus sarbecovirus, Orthocoronavirinae subfamily)⁽³⁾. Coronaviruses (CoV) are divided into four genera, including α - β - γ - δ -CoV. α - and β -CoV are able to infect mammals, while γ - and δ -CoV tend to infect birds. Previously, six CoVs have been identified as human-susceptible virus, among which α -CoVs HCoV-229E and HCoV-NL63, and β -CoVs HCoV-HKU1 and HCoV-OC43 with low pathogenicity, cause mild respiratory symptoms similar to a common cold, respectively. The other two known β -CoVs, SARS-CoV and MERS-CoV lead to severe and potentially fatal respiratory tract infections⁽⁴⁾. It was found that the genome sequence of SARS-CoV-2 is 96.2% identical to a bat CoV RaTG13, whereas it shares 79.5% identity to SARS-CoV. Based on virus genome sequencing results and evolutionary analysis, bat has been suspected as natural host of virus origin, and SARS-CoV-2 might be transmitted from bats via unknown intermediate hosts to infect humans.



Clinical Symptoms and Manifestation

Epidemiological data suggested that, the incubation period of 2019-nCoV ranges from 1 to 14 days, mostly ranging from 3 to 7 days.

Symptoms of COVID-19 are varied ranging from flu like symptoms, to ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. The common clinical symptoms include fever, sore throat, cough, myalgia, headache, fatigue and breathlessness or dyspnea. Conjunctivitis has also been decribed^(2, 3).

So this COVID-19 is indistinguishable from other respiratory infections. Disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in the level of inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF α .

In some patients - particularly the elderly and other with other chronic health conditions - these symptoms area easily develop into pneumonia, with chest tightness, chest pain, and shortness of breath (dyspnea).

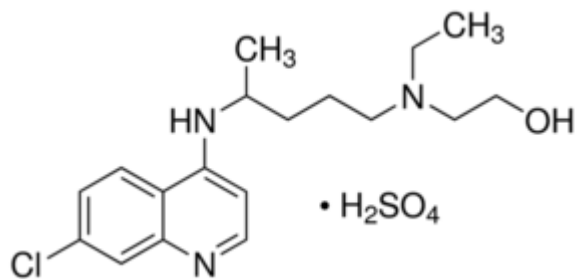
COVID-19 starts with a fever, followed by a dry cough. After a week, it can lead to shortness of breath (dyspnea), with about 20% of patients requiring hospital treatment.^(3, 4, 30)

Diagnostic criteria

The viral research institution in China has conducted preliminary identification of the SARS-CoV-2 through the classical Koch's postulates and observing its morph- ology through electron microscopy. So far, the golden clinical diagnosis method of COVID-19 is nucleic acid detection in the nasal and throat swab sampling or other respiratory tract samplings by real-time PCR and further confirmed by next-generation sequencing.ad to shortness of breath (dyspnea), with about 20% of patients requiring hospital treatment^(3, 4)

1.2 Hydroxychloroquine Sulphate

Hydroxychloroquine Sulfate is a synthetic derivative of quinolyl with chemotherapeutic and antibiotic properties. Hydroxychloroquine belongs to Antimalarial class of drug.



Hydroxychloroquine Sulphate

Mechanism of Action

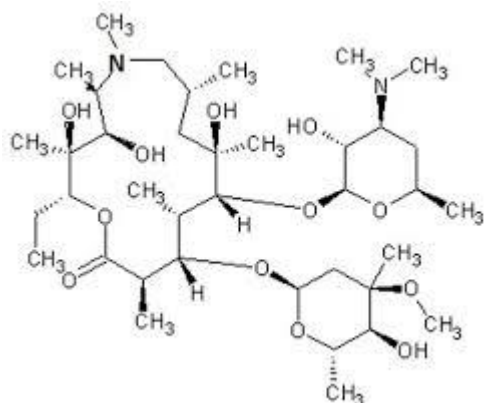
The mechanism of action of these drugs against Plasmodium parasites is believed to be partly related to its interaction with DNA and through inhibition of the polymerization of heme^(5,6). The immunomodulatory activity of Hydroxychloroquine is related to a broad spectrum of immunoregulation networks discussed extensively in other work^(7,8,9). In addition to activity against rheumatic diseases, the two antimalarial agents have also shown therapeutic activity or immune modulatory effects in a wide range of other diseases including antiphospholipid syndrome, amebiasis, HIV/AIDS, and some cancers⁽¹⁰⁾.

Safety Measure:

- Risk of damage of Retina, especially with long term use
- Take Caution in patients who are suffering from G6PD deficiency
- Physician should do dose adjustment in Diabetic Patient
- This drug have serious drug interactions.^(11,12)

1.3 Azithromycin

Azithromycin is a macrolide antibiotic. Azithromycin is bacteriostatic, and macrolides may have immunomodulatory properties.



Azithromycin

Mechanism of Action

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected. In pulmonary inflammatory disorders, Macrolides may have immunomodulatory properties. They may suppress inflammatory responses and reduce the excessive production of cytokines which is associated with respiratory viral infections; however, their direct effects on viral clearance is not clearly known. Immunomodulatory

mechanisms suggested that Azithromycin reduces chemotaxis of neutrophils (PMNs) to the lungs by inhibition of cytokines (IL-8) and inhibition of mucus hypersecretion, decreased production of reactive oxygen species, increase neutrophil apoptosis, and activation of nuclear transcription factors is blocked^(12, 13, 14).

Safety Measure:

- There is Risk of prolongation of QT wave which leads to cardiac arrhythmias.
- Some significant drug interactions is also there^(16, 17).

2. COVID-19 Treatment

The mechanism of action of Hydroxychloroquine against SARS-CoV-2 has yet to be fully elucidated. Based on studies initially performed on SARS-CoV, it is believed that SARS-CoV-2 enters cells by binding to the angiotensin converting enzyme 2 (ACE-2) receptor⁽¹⁸⁾. New research has proposed that Hydroxychloroquine may additionally prevent SARS-CoV-2 from binding with gangliosides, which in turn may inhibit virion contact with the ACE-2 receptor⁽¹⁹⁾. Hydroxychloroquine additionally can incorporate into endosomes and lysosomes, resulting in an increased pH of intracellular compartments. These organelles normally require an acidic environment for homeostasis. Ultimately, this increase in pH results in their dysfunction, leading to defective protein degradation, endocytosis, and exocytosis needed for viral infection, replication, and propagation. Prior work has also demonstrated that coronaviruses can use proteins on the surface of endosomes and endolysosomes for viral entry into host cells. Entry into the endolysosome may be necessary for the viral genome to be released into the cytoplasm of infected host cells. However, it remains unclear how changes in the endosomal environment, particularly changes in pH, may affect the integrity of the SARS-CoV-2 viral genome. Overall, Hydroxychloroquine are capable of affecting several cellular pathways and therefore may have several mechanisms of action against SARS-CoV-2^(21, 22). Hydroxychloroquine in combination with Azithromycin shows synergistic in reduction/disappearance of viral load in COVID-19 patient.

3. Adverse Events Related to Treatment

Along with common adverse effects such as pruritus, nausea and headache, Hydroxychloroquine can predispose patients to life-threatening arrhythmias (Prolongation of the QTc interval), an effect that may be enhanced by concomitant use of Azithromycin. Other uncommon but serious potential harms include hypoglycemia, Hematologic toxicities, neuropsychiatric effects, idiosyncratic hypersensitivity reactions and drug-drug interactions, with genetic variability playing an important role in each of these⁽²²⁻²⁶⁾

4. Conclusion

The use of Hydroxychloroquine and Azithromycin for treatment or prevention of SARS-CoV-2 infection is currently supported primarily by in vitro data and two weak studies involving humans (an open-label non-randomized clinical trial and a pilot observational study) with small

sample size and these studies are not up to the standard. Also the reports from some other research shows that this combination is not effective in COVID-19 treatment. This shows the conflict and dissimilarities in data. Further research is necessary to assess the safety and effectiveness of these drugs. The possibility that these drugs might be the cure for COVID 19 increases the urgent need for high-quality randomized controlled trials in the face of a growing pandemic.

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