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The Virology of COVID-19 and Quinine – Quinine in COVID-19

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Abstract

LiveWell Initiative LWI is a self-funded nonprofit social enterprise which thrives on innovation. (www.livewellng.org) The organisation has, for 5 years, supervised MPH and DrPH Practicums for the Harvard University, Boston USA. It also supervises PhD thesis at University of Helsinki, Finland.

At the inception of COVID-19, LWI designed and compiled three sets of STUDY PROTOCOLS in response to the COVID-19 RESPONSE in Africa with a goal to arriving at a practical and affordable solution to the pandemic. The 3 sets of Protocols have undergone professional debates among physicians, researchers and pharmacists for Hypothesis Testing over a 5-week period.

The Study Protocols are currently undergoing random Physician – Patient Trials at the discretion of Prescribing Clinicians and Clinical Researchers, they are as recommended in a compilation of recent findings by LiveWell Initiative LWI on COVID-19. LiveWell Initiative LWI, a nonprofit organization, takes no liability for damage from the use of the above suggested STUDY PROTOCOLS FOR COVID-19 RESPONSE IN AFRICA. It is a Study Protocol designed to 'evolve' as an African Solution to COVID-19 Response.

The Protocols strongly suggest the use of Quinine for COVID-19 Treatment in moderate to advanced disease, recommending intravenous infusion of Quinine for critical care in COVID-19. The sample size is small and further studies are recommended but the result is significant.

In conclusion, Quinine is recommended for severe or advanced COVID-19 especially after the Cytokine Storm.

Keywords: Quinine; Haemozoin Inhibition; Immunomoduulation; BloodBrainBarrier

Introduction

Coronavirus to be an enveloped, positive single-strand RNA virus which belongs to the Orthocoronavirinae subfamily, as the name, it possesses the characteristic "crown-like" spikes on their surfaces.9

Alongside SARS-CoV, bat SARS-like CoV and others, it also fall into the genus beta-coronavirus. COVID-19 (caused by 2019-nCoV infection) is classified as a fifth-category notifiable communicable disease in Taiwan on January 15, 2019.[1] The genus beta-coronavirus can be divided into several subgroups. The 2019-nCoV, SARS-CoV, and bat SARS-like CoV belong to Sarbecovirus, while the MERS-CoV to Merbecovirus.[2] SARS-CoV, MERS-CoV, and 2019-nCoV all cause diseases in humans but each subgroup may have mild diverse biologic characteristic and virulence.[2–4]

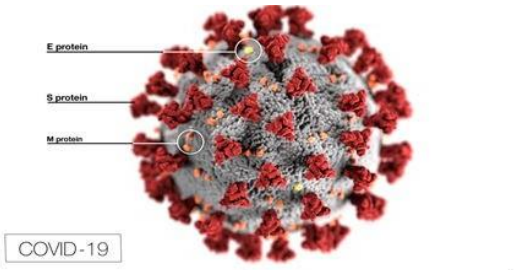


Figure 1: SARS-CoV-2 (virus)

The actual origin, location, and natural reservoir of the 2019-nCoV remain unclear, although it is believed that the virus is zoonotic and bats may be the culprits because of sequence identity to the bat-CoV. [5] According to previous studies on the SARS- and MERS-CoV, epidemiologic investigations, their natural reservoir is bat, while palm civet or raccoon dog may be the intermediate (or susceptible) host for SARS-CoV and the dromedary camel for MERS-CoV. A field study for the SARS-CoV on palm civet ruled out the possibility as the natural reservoir (low positive rate); instead, the prevalence of bat coronavirus among wild life is high and it shares a certain sequence identity with the human SARS-CoV. Therefore, bats are considered the natural host reservoir of SARS-like coronavirus. However, the origin or natural host for the 2019-nCoV is not clear, although it might come from a kind of wild life in the wet market.[6] Theoretically, if people contact or eat the reservoir or infected animal, they could be infected. However, to result in large scaled person-to-person transmission as in the past SARS outbreak, the virus must spread efficiently.

The case fatality for SARS-CoV and MERS-CoV was 10% (total affected more than 8000) and 34.5% (total affected cases were 2465) respectively. Though the case fatality of COVID-19 is 2.3%, the increasing number of cases is a concern now.

COVID-19 can affect any age group. Most of the cases (77.8%) were in 30 - 69 years age group. Pre-existing hypertension, diabetes, cardiovascular, cancer, and chronic respiratory illness are at risk of complications with a little male predominance (51.4%).

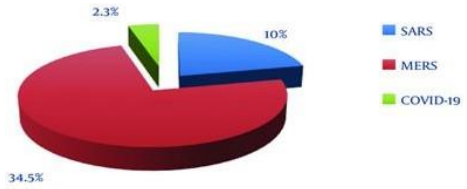


Figure 2. Fatality Rate of SARS, MERS and COVID-19

Initially, the 2019-CoV outbreak was reported as limited person-to-person transmission and a contaminated source from infected or sick wild animals in the wet market may have been the common origin. But more and more evidences came out with clusters of outbreaks among family confirmed the possibility of person-to-person transmission.[7-8] Furthermore, the presence of human angiotensin-converting enzyme 2 (hACE2) as the cellular receptor (like SARS) made droplet transmission to the lower respiratory tract possible.
[9] Furthermore, it is similar to contact transmission like SARS, although the survival time in the environment for the 2019-nCoV is not clear at present. Currently, there was no evidence of air-borne transmission.

Viral RNAs could be found in nasal discharge, sputum, and sometimes blood or feces. However, oral-fecal transmission has not yet been confirmed. Once people are infected by the 2019-nCoV, it is believed that, like SARS, there is no infectivity until the onset of symptoms. The exact survival of it in the environment is unknown. Though considering characteristics of SARS-CoV and MERS-CoV, it may survive on a surface for hours to days at room temperature (average 20°C) and with high humidity. It can be killed by soap wash and disinfectants such as 75% alcohol. The incubation period is two days to 14 days. Initially, asymptomatic carriers were thought to be non-contagious. Later on in China, a cluster of cases in a family was reported to be contracted from an asymptomatic carrier who recently traveled from Wuhan. The infectious doses for 2019-nCoV is not clear, but a high viral load of up to 108 copies/mL in patient's sputum has been reported. The viral load increases initially and still can be detected 12 days after onset of symptoms. Therefore, the infectivity of patients with 2019-nCoV may last for about 2 weeks. However, whether infectious viral particles from patients do exist at the later stage requires validation.

The cytokine storm and COVID-19

The immune system protects us from microbes such as bacteria or viruses, when they invade the body. A host of specialized white blood cells that make up the immune system usually seek to identify pathogens and destroy them. When these pathogens are identified, the immune cells need to respond in defense and recruit more immune cell thus signaling to the cytokines.

Once released, the cytokines stimulate localized inflammation. This is a physiological response by the body which aims at destroying the pathogen. Notable signs of inflammation include redness, pain, swelling, and elevated temperature.

Cytokines released, work by binding to receptors found either on nearby cells or even on the same cell that released them. Some cytokines can stimulate further release of cytokines, creating a positive feedback loop and amplifying the inflammation. Often this results in fever, a key hallmark of inflammation.

Sometimes, the immune system overreacts during an infection, releasing more cytokines than required, hence, recruiting new hordes of activated "angry" white blood cells, which produce even more cytokines. This means a "cytokine storm" is emerging.

COVID-19 Treatment with quinine

As of present, there is yet to be an ideal treatment for COVID-19, the treatment is mainly supportive. All patients should be treated in the hospital. However, due to a shortage of beds and resources, uncomplicated mild cases may be treated at home isolation with minimum contact of a few caregivers preferably one-on-one with the practice of hand hygiene and using of masks. The caregiver should be a healthy individual without any immune-suppression. The room should be well ventilated with windows open. A minimum of one-meter space should be maintained.

Patients with SARS-COV2 require vital organ support. Antibiotics need to be started if secondary bacterial infection is suspected after sending an appropriate sample for culture. The role of steroids is controversial as it delayed viral clearance. ICU admission is necessary if critically ill. Favilavir, the first anti-viral got approval for marketing in COVID-19 pneumonia (clinical trial ongoing; showed efficacy in human trial). Remdesivir and Chloroquine were found to be effective in vitro shown by Wang et al. (2020). Randomized control trial of remdesivir is started on 761 patients in Wuhan. Newer therapies like brilacidin, leronlimab (PRO 140), a CCR5 antagonist and neutralizing monoclonal antibodies are being tested along with trials of different other antivirals like ritonavir, lopinavir, oseltamivir.[10] Plasma from recovered patients is being used to treat patients with a light of hope.

Why quinine?

- Quinine a senior counterpart 4-Aminoquinoine holds sway in the treatment of COVID-19.
- It is a repurposed drug with unique strengths 37.
- All the Aminoquinolines have unique properties against COVID-19 namely:
- Anti-inflammatory
- Antiviral
- Antiprotozoal
- Ant parasitic
- Haemozoin Inhibitors
- Zinc Ionosphere
- PCR Inhibitor

In addition, Quinine crosses the blood-brain barrier BBB, and it will therefore cross into the membranous alveoli in COVID-19 and clear out the viruses in situ.

Repurposing the aminoquinolines

The process of 'repurposing', is receiving growing attention. This involves finding new therapeutic indications for old or currently used drugs such as Quinine, with an original indication to cure malaria, have now been successfully used to treat several other infectious diseases.

Indeed, they have anti-inflammatory, immunomodulation, anti-infective, antithrombotic, and metabolic effects. Among the biological effects of Quinine, it is important to highlight their strong ant proliferative, ant mutagenic, and inhibiting autophagy capacities.

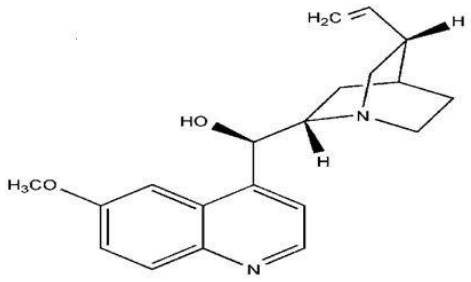
Prognosis

Prognosis is good, especially no death occurred except in critically ill. It took about 10 days on average for recovery.[11] Prior to discharging a patient during recovery case, two respiratory samples should be taken 24 hours apart and must be negative.28

Recently few confirmed COVID-19 cases (HCWs) tested positive again by rRT-PCR after hospital discharge. They were tested positive

after 5 - 13 days of discharge during the home quarantine. However, they were asymptomatic and chest CT did not show any change from previous images.[12-14]

Structure of Quinine



Mechanism of action – quinine

- Quinine has a multiple modes of action on the virus.
- It prevents the virus from penetrating the host cell using its S protein and Protease.
- It breaks the polymerase chain and prevents viral replication.
- It is a zinc ionophore and ensures penetration of zinc into the viral cell, altering the pH.
- Zinc also potentiates Quinine action, and Quinine has a good safety profile in therapeutic doses, with self-limiting ototoxicity which is reversible upon completion of the regimen.
- Suppress exagerrated Immunoglobulin response IgG and IgM through Immunomodulation and therefore also exerts
- Anti-inflammatory action.
- A highly soluble and more potent 8-Aminoquinoline, Quinine, will cross the BBB
- Will therefore penetrate the Alveoli and displace the viruses, disseminate the glass ground opacity, restore heme iron and normalcy.
- Haemozoin Inhibitor – starves the virus of its food vacuoles.
- In addition, Quinine is a muscle relaxant and a non-narcotic analgesic, taking care of the accompanying severe myalgia which characterizes n severe COVID-19.

Categorisation of quinine use in COVID-19

- Moderate COVID-19 – Symptomatic, Laboratory Tested Positive COVID-19 Patient on admission at Isolation Center / Oxygen saturation above 90 – Oral Quinine Sulphate, 600mg t.i.d. for 5 days
- Severe COVID-19 - Symptomatic, Laboratory Tested Positive COVID-19 Patient on admission at Isolation Center / Oxygen saturation below 90 – Intravenous Quinine Infusion, dose-determined by physician
- Acute Severe COVID-19 - ICU Patient - Symptomatic, Laboratory Tested Positive COVID-19 Patient on admission at Isolation Center / Oxygen saturation below 80 – Intravenous Quinine Infusion, dose-determined by physician
- Administration of anti-inflammatory, anticoagulant, antibiotic and bronchodilator medications is an essential additive component of care in Severe COVID-19 Patients. Please refer to LWI Study Protocols.

Conclusion

The re-purposing of Quinine, sets the benchmark for the management of moderate to severe COVID-19, and therefore completes the treatment curve for COVID-19 in today's modern scientific world.

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