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A recommendation for the use of chloroquine, hydroxychloroquine, primaquine, or tafenoquine for prophylaxis against the 2019 novel coronavirus (COVID-19) with note to the ophthalmic considerations

Fouad Alshaban, MD, MSC, PhD

Lead of the Autism Epidemiology Research Team, Neurological Disorders Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Doha, Qatar

Abstract

With the ongoing pandemic of infectious disease termed coronavirus disease 2019 (COVID-19) caused by the novel coronavirus identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), prevention of infection and spread is critical in preventing morbidity and mortality. Prophylaxis, specifically chemoprophylaxis, is particularly critical to breaking the spread and rapid rate of increase of SARS-CoV-2. Pre-exposure and post-exposure prophylaxis are both required components of this public health measure. As the use of anti-malarial agents, specifically the 4-aminoquinolones, chloroquine and hydroxychloroquine, for the treatment of SARS-CoV-2 is now being reported, attention must be turned to their role in the chemoprophylaxis of SARS-CoV-2. In a search of the peer-reviewed medical literature (using MEDLINE and cross-referenced literature), this report is first peer-reviewed publication to present the use of these anti-malarial agents as prophylaxis against SARS-CoV-2. The ophthalmic consideration of the use of these drugs is highlighted in this report.

Antiviral Role of the Anti-Malarial Agents

In the 17th century, the indigenous peoples of Peru used the extract of the native Peruvian Cinchona tree bark to fight fevers; this extract was introduced in 1633 in Europe where it was used against malaria and later determined to contain quinine, a potent anti-malarial drug.[1] In 1934, Johann "Hans" Andersag created the synthetic analogue of quinine: chloroquine.[2] Although chloroquine's intended use was against the parasite, *Plasmodium malariae*, causing malaria, in the 1960's, the antiviral effects of chloroquine were identified. The first report in the peer-reviewed literature is the treatment of viral hepatitis with chloroquine in 1963,[3] followed by elucidation in 1966 of the possible mechanism of action of the chloroquine by altering the stability of lysosomal membranes that the hepatitis virus requires for uncoating itself within the host.[4] Further data was presented in 1967 to suggest that chloroquine has anti-viral capabilities by inhibiting viral-directed nucleic acid synthesis.[5] There was even suggestion in 1968 that chloroquine suppresses interferon production.[6]

Correspondence:
Fouad Alshaban, MD, MSC, PhD
Neurological Disorders Research Center
QBRI, Hamad Bin Khalifa University
PO Box 34110, Doha, Qatar
E-mail: falshaban@hbku.edu.qa
Phone: (974) 445-41072

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Through the years, chloroquine has been reported to have antiviral activity against a wide range of RNA and DNA viruses including: influenza A virus, influenza B virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), herpes simplex virus, poliovirus, rabies virus, Zika virus, Ebola virus, Chikungunya virus, Dengue virus, Lassa virus, and others.[7] More recently, chloroquine, and its derivative hydroxychloroquine, have been demonstrated to have in-vitro activity against severe acute respiratory syndrome coronavirus (SARS-CoV), the positive-sense single strand RNA virus of the beta-subgroup of coronaviruses responsible for the initially-2002 severe acute respiratory syndrome (SARS) disease outbreak, and against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the predominantly homologous virus responsible for the infectious disease termed coronavirus disease 2019 (COVID-19).[8,9,10] An anecdotal report of ongoing clinical trials in China on the use of chloroquine in COVID-19 suggests that chloroquine shortens the disease course, improves lung function, inhibits exacerbation of pneumonia, and promotes virus-negative conversion.[11] Early clinical results from an open-label non-randomized clinical trial of a small sample-size of 36 patients demonstrated that patients treated with hydroxychloroquine had a significant viral load reduction compared with control patients.[12]

Multiple mechanisms have been postulated as to the antiviral effects of chloroquine, which importantly may differ from virus to virus. Among these mechanisms is the interference by chloroquine in the ability of the virus to bind to its host cell surface receptor. Chloroquine inhibits quinone reductase 2, the enzyme involved in the biosynthesis of sialic acids, the acidic monosaccharides present on cell transmembrane proteins involved in ligand recognition.[7] Human coronaviruses attach to sialic acids at the surface of host cell membranes to gain entry into the host.[13] Another key viral-entry pathway that chloroquine modulates, via alkalization of endosomes, is the autophagosome pathway in which the coronavirus fuses with the endosomal membrane to release viral genome into the host cytosol.[7] Furthermore, chloroquine is believed to interfere with coronavirus replication through reduction in cellular mitogen-activated protein kinase (MAPK) activation, through post-translational modification of viral proteins in host Golgi such as altering maturation of the coronavirus envelope "M" protein which is critical for viral assembly, and through other mechanisms of immune system modulation.[7]

Quinoline Derivatives: 4-Aminoquinolines and 8-Aminoquinolines

Chloroquine and its derivative hydroxychloroquine, which was developed to combat chloroquine-resistant malaria, have extensive total apparent volumes of distribution as well as terminal elimination half-lives of one month or longer, taking nearly a year for full elimination from the body.[14,15] This long half-life has made these drugs powerful prophylactic agents against malaria. Hydroxychloroquine, in addition, is commonly used for autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis.

However, as ophthalmologists know very well, both chloroquine and hydroxychloroquine bind to melanin within retinal pigment epithelial (RPE) cells, resulting in long-term damage to adjacent macular photoreceptors. The pattern of toxicity, termed a bulls-eye maculopathy, is reversible in its early stages but leads to irreversible loss of central vision, reduced visual acuity, scotoma formation, and/or color vision deficits. Cumulative dose, specifically a total cumulative dose of 1 kg (e.g., 7 years at 400 mg per day) is the strongest predictor of toxicity, and may pose a risk even after discontinuation of the medication. Other ocular drug-induced side effects include corneal deposits that may be symptomatic as well as increased dry eye.[16]

Systemic side effects include symptoms such as nausea, diarrhea, abdominal cramping, headaches,

tinnitus, and vertigo, as well as more severe disorders such as anemia and other blood dyscrasias, liver failure, muscle paralysis, neuropsychiatric changes, convulsions, cardiac arrythmias, and cardiomyopathy.[15]

As opposed to the 4-aminoquinolines, chloroquine and hydroxychloroquine, the 8-aminoquinolines, primaquine and tafenoquine, have shorter half-lives but less toxicity. The half-life of primaquine is particularly short at 6 hours, while the half-life of tafenoquine is relatively long, at 14 days, which is about half that of the 4-aminoqunolines, chloroquine and hydroxychloroquine.[15] In regard to their lower toxicity compared to the 4-aminoquinolines, these 8-aminoquinolines cause symptoms such as vomiting and headache as well as more severe disorders such as neuropsychiatric changes and blood dyscrasias, but to a lower extent. Notably, the 8-aminoquinolines are contraindicated in individuals who have glucose-6-phosphate dehydrogenase (G6PD) deficiency as hemolytic anemia may occur and may be fatal.[15,17,18]

In regard to the ophthalmic toxicity, the 8-aminoquinolines are notably less toxic. Specifically, while corneal deposits do occur with the 8-aminoquinolines, they are found to be less frequent, less extensive, and likely asymptomatic. In addition, the bulls-eye maculopathy is not known to occur with the 8-aminoquinolines. However, mild retinal pathology has been noted in cases, including RPE abnormalities and intraretinal hemorrhage.[19,20] Further clinical studies are required to fully elucidate the prevalence and extent of retinal pathology with the 8-aminoquinolines.

Chemoprophylaxis Using 4-Aminoquinolines and 8-Aminoquinolines Against SARS-CoV-2

With the ongoing pandemic of infectious disease termed coronavirus disease 2019 (COVID-19) caused by the novel coronavirus identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), prevention of infection and spread is critical in preventing morbidity and mortality. Prophylaxis, specifically chemoprophylaxis, is particularly critical to breaking the spread and rapid rate of increase of SARS-CoV-2 infections. Pre-exposure and post-exposure prophylaxis are both required components of this public health measure.

While repurposing of anti-malarial agents, specifically the 4-aminoquinolones, chloroquine and hydroxychloroquine, for the treatment of SARS-CoV-2 is now being reported,[21] attention must be turned to their role in the chemoprophylaxis of SARS-CoV-2. These anti-malarial agents, specifically primaquine and tafenoquine, have been evaluated as long-term prophylaxis for malaria as well as in both short-course or single-dose formats.[22,23] Therefore, based on their antiviral mechanisms of action, specifically against coronavirus, it is recommended that these drugs be evaluated as chemoprophylaxis against SARS-CoV-2. In addition to the evaluation of chloroquine and hydroxychloroquine, the 8-aminoquinolones particularly tafenoquine should be evaluated based on their lower ophthalmic toxicity profile. The advantageous possible non-daily dosing regimens, such as weekly or biweekly dosing, of these anti-malarial agents would make them particularly convenient for patients and improve patient compliance with the chemoprophylactic regimen.

In a search of the peer-reviewed medical literature (using MEDLINE and cross-referenced literature), this report is first peer-reviewed publication to present the use of these anti-malarial agents as prophylaxis against SARS-CoV-2. In the face of a defining COVID-19 pandemic, it is imperative that prompt consideration be given to identifying and initiating chemoprophylactic measures to stop the spread and rapid rate of increase of SARS-CoV-2 infections.

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