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Hydroxychloroquine: The Second Revolution in Medical Science After Penicillin

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Abstract: This manuscript was written under the urgent pressure of being motivated in saving lives of Covid-19 epidemics which has claimed more than 500,000 American lives since February 2020, most likely due to virtual absence of correct therapy. The author is not a professional virologist/epidemiologist. With family background of Chinese traditional herbal medicine, this author had extensive learning experience interacting in appendices nature with the world's improved ways to produce and concentrate on the drug and prove its antiviral effects following topnotch scientists in medical science mostly in the NIH, the world's most prestigious headquarter compound representing the most cutting-edge life science development.
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Introduction

This manuscript was written under the urgent pressure of being motivated in saving lives of Covid-19 epidemics which has claimed more than 500,000 American lives since February 2020, most likely due to virtual absence of correct therapy. The author is not a professional virologist/epidemiologist. With family background of Chinese traditional herbal medicine, this author had extensive learning experience interacting in appendices nature with the world's improved ways to produce and concentrate on the drug and prove its antiviral effects following topnotch scientists in medical science mostly in the NIH, the world's most prestigious headquarter compound representing the most cutting-edge life science development. Since January 2020, this author contributed 5 Covid-19 alternative therapy package involving hot-lemon ginger tea to ways to reverse protein deficiency and over-fatigue, to HCQs, in China, as partially accepted methodology guidelines whose mere motive is to save lives from devastating Covid pandemics. The driving cause pushing this author to involve himself in humanitarian crusade in saving lives of Covid-19 patients during starting the darkest period is what he was shocked by what he watched video footage taken in Wuhan, China that many collapsed in the streets and deeply scared people having committed suicide by jumping off from the windows of the high rise apartment buildings. "You don't have to die with this kind of disease as corona virus infected syndrome!" He out-cried. He has the answer to get fully recovery, for the super majority of Covid patients. Mr. Ye accurately forecast in earlier February, 2020 that the turning point with 95%+ death toll reduction throughout China should appear in March 2020, in comparison to Academician Zhong Nanshan's forecasting that the turning point would be in May 2020. Mr. Ye's forecasting that the turning point in the United States should be May 2020 was unfortunately failed because President Donald Trump's courageous advocacy of HCQ was defeated by the establishment in April followed with FDA's revocation of temporary "clinical trial" permit, and further followed with swift climbing up of death tolls of Covid-19 casualty from hospitals throughout the nation. Ning Ye's legal battle for the sake of HCQ seeking for Writ of Mandamus with U.S. District Court for the Southern District of New York (20-3067-RA) did not result in prompt and positive outcome. Now, with all non-medical aspects in interfering the HCQ as the crusade to treating filtering lentivirus epidemics dying down after general election, it is high time to concentrate upon this noble cause in saving lives.

1. The discovery of HCQ and its anti-virus effects

Chloroquine (CQ), a 9-aminoquinoline that was identified in 1934. Hydroxychloroquine (HCQ), the advanced type of CQ with more effective therapeutic, is an ancient drug in the random selection during the clinical trials starting in China, which has

been used in fighting against lethal pandemic. Before, HCQ, there has been no effective drug for the treatment of various infectious diseases caused by lentivirus from Flu to Covid-19, even AIDS. It has been shown that HCQ has effective therapeutic, virus-suppression and lower by effect has strong antiviral effects on filtering lentivirus ranging from flu virus SARS-CoV and SARS-CoV2 and its variation ramification Covid-19 virus infection of primate cells. In addition, clinical trial proves that each member receiving 200-600mg HCQ daily dosage showed 100% recovery result during the three to five-day treatment for acute Flu patients.

2. Clinical evaluation of HCQ in the treatment of Covid-19

Severe acute respiratory syndrome (SARS) and its neo-type variation, Covid-19, is caused by a newly discovered coronavirus SARS-CoV2. Covid-19 is an emerging disease that was first reported in Hubei Province, China, in late 2019. The disease rapidly spread to the entire world with most severe impact upon the United States having claimed six digits Covid-19 related deaths and worldwide efforts have failed for non-medical complications, very unfortunately to humanity, in the identification of the etiological agent coronavirus, a novel member of the family Coronaviridae, coupled with wasteful failure in finding and identification of most effective and available treating drug for complications irrelevant to medical science for its own sake. No effective prophylactic or post-exposure therapy had been available before 2005.[1]

Of note, it has been reported that HCQ administration with daily dosage of 400-800mg HCQ treating Covid-19 pre-complication patients received 100% sweeping and miracle results, all virus were eliminated.[1] Dr. Vladimir Zelenko and others used his HCQ-based cocktails has successfully treated hundreds of Covid-19 patients in clinic trial and he recently predicted that neo-variation of Covid-19 virus spreading from the UK is also within the sphere of HCQ's therapeutic zone.[2]

In addition, there are some reports of failure or inadequacy in the clinical trials of using HCQ to treat Covid-19 patients. Such sporadic failures were used to maliciously attack HCQ. The unrevealed reason is probably due to insufficient or excessive dosage, or too late. Cocktail therapy is not necessarily required in all Covid-19 cases, and large doses of antibiotics are not required for early stage Covid-19 patients without bacterial infection or inflammation. Using HCQ too late, however, for late-stage patients who have experienced non-viral complications triggered by the Covid-19 virus. In the late stages, the process requires supportive symptomatic treatments such as antibiotics, anti-inflammatory, antithrombotic/anticoagulation and/or anti-autoimmune storm. In addition, as the experience in Sweden shows, preventive measures must be taken.

3. Low toxicity of HCQ

The improved formula HCQ has been widely used to treat human diseases such as malaria, amoebiosis, HIV, Lupus and autoimmune cytokine storms, without significant detrimental side effects which appears absolutely safe even to pregnant women. Though such safety by effects, which appears much, much safer than most, if not all, FDA approved chemical agents in chemotherapy treating cancer patients, have long been contained in the Drug Codes in the most civilized nations, however, a one-year long clinical trial to observe HCQ's safety was conducted by NIH related clinic for a control group of 103 Lupus patients from March 2012 to March 2013. Daily dosage of HCQ 200-400 mg for each member of controlled group, the accumulated total quantity was up to 144000 mg. None, repeat, none in the HCQ group suffered any visible side effects.[3]

An HCQ's molecule "weight" is 434 (433.96). An effective elimination *in vitro* shows 10μM CQ or 5 μM HCQ, eliminated broad spectrum filtering lentivirus by 100%. After all possible degrading ratio is taken into account through mathematical models, the average dosage to heal a Covid-19 or Flu patient with HCQ should be 2.17 mg/kg body weight. For mid and later phase Covid-19 patients, 6.21 mg/kg body weight. Therefore, a daily dosage 200-600mg, oral is sufficient, and a weekly dosage will effectively repeal all viral infection with elimination of virus *in vivo*. Due to the fact that HCQ shows extreme low toxicity which does not show any statistical value for short period (*e.g.*, less than 6 months period of continuous prescription) administration in clinical trials, if the clinical dosage be increased up to 400-800 mg daily oral dosage for the first two days to relatively overweight patients, it causes no toxicity response.

4. Preinfection and postinfection effect of CQ and HCQ

HCQ demonstrates full-scale effective in preventing the spread of filtering lentiviral epidemics ranging from acute Flu to Covid-19 and SARS in cell culture. Favorable inhibition of virus spread was observed when the cells were either treated with HCQ prior to or after such filtering lentivirus infection on both *in vitro* experiment in laboratories and *in vivo* clinical trials in China.[1]

Recently, Vincent *et al*., reported that pretreatment with 0.1μM CQ or 0.05μM HCQ, reduced infectivity by 28%, and 10μM CQ or 5 μM HCQ, reduced infectivity by 100% in Vero E6 cells (Figure

1).[1] The antiviral effects by CQ immediately after virus adsorption was also evaluated, they found that adding chloroquine 3 and 5 h after virus adsorption effectively removed infected virus (Figure 2).[1] Electron microscopic analysis indicated the appearance of significant amounts of extracellular virus particles 5-6 h after infection.[4] These data demonstrated that pretreatment of Vero E6 cells with CQ rendered these cells refractory to SARS-CoV infection, and that administration of CQ after infection also showed curative effect.

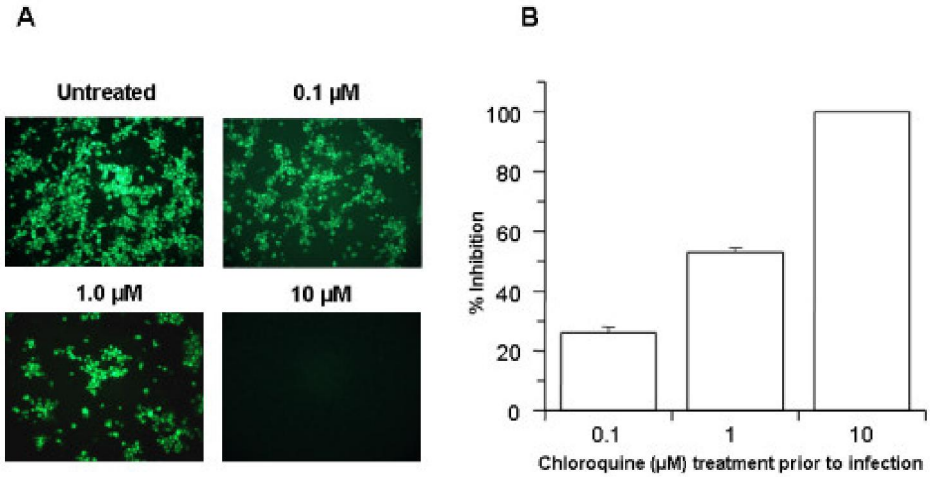

Figure 1. Prophylactic effect of chloroquine.

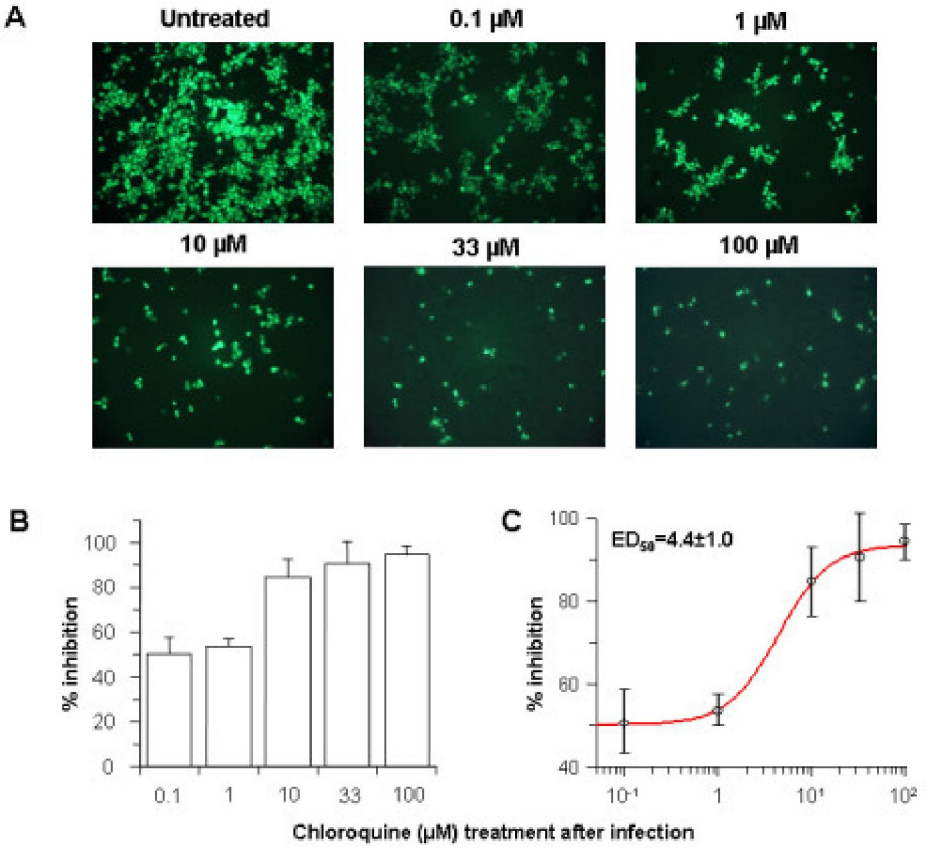

Figure 2. Timed post-infection treatment with chloroquine.

4.2 HCQ prevented the binding of Covid-19 with spike glycoprotein

When added extracellularly, the non-protonated portion of CQ enters the cell, where it becomes protonated and concentrated in acidic, low-pH organelles, such as endosomes, Golgi vesicles, and lysosomes. CQ can affect virus infection in many ways, and the antiviral effect depends in part on the extent to which the virus utilizes endosomes for entry. In addition to the well-known functions of HCQ's such as elevations of endosomal pH balancing, the drug appears to interfere with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme 2 (ACE2). This may negatively influence the virus-receptor binding and abrogate the infection, with further ramifications by the elevation of vesicular pH, resulting in sweeping and miracle inhibition of infection and spread of Flu syndrome, SARS CoV and Covid-19 at clinically admissible concentrations by all clinical trials in hospitals throughout China.

Over eighty years of antiviral drug research, scientists have long focused on blocking the attachment between the viral spike glycoprotein (similar to the signal output antenna) and the host cell's ACE2 receptor, to eliminate viral attachment to the cellular receptor that initiates a viral infection. Taking example of Covid-19 and Sars, budding of the SARS-CoV occurs in the Golgi apparatus and results in the incorporation of the envelope spike glycoprotein into the virion. The spike glycoprotein is a type I membrane protein that facilitates viral attachment to the cellular receptor and initiation of infection, and angiotensin-converting enzyme-2 (ACE2) has been identified as a functional cellular receptor of such filtering lentivirus including SARS-CoV and Covid-19. Vincent *et al.*, have recently shown that the processing of the spike protein was affected by furin-like convertases and that inhibition of this cleavage by a specific inhibitor abrogated cytopathicity and significantly reduced the virus titer (Figure 3).[1] In contrast, the antiviral effect of HCQ is probably not due to alteration of virus glycoprotein biosynthesis and processing. Consistent with this previous analysis,[1] they observed the presence of a larger protein, which is referred to here as oligomers. Recently, Song et al. provided evidence that these are homotrimers of the SARS-CoV spike protein and were incorporated into the virions.

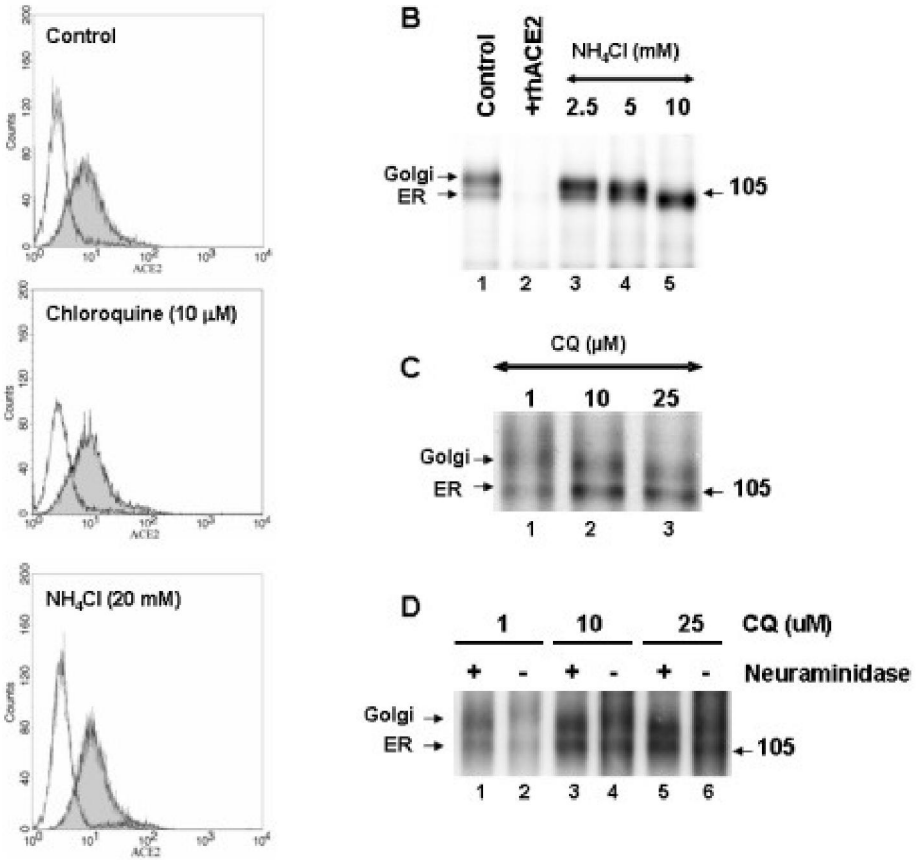

Figure 3. Effect of lysomotropic agents on the cell-surface expression and biosynthesis of ACE2.

Future clinical application of HCQ in the treatment of Covid-19

Vaccines belongs to *in vivo* immune system enhancement, not a chemical agent virus killer that directly eliminates viruses, which was shown 100% elimination of virus *in vitro* when the density of HCQ reached 10MU. For such viruses with too fast intergenerational mutations, such as that of Covid-19, whether the vaccine development speed can match that intergenerational mutation, and the toxicity evaluation may not have been crystal clear. Hydroxychloroquine has proven effective or even full effect with none or insignificantly little toxic side effects *in vivo*. We have witnessed today that a landmark turning point led by the HCQ as a proven effective broad spectrum anti-virus agent with insignificant little by-effect of toxicity has brought the Good News of Great Grace from Lord, in saving millions of pandemic virus patients as a groundbreaking medical science revolution just like discovery of Penicillin to eliminate various lethal bacteria eighty some years before. In addition, chloroquine itself has the beneficial function of degrading autoimmune storms. Moreover, chloroquine also has the effect of improving the pH balancing level of the patients.

Is HCQ the second revolution in medical science after penicillin?

Before Penicillin was discovered in 1928 by Scottish scientist Alexander Fleming, bacteria was the primary cause of death. This long night of darkness in medical science treating human disease has been ended when Penicillin was used to by medicinal society to treat bacteria infections starting 1942. It is making a new era started when there are several enhanced penicillin families which are effective against additional bacteria; these include the antistaphylococcal penicillins, aminopenicillins and the antipseudomonal penicillins.[5] They are derived from Penicillin fungi. Discovery of Penicillin is a great revolution in medical science treating human diseases many of which had been deadly before Penicillin. Consequently, in recognition of Dr. Alexander Fleming, a Nobel Prize in Physiology or Medicine was awarded to him sharing with Dr. Howard Florey and Dr. Ernst Boris Chain, scientists with Oxford University who developed improved penicillins formulas.

During the same period of approximately eight decades after discovery of Penicillin, the entire medical community through out of the world with orchestrated efforts by generations, has made little progress, if any, to find effective way to discover, formulate and made it available any chemical agents or drugs in fighting against any filtering lentivirus, ranging from that of Flu, of Ebola, of AIDS, of SARS-CoV, and of Covid-19. We have witnessed in great celebration that humanity, thanks the God, has encountered her second year of 1928, this time, yet to be defeated lethal enemy is filtering lentivirus probably by its entire family, which causes such crippling or deadly virus triggering human diseases ranging from Flu, Covid-19 to AIDS. Due to the severity of Covid-19 as well as acute Flu infection, the potential for rapid spread of the filtering lentivirus triggered diseases, and the absence of proven effective and safe in vivo inhibitors of the virus, it is important to identify anti-pandemic drug that can effectively be used to both treat and prevent potential lentiviral infections.

Together with data presented here, showing virus inhibition in cell culture by HCQ doses compatible with patient treatment, recommendation of immediate, full and permanent FDA approval of HCQ to be used in prevention and treating such filtering lentivirus triggered epidemic as Acute Flu，Covid-19 and SARS epidemic patients is strongly recommended.

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