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Review Article

Hydroxychloroquine and Interferons for the Prophylaxis and Early Treatment of Covid-19-Current Clinical Advances

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ABSTRACT

Coronavirus disease 2019 (Covid-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) calls for unprecedented measures to control the spread of the virus. SARS-CoV-2 enters into the cell by direct fusion to the cell membrane or fusion to the membrane of endocytic vesicles. Hydroxychloroquine (HCQ) inhibits enzymes in the endocytic vesicle and has been studied for its efficacy since the beginning of the pandemic. Retrospective analysis of healthcare workers (HCWs) and observational studies suggest protective effect of taking HCQ prophylactically. However, studies on autoimmune patients taking HCQ provide conflicting results. In a postexposure prophylaxis randomized controlled trial (RCT), Boulware et al. found a non-significant difference in incidence between HCQ and placebo group (11.8% vs. 14.3%, p=0.35). However, our re-analysis of the data suggests HCQ use for Covid-19 is time-sensitive. Early use of HCQ after exposure appears to confer some protection from symptomatic Covid-19 (p=0.0496). Another RCT by Mitja et al. found that on day 14 after the exposure, 55.6% more patients given HCQ had IgM/IgG against the virus (p=0.01) compared to placebo group, suggesting early activation of adaptive immune response. No reportable major side effects occurred in either study. In the current urgent pandemic crisis without any established protocols for prophylaxis, these results indicate that the use of HCQ in prophylaxis and early treatment of Covid-19 soon after exposure offers benefit. Initial data using interferon (IFN) beta-1 and nebulized IFN alpha-2 for the treatment of Covid-19 have been promising. The prophylactic use of IFN alpha-2b intranasally against Covid-19 as suggested by us at the early stage of the pandemic has not yet been tested. More RCT studies are needed to evaluate the efficacy of HCQ and IFN alpha-2 separately and in combination for prophylaxis against Covid-19. Future studies should give us more definitive answers.

Keywords: Covid-19; Hydroxychloroquine; Interferon; Prophylaxis; Treatment; Randomized controlled trial

INTRODUCTION

The Covid-19 pandemic caused by SARS-CoV-2 virus has caused enormous damage to humanity. By August 14, 2020, the virus has infected more than 5 million people with over 162,000 deaths in the U.S. and approaching 20 million of infected people around the world despite worldwide lockdown. There is an urgent need to develop effective prophylactic and treatment protocols to contain the spread of the virus.

Hydroxychloroquine (HCQ) has been shown to have antiviral activity against SARS-CoV-2 *in vitro* [1] and was touted as a cure early on. However, conflicting results of the drug have led to obfuscation of the efficacy of HCQ in hospitalized patients. Confounding variables such as time of treatment, dosage, admission criteria in different hospitals make results difficult to interpret. Consensus is forming that treatment using HCQ in late stage of Covid-19 does not provide benefit [2,3].

In patients with severe Covid-19, type I interferon (IFN) response has been shown to be down regulated compared to patients with mild Covid-19 [4,5]. Thus, type I IFNs could be used to prevent disease progression from mild to severe Covid-19. In our review, we will analyze the major studies for HCQ as prophylaxis and type I IFN for early treatment against Covid-19. There have not yet been any studies conducted for type I IFN for prophylaxis, as suggested previously in our hypothesis paper [6].

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MECHANISM OF VIRAL ENTRY AND HALLMARKS OF SEVERE COVID-19

The S protein of SARS-CoV-2 has high affinity for angiotensin-converting enzyme 2 (ACE2) receptor on epithelial cells. Proteolytic cleavage of the S protein by TMPSS2 or endosomal Cathepsin B/L results in S1 and S2 subunits. The S1 subunit is responsible for binding to the receptor, and the S2 subunit initiates the fusion of viral envelope to the cell membrane or endocytic membrane. This results in the dumping of the viral nucleocapsid into the cytosol of the host cell [7].

After initial infection, SARS-CoV-2 proteins can downregulate host IFN production leading to a suboptimal innate immune response. Patients with severe disease have no production of IFN-beta and low production of IFN-alpha and lambda compared to mild patients [4,5]. As a result of the decreased IFN response, there is decreased activation of NK cells, plasmacytoid dendritic cells and CD16+ monocytes in the innate immunity. In the adaptive immunity, there are lower activated CD4+ and CD8+ T cells [4]. The suboptimal immune response leads to higher viral load, lymphopenia, and unregulated inflammation seen in severe Covid-19 patients. Acute respiratory distress syndrome (ARDS) and the failure of other organs separately or together results in death [8].

THE IDENTIFICATION OF HCQ AND TYPE I INTERFERON AS POTENTIAL THERAPY FOR COVID-19

Jeon et al. have screened about 3000 FDA approved drugs or investigative drugs using kidney cell line Vero cells for treating SARS-Cov-2 [9]. They have identified 24 drugs that have potential to treat Covid-19 including Remdesivir and HCQ. *In vitro* study using cell lines also identified that HCQ and type I IFN are useful in inhibiting viral replication [10]. This promising *in vitro* data generated enormous interest worldwide. FDA initially gave the emergency use authorization (EUA) of HCQ for Covid-19 but later revoked the EUA. In the announcement, FDA noted that FDA-approved products may be prescribed by physicians for off-label uses if they determine it is appropriate for treating their patients, including Covid-19.

At the beginning of pandemic, we proposed to test HCQ and IFN-alpha 2b for the prophylaxis of SARS-COV-2 infection [6]. We argued that it would be better to use dual antiviral therapy with low side effect for prophylaxis as we anticipated that it is too optimistic to assume that monodrug would be adequate to inhibit the replication of SARS-CoV-2 in patients. This proposal has not been investigated because of lack of funding.

RETROSPECTIVE AND OBSERVATIONAL STUDIES USING HCQ FOR PROPHYLAXIS

Based on the initial *in vitro data* and multiple-decade historical safety data on HCQ worldwide, National Task Force for Covid-19 in India recommended use of HCQ for HCWs working with suspected and/or confirmed infected patients. Asymptomatic household contacts with confirmed cases are also included in the advisory. They recommended the typical prophylaxis dose used for malaria for high risk population. After seven weeks, the investigators collected the pool of HCWs; including 21,402 qualified records were obtained. RT-PCR was used to confirm the infection and non-infection. Among them, 1073 (5%) of the HCWs were infected. They found that HCWs taking more than 6 doses reduced infection rate by 81% and a dose-dependent risk reduction for HCQ ($p<0.001$) [11]. Based on these findings, India recommended the expanded use of HCQ. In addition, Khurana et al. did a cohort study of HCWs in an Indian tertiary hospital. They analyzed a cohort of HCWs taking HCQ according to the advisory of Indian government comparing with a control cohort of HCWs who did not take HCQ. They concluded that HCWS taking HCQ has significant lower infection with a relative risk of 0.193 ($p=0.021$) [12].

Patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) have been taking HCQ regularly for years to treat the disease. Analyzing the susceptibility to SARS-CoV-2 infection of these autoimmune-related patients can give us insight for the use of HCQ in prophylaxis. Ferreira et al. reported among 26815 confirmed SARS-CoV-2 infections in Portugal, 77 cases (0.29%) taking HCQ regularly were tested positive for SARS-CoV-2 infection, while 1215 cases (0.36%) tested negative who are also taking HCQ regularly. These negative cases are among 333,489 that tested negative in the country. The adjusted odds ratio of a positive PCR test for HCQ chronic treatment was 0.51 (0.37-0.70) [13]. However, Singer et al. analyzed data in TriNetX Research Network with the data from 36 US healthcare organizations. They analyzed autoimmune patients taking HCQ regularly, patients with diagnosed respiratory infection and all the outpatients last year. They found that there is no difference in infection rate among these three groups, suggesting HCQ does not provide protection for autoimmune patients taking HCQ [14]. Infection rates in different regions are very dynamic, which may provide unreliable analysis.

Zhong et al. analyzed the data in Hubei Province, China, where the SARS-COV-2 started. They studied 42 families in the same household and concluded that rheumatic diseases increased risk of infection (OR 2.68, $p<0.023$).Adjusted for all other factors, patients with rheumatic disease who were taking HCQ had a lower risk of Covid-19 infection than patients taking other disease-modifying anti-rheumatic drugs (OR 0.09, $p=0.044$) [15].

Overall, these retrospective studies and other retrospective studies about HCQ as a prophylaxis give conflicting results [16]. Patients with SLE and RA may be more susceptible to the infection thus offset the potential prophylactic benefit of HCQ as shown in other studies. However, no firm conclusion can be made using these retrospective and observational studies. The presence of TMPSS 2 in the lung cell may explain why HCQ is not as potent as *in vitro* studies as the virus does not have to rely on endocytosis to enter the host cell [7].Thus, it is important to analyze the gold standard randomized controlled trials (RCTs) using hydroxychloroquine.

RANDOMIZED CONTROLLED CLINICAL STUDIES

Boulware et al. conducted a double blinded RCT to evaluate the effect of HCQ in postexposure prophylaxis [17].They initially intended to enroll the participants who were exposed to a confirmed case with SARS-Cov-2 infection within 3 days. One week later, they decided to extend the exposure to 4 days after the exposure. The study design has limitations as discussed by Cohen [18]. As there were difficulties in laboratory diagnosis, they used a combination of laboratory and symptoms as method of diagnosis. Once a participant was enrolled in the study, they used overnight shipment to deliver HCQ and placebo to the participants in Canada and USA. They concluded that HCQ is not effective in postexposure prophylaxis within 4 days of exposure as there is no difference in incidence between HCQ (49/414, 11.8%) compared to placebo (58/407, 14.3%), $p=0.35$.

However, this intension to treat (ITT) analysis ignored temporal heterogeneity in days after exposure to enrollment days. It is reasonable to assume a long delay in enrolling to treatment after exposure would result in decreased efficacy of HCQ treatment. Indeed, after our re-analysis of their data reported in Supplemental Table S6, according to the days after exposure, the earlier the

HCQ is taken after exposure, the more protection there is against symptomatic Covid-19 using Cochran-Amitage test for trend (p<0.0497).Their mailing of the drugs took 1 to 3 days, thus treatment started at least two days after the exposure. Those enrolled to HCQ arm one day after exposure had a 6.2% reduction of incidence, and a relative reduction of 48.9% compared to the placebo arm. Using this trend, it can be conjectured that using HCQ on day 1, day 0 and pre-exposure can have better protection against symptomatic Covid-19.There was no serious side effect reported in the study. Based on their available data, it can be concluded that HCQ provides some benefit for the postexposure prophylaxis at the early days of exposure.

In a preprint released to the public Mitja et al. [19] carried out an open label cluster-randomized RCT using HCQ for postexposure prophylaxis (laboratory technicians were blinded).They recruited the close contacts of a confirmed SAR-CoV-2 infection. There are 2314 participants who were exposed on average 4 days after the exposure (IQR 3.0-6.0). Mitja et al. measured the baseline RT PCR analysis on Day 1 and on Day 14.They also measured IgM and IgG on Day 14. At baseline, they had 11.5% participants in control group, and 13.1% in the treatment group who are positive. They have a low infection rate of 6.2% in the control, 5.7% in the treatment group according to RT PCR test. After excluding the PCR positive participants at the baseline, the infection rate is 4.3% in the control group vs. 3.0% in the treatment group (PCR positive and symptomatic), chi square test p<0.156.The differences are not statistically significant. Considering the false negative PCR test, they re-analyzed all participants who are either PCR positive regardless of symptom or symptomatically compatible regardless of PCR test resulting in an infection rate of 17.8% in control group compared to 18.7% in treatment group. They thus concluded that there is no difference in both groups, and postexposure prophylaxis with HCQ is not recommended. However, when the serology test is analyzed as reported in Table 2, there are significant more participants with IgM/IgG positive on day 14 that were treated with HCQ compared to control (14.4% vs. 8.7%, p<0.0006).Considering only the infected participants, with 137 out of 179 infected participants (76.5%) in treatment group, 91 out of 185 infected participants (49.2%) in control group, the increase of participants with serologic conversion is 55.6% (p<0.01).It thus can be concluded that HCQ can increase activation of adaptive immunity. They also presented enrollment data with participants in three groups, <3 days, 4-6 days, >7 days after the exposure to the contact. There is also a trend that the longer the delay in enrollment after the exposure, the less effective is the HCQ treatment, consistent with the trend we found from the data of Boulware et al. However, this trend is not statistically significant. Mitja et al. used a lower dose of HCQ and also has longer delays of treatment after exposure than the study by Boulware et al. It is thus possible that the lower dosage and the longer delay explain the insignificant trend in results. In both studies, there are no serious side effects reported and there is evidence of a trend indicating the longer the delay in starting treatment after exposure to SARS-CoV-2, the lower the efficacy for the HCQ treatment. In both RCTs, the HCQ treatment group has lower incidence rates according to the reported primary outcome. The lack of significance is potentially due to long delays in starting HCQ after exposure. Major studies using HCQ for prophylaxis are summarized in Table 1. Majority of them support the beneficial use of HCQ for prophylaxis.

Table 1: Major Studies Using HCQ as Prophylaxis for Covid-19.

First Author	Country	Study Design	Participants	Intervention	Primary Outcome	Reported Incidence Intervention/ Control
Boulware	USA	RCT, Placebo Controlled	821 participants 1-4 days after exposure to confirmed case	HCQ sulfate, 800 mg, 600 mg (after 6 hours) 600 mg/day for 4 days	Incidence of confirmed or symptomatic within 14 days after the intervention	11.8%/14.3% p<0.35
Mitja	Spain	RCT, Open Label Technician Blinded	2250 Participants Median 4 days after exposure to confirmed case	800 mg Followed by 400 mg/day for 6 days	Onset of Symptomatic and + RT-PCR 14 days after the intervention	5.7%/6.2% OR 0.89 (0.54-1.46)
Chatterjee	India	Retrospective case-control study	21402751 HCWs tested, 5% infected, 624 cases and 549 controls	400 mg Bid Followed by 400 mg once weekly for 7 weeks	Symptomatic and +RT-PCR	OR 0.44 (0.22-0.88)
Feirreira	Portugal	Retrospective	77 on HCQ among 26815 infected patients 1215 on HCQ among 333489 Negative non-infected participants	Autoimmune patients taking HCQ Likely 200-400 mg daily	RT-PCR	OR 0.51 (0.37-0.70)
Zhong	China	Retrospective	42 families with lupus patients totaling 126 family members	Autoimmune patients taking HCQ Likely 200-400 mg daily	RT-PCT	OR 0.09 (0.01-0.94)
Khurara	India	Retrospective	181 Hospital staff	400 mg Bid Followed by 400 mg once weekly for 7 weeks	Symptomatic and +RT-PCR	Negative Rate 18.4%/6.4% p<0.021
Singer	USA	Retrospective	159 Autoimmune HCQ users, 32599 common HCQ Takes	Autoimmune patients taking HCQ Likely 400 mg Daily	Diagnosis	34.6%/32.7% p<0.6115

In conclusion, data from the two RCT prophylaxis studies currently available indicated that the early use of HCQ provided some benefit in postexposure prophylaxis. This conclusion is significant as there is still no vaccine or drug available for SARS-Cov-2 after exposure. It also can be conjectured that pre-exposure use of HCQ can provide benefit, however rigorous studies will also need to be performed for pre-exposure prophylaxis. In the current urgent crisis, these studies provide some valuable evidence to support the use of HCQ shortly after exposure for prophylaxis against Covid-19.

ANTIVIRAL ACTIVITY OF INTERFERONS

In an *in vitro* study, SARS-CoV-2 is very sensitive to IFN-alpha comparing to SARS-CoV virus [10]. In patients, the SARS-CoV-2 virus can replicate in high amount without causing any symptoms, suggesting that the virus can escape the monitoring of innate immune system for a long period of time. We thus proposed to use IFN alpha-2b at the early stage of the infection for the initial three days of prophylaxis [6]. More recently, IFN-beta was shown to be more effective in inhibiting the replication of SARS-Cov-2 *in vitro* [20]. IFN-beta is also known to be able to back-loop the production of IFN-alpha. It is thus not a surprise that more clinical trials are using IFN-beta instead of IFN-alpha (Table 2).It remains to be seen which one is better *in vivo*. The receptor for IFN lambda is only expressed on epithelial cells. Initially it was thought to be a better choice for prophylaxis compared to IFN-alpha or beta due to decreased systemic effects. However, a recent animal study by Broggi et al. found that the receptor for IFN lambda is only expressed in the lung and not in the upper respiratory tract. Furthermore, the production of IFN lambda disrupts the lung epithelial barrier, causing lethal bacterial infection [21]. These results cast doubt in using IFN lambda for the prevention and treatment of Covid-19.

TREATMENT USING IFNs

In a multicenter, prospective, open label, randomized trial from six hospitals in Hong Kong, triple antiviral therapy of lopinavir-ritonavir, ribavirin, and subcutaneous injection of interferon beta-1b was compared to lopinavir-ritonavir alone [22]. Patients in the triple antiviral therapy group had a significantly shorter course of the virus (7 days) compared to lopinaivir-ritonavir alone (12 days) as detected by RT-PCR. As a result of the shortened course of the virus, patients treated with triple antiviral therapy had significant alleviation of symptoms (4 days) compared to combination therapy alone (8 days) and overall shorter hospital stay time (9 days) compared to combination therapy as well (14.5 days). The improvement in both virologic and clinical outcomes without a significant increase in any adverse events suggests the efficacy of interferon beta-1b as part of an antiviral regimen for Covid-19.

In an exploratory study of 77 patients, Zhou et al. used nebulized IFN-alpha 2b (5mIU Bid), Arbitol, IFN alpha2 combined with Arbitol to treat Covid-19 patients. They have found IFN alone or in combination accelerated the viral clearance by 7 days. The treatment lowered IL-6 and CRP, markers for inflammation [23].In a press release, Synairgen announced that they tested nebulized IFN beta to treat Covid-19 in Phase II double-blind placebo-controlled trial. They recruited 101 patients from 9 sites in the UK and found that patients receiving IFN-beta had a 79% lower risk of developing severe disease compared to placebo. Additionally patients who received IFN-beta were more than twice as likely to recover from Covid-19 as those on placebo (Retrieved 8/13/2020, https://www.lsegissuerservices.com/spark/Synairgen/events/97cda0b9-0529-4be1b1ca471cc8dc1e94). However, these results are yet to be published. These clinical trials combined with the deficient type I

Table 2: Important Prophylaxis and Treatment Studies Using IFN.

First Author/ Sponsor of Investigation	Study Design	Participants	Intervention	Primary Outcome	Incidence Intervention/Control
Hung	Multicenter, randomized, open label	127 patients Median 5 days (IRQ 5-11) after Symptom	Combination therapy with IFN-beta 1	RT-PCR negative and mortality	Cured 7 days/12 days
Zhou	One Hospital Open Label	77 Patients	IFN 5 mIU Bid, Arbitol 200 mg Tid	RT-PCT, Inflammation	Cured 21.1 days/27.9 days
Synairgen	RCT double blinded	101 patients	Likely once a day for 14 days dose undisclosed	Change of conditions according OSCI#	Reduce odds of severe disease by 79%. Increase likelihood of recovery 2-3 fold
Toronto General Hospital	RCT double blinded	140	Single dose peginterferon lambda 180 µg SC	RT-PCT, Time Course	Expected Completion 11/30/2020
NIAID	RTC double blinded	1038	Remdesivir and IFN-beta 1a	Days to recovery	Expected Completion 11/1/2023
JHU and EigerBioPharm.	RTC single blinded	164	IFN lambda-1a	Infection Rate and Time to Recovery	Expected Completion 6/2021
Bayer and Hamilton Health	RCT, Open Label	4000	0.25 mg IFN beta alternate days for 4 doses	Disease Progression	Expected Completion 6/30-2021

#: Ordinal Scale for Clinical Improvement

interferon signature found in severe patients suggest the efficacy of type I interferon as a part of an antiviral therapy for Covid-19.

CONCLUSION

Our review and analysis of the available clinical studies have identified that HCQ provides some benefit in postexposure prophylaxis and it is conjectured that HCQ has pre-exposure prophylaxis effect.Data also indicates type I IFN is safe and effective in treating Covid-19. In the current urgent crisis, these results are evidences to support the early use of HCQ in postexposure prophylaxis and perhaps in combination with other drugs such as Type I IFN to increase efficacy.

CONTRIBUTIONS

Bing Yang organized the writing of the review and provided the references. Alexander Chuan Yang wrote the review with the instructions from Youcheng Liu and Bing Yang. Yongzhao Shao did the statistical analysis and reviewed the statistical analysis in the cited publications. JinpingXu provided the medical guidance about the drugs and clinical trials. Charlotte Yang provided the clinical experience of the drugs.

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