REVIEW ARTICLE

Recapitulation of Antimalarial Drugs use in the Prevention and Treatment of Novel Coronavirus Disease

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused Coronavirus pandemic (COVID-19). Repurposing of antimalarial drugs as a potential treatment option for hospitalized, non-hospitalized as well for prevention against SARS CoV-2 have been researched as potential COVID-19 treatments, with some moving into clinical trials. This review article revisits the evidence and draws comparison regarding their safety and efficacy.

Key Words: *Antimalarial Drugs, COVID-19, Chloroquine and Hydroxychloroquine, SARS CoV-2.*

Introduction

Novel coronavirus disease is an infectious illness caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) originated from city of Wuhan, Hubei Province, China in December 2019.[1] World Health Organization stated novel coronavirus disease a Public Health Emergency of international concern on 30th January 2020. This infectious disease was named as "COVID-19" by World Health Organization on 11th February 2020, followed by declaration of COVID 19 pandemic on 11th March 2020.[2] The infection has invaded 213 countries and territories around the world and caused infection to approximately 23 million people and 7.9 million deaths.[3]

This has placed a huge burden on both developed and developing countries healthcare system and has led to unmet medical needs.[4] Currently no approved clinical therapy exists for the treatment of novel coronavirus disease. Many national and international research organizations and medical institutes are in a process to develop evidence-based treatment options for treating and preventing novel

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coronavirus disease.[5] Vaccine development, monoclonal antibodies, interferon-targeted therapies, convalescent plasms, phytochemicals and herbal drugs are being researched to find an effective treatment of novel coronavirus disease. Drug discovery and development is time consuming and resource intense process, which on average takes around 10-15 years to develop a drug and commercialize it for public use.[6]

In the context of current pandemic, efforts are underway to explore approved drugs with established safety guidelines for repurposing into potential SARS-CoV-2 treatment. As the genomic structure of SARS-CoV-2 is reported to be similar to previous epidemic coronaviruses including MERS-CoV and SARS-CoV, researchers are targeting drug classes which had proven efficacy against these viruses.[7]

Antimalarials are one of the very first potential treatment drugs. Initially in-vitro data published supported the anti-viral and immunomodulatory action of these drugs against SARS-CoV-2.[8] Some clinical studies from China and United States were published in April 2020, favoring the effectiveness of antimalarial drugs in treating confirmed novel coronavirus patients, most of them were observational clinical studies and a few randomized controlled trials. At the same time adverse drug reactions linked to antimalarial drugs started to come in notice, and due to health concerns caused by these studies a lot of clinical trials stopped

randomizing patients to these treatment arms.[9] Subsequently a lot of debate and questions were raised on the authenticity of safety data published in these studies, with a few publications retracted from renowned journals. Following these events, based on the results of interim analysis, some trials resumed enrolling patients to antimalarials while other completely stopped the enrolment.[10] In this review we had tried to sum up the evidences available from clinical trials published till date, in favor or against the usefulness of chloroquine and hydroxychloroquine, alone or in combination (Table 1).

Table 1: Summary of Clinical Trials discussed in the study

Scope of treatment	Sample size	Study Arms	Primary outcome	Result	Ref
Prophylactic use	821	HCQ (n=414) Placebo (n=407)	Laboratory confirmation of covid-19 or comparable symptoms within 14 days of enrollment	No significant difference (HCQ 11.8% vs Placebo 14.3%, p=0.350)	21
Hospitalized patients	11,000	HCQ (n=1542) SOC (n=3132) Remaining patients randomized to other arms	28-day mortality rates	No significant difference [25.7% vs 23.5%, HR=1.11, 95% CI 0.98-1.26, p=0.10]	10
	3500	HCQ (n=1000) SOC (n=1000) Remaining patients randomized to other arms	28-day mortality rate	no or little reduction in mortality of hospitalized patients	27
	665	HCQ + Azi (n=217) HCQ (n=221) Control (n=227)	Improvement in clinical status at 15 days	No significant improvement (HCQ OR=1.21, 95% CI 0.69-2.11, p=1.0 vs HCQ+Azi OR=0.99, 95% CI 1.57-1.73, p=1.0)	29
	62	HCQ (n=31) SOC (n=31)	Time to clinical recovery (TTCR)	Significantly shorter TTCR in HCQ group (80.6% recovered in HCQ group vs 54.8% in SOC, p<0.001).	30
	150	HCQ (n=75) SOC (n=75)	negative seroconversion of SARS-CoV-2 by 28 days	no significant difference (85.4% for HCQ vs 81.3% negative seroconversion for SOC, p=0.1) More adverse effects in treatment arms	31
	20	HCQ (n=20) + Azi administered to 6 patients	viral load in nasopharyngeal swabs at 6-day	100% viral clearance in HCQ plus Azi group, 57.1% viral clearance in HCQ alone	32
Non hospitalized patients	423	HCQ (n=212) Control (n=211)	Hospitalization, admission to ICU or death And Clinical symptoms at 14-day	No significant difference in hospitalization rate (1.8% vs 4.7, p=0.29) Ongoing symptoms at 14-day (24% vs 30%, p=0.21) More ADRs in HCQ group (43% vs 22%, p<0.001).	35

HCQ=Hydroxychloroquine, Azi=Azithromycin, SOC=Standard of care, ADR=Adverse drug reaction

Chloroquine and Hydroxychloroquine

Hydroxychloroquine is a 7-chloro-4-amino-quinoline compound, hydroxylate derivative of Chloroquine which is comparatively safer than chloroquine itself.[11] Chloroquine and hydroxychloroquine both are commonly used antimalarial drugs, also indicated for the treatment of autoimmune disorders due to their immunomodulatory effects and thus were found to be effective against SARS-CoV and MERS-CoV viral infections in the past.[12]

a. Pharmacokinetics

Chloroquine and hydroxychloroquine are completely absorbed from stomach and gain a peak serum concentration within 1-2 hours of administration. These drugs have high protein binding, linear kinetics and a large volume of distribution, to a number of body tissues. The major route of elimination is renal, half of chloroquine and quarter of hydroxychloroquine drugs remains unchanged in urine. The elimination half-life is long, ranging from 5-40 days and both the drugs readily cross the placenta membranes.[13]

b. Adverse reactions

Drug-induced prolongation of QT interval and torsade de pointes (TdP) are the two major adverse reactions reported for chloroquine and hydroxychloroquine among susceptible population. Co-administration of these drugs with other drugs including azithromycin, quinolones and antihistamines may increase the risk of these adverse reactions. 4-amino quinolones can also increase plasma concentrations of other cardiac drugs including digoxin, warfarin and beta-blockers.[14]

c. Mechanism of action

The mechanism of action of hydroxychloroquine encompasses inhibition of ACE2-receptor mediated viral entry into the host cells, mainly by changing the pH of host cell membrane which hinders fusion of virus with ACE-2 receptors, as virus requires acidic pH to attach to the host membrane receptors. Additionally, 4-amino quinolone drugs get concentrated into intracellular organelles e.g. lysosomes / endosomes thus raising the internal pH which in turn interferes with replication of nucleic acids, viral protein glycosylation, viral assembly and release.[15] These anti-malarial drugs also inhibit phospholipase enzyme activity, block production of pro-inflammatory cytokines, stabilize lysosomal membrane, and impair antigen-antibody reactions. Chloroquine and hydroxychloroquine are also said to possesses anti-inflammatory, immunomodulatory and anti-aggregate actions which are hypothesized to be appropriate in combating with cytokine-storm crisis.[16]

d. In-vitro activity against SARS-CoV-2

Many studies confirmed in-vitro anti-viral action against SARS-CoV-2 based on cell cultures and physiologically-based pharmacokinetic modelling techniques.[9] Both the chloroquine and hydroxychloroquine showed in-vitro action against MERS-CoV, SARS-CoV and SARS-CoV-2, where hydroxychloroquine has shown highest potency against SARS-CoV-2.[17] Studies have also predicted drug concentrations under different dosing regimens that are most effective against SARS-CoV-2 infection.[18] Lui at al[11] performed a study on human cell lines to confirm the efficacy of hydroxychloroquine and chloroquine against SARS-CoV-2 infection and cytokine storm crisis. Hydroxychloroquine was found to be safer than chloroquine and more effective in inhibiting the SARS-CoV-2 infection in-vitro, and with its anti-inflammatory activity, significantly reduced the cytokine production and pro-inflammatory factors.[11] A systematic review published by Cortegiani et al, highlighted a study conducted in China on Vero E6 cell line diseased by SARS-CoV-2, and reported effectiveness of chloroquine in decreasing the viral replication, at an effective concentration (EC-90) of 6.90 µM which was attainable with standard dose because of high tissue penetration and also anticipated that immunoregulatory property of chloroquine might improve its antiviral effect in-vivo.[19]

e. Registered Clinical Trials

There are 160 clinical studies registered with clinical trials registry formed by United States National Library of Medicine at the National Institutes of Health [accessed 21st Aug 2020].[20] Out of 160 there are 145 interventional studies with 6 phase I, 50 phase II, 71 phase III, and 18 Phase IV clinical trials. Nine (6.2%) studies have been completed, results are not published as yet, while 66 (45.5%) studies are currently active and recruiting patients, and remaining 48.2% studies (70/145) have either

terminated, suspended, or not currently recruiting (table 2).

Table 2: Clinical Trials Registered for Hydroxychloroquine / Chloroquine and COVID-19[20]

Characteristics	Number	Percentage
Study Type (n=160)		
• Observational	15	10.3%
• Interventional	145	90.6%
Phase of Clinical Trial (n=145)		
• Phase I	06	4.1%
• Phase II	50	34.4%
• Phase III	71	48.9%
• Phase IV	18	12.4%
Study Status (n=145)		
• Currently recruiting	66	45.5%
• Suspended/terminated/not actively recruiting	70	48.2%
• Completed	9	6.2%

Although many research studies published in early outbreak have suggested benefits of anti-malarial drugs for prophylaxis, viral load clearance and controlling aggressive cytokine release syndrome, especially in critically ill patients but the evidences is still inconclusive because of lack of consensus on dosage regimen, disease severity and outcome measures.[8]

f. Prophylactic use for the prevention of infection

A randomized placebo-controlled double-blind trial conducted by Boulware DR et al [21] at United States evaluated the post-exposure prophylactic use of hydroxychloroquine among 821 asymptomatic participants with confirmed exposure to high-risk covid-19 contact. Participants were randomized to either hydroxychloroquine (414 participants) or placebo (407 participants) within four days after exposure and the primary outcome was laboratory confirmation of covid-19 or comparable symptoms within 14 days of enrollment. Results reported no significant difference in the incidence of coronavirus disease among intervention and control group (11.8% vs 14.3% respectively, p=0.350]. Intervention group experiences more adverse events as compared to control group i.e. 40.1% vs 16.8% respectively.[21] The study had limitation including lack of consistent proof of exposure to the virus, lack of laboratory confirmation of the disease in participants who developed novel coronavirus disease-like symptoms, adherence to the treatment was not monitored, study population was relatively younger in age with mild or no coexisting comorbidities. Another observation was that the

mean time to start the prophylaxis treatment was three or more days after exposure, which is more indicative for prevention of signs & symptoms rather than infection prevention. Many studies[22-26] are registered to study the prophylactic use of hydroxychloroquine on general and specific population for example health care workers, results of which are awaited.[21]

g. Treating patients hospitalized with novel coronavirus disease

The Recovery Trial was a national randomized trial of United Kingdom initiated in early March 2020, with an aim to evaluate a range of potential treatment regimens beneficial for the patients with confirmed SARS-CoV-2 infection. Various treatment arms including hydroxychloroquine, dexamethasone, azithromycin, lopinavir/ritonavir, toclizumab, convalescent plasma and treatment as usual were included in the trial. Around 1542 patients were randomized to hydroxychloroquine group while 3132 to standard treatment. Initial results reported no significant difference in the main outcome measure that was 28-day mortality [25.7% vs 23.5% respectively, HR=1.11, 95% CI 0.98-1.26, p=0.10] and no beneficial effect on hospital stay duration was found. As a result, randomization of patients to hydroxychloroquine arm was stopped and a statement was made by Chief Investigator Martin Landray that these preliminary results are clear enough to show that hydroxychloroquine does not reduce the mortality risk among patients hospitalized for novel coronavirus disease.[10]

Another international global clinical trial, the Solidarity trial [27] was initiated on 18th March 2020, by World health Organization with an aim to identify treatment for novel coronavirus disease and comprised of various potential treatment arms, including hydroxychloroquine as one of the arms. A temporary halt to the hydroxychloroquine arm of the Solidarity trial was made by the Executive Group of the trial team on 23rd May 2020, because of safety concerns.[27] Mehra MR et al [28] from Brigham, Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, reported in a paper published in Lancet (22nd May 2020) that increased mortality and cardiovascular arrhythmias were observed in patients administered chloroquine or hydroxychloroquine as compared to control group.

Later on, serious questions were raised by the scientific committee about data reported by Mehra MR et al [28] and an expression of concern was published by Lancet, and followed by retraction of article. After reviewing the data, on June 3rd 2020, World Health Organization's Director General publicized that there are no reasons to change the trial protocol and recommended continuation of all arms of the Solidarity Trial, including the hydroxychloroquine drug from June 4th 2020. A month later, on 4th July 2020, World Health Organization announced to permanently discontinue enrollment to hydroxychloroquine and lopinavir/ritonavir arms of Solidarity trial. Based on interim trial results which showed no or little reduction in mortality of hospitalized patients with novel coronavirus disease as compared to treatment as usual.[27]

In another multicenter, randomized, open-label trial conducted in Brazil on 665 patients, including 504 hospitalized patients of mild to moderate novel coronavirus disease, showed no significant improvement in study group. Hydroxychloroquine use alone or in combination with Azithromycin failed to improve the clinical status among study participants as compared to standard of care treatment, at 15 days follow up. Patients randomized to intervention group were found to have prolonged QTc interval and raised liver enzymes as compared to control group.[29]

A randomized controlled clinical trial conducted in China enrolled 62 patients hospitalized with mild novel coronavirus disease, out of which 31 patients were randomized to hydroxychloroquine plus standard of care therapy. It was reported that the time to clinical recovery significantly shortened for intervention group and a greater number of patients belonging to intervention group had improved pneumonia as compared to the control group (80.6% vs 54.8%, p<0.001).[30]

Another multicenter, open-label, randomized controlled trial from China enrolled 150 patients, 75 randomized to hydroxychloroquine plus standard treatment and 75 to standard treatment alone. Primary outcome comprised of negative seroconversion of SARS-CoV-2 by 28 days. Results reported no significant difference in negative seroconversion among two study groups (85.4% for intervention vs 81.3% negative seroconversion for control, p=0.1), and adverse effects were more commonly reported among hydroxychloroquine group.[31]

In France, a single arm study performed by Gautret et al [32] on 20 confirmed cases of covid-19 who were administered 600 mg of hydroxychloroquine daily in addition to azithromycin administration to six patients, depending on clinical presentation. Viral load in the nasopharyngeal swabs was assessed daily for all patients and results reported 100% viral clearance after 6 days of hydroxychloroquine and azithromycin administration, while 57.1% viral clearance in hydroxychloroquine alone. On the basis of this study, the French ministry of Health declared legal use of hydroxychloroquine for the treatment of covid-19. However, the limitation of this study was that only 26 patients were initially enrolled in the hydroxychloroquine group with 16 patients in control group receiving standard of care therapy, then six patients from the intervention group were excluded from the analysis because of missing data, remaining twenty patients showed to have significant viral clearance as compared to controls. Secondly, four of the six excluded patients encountered severe adverse outcomes including death and ICU admission, still were not included in the analysis. Thirdly patients who declined to consent for intervention were included in the control group, which might have led to serious selection bias in the study. Lastly, six patients who were administered azithromycin for superinfection reported to have 100% viral load clearance but in-depth study revealed that these patients already had lower viral load at initial stage, and when compared with patients with similar initial viral load receiving hydroxychloroquine alone, results were similar for both the groups [100% vs 77.7% respectively].[33]

Subsequent clinical trials conducted to confirm these findings failed to support the results reported by Gautret et al, [32] Molina et al [34] enrolled 11 covid-19 patients who were administered hydroxychloroquine and azithromycin to assess the virologic and clinical outcomes. Results showed that viral load in nasopharyngeal swabs remained positive for 8/10 (80%, 95% CI 49%-94%) of the patients after six days of treatment. Hydroxychloroquine had to be stopped for one

patient who developed prolonged QT interval.

h. Treating non-hospitalized patients with novel coronavirus disease

In a randomized placebo-controlled trial conducted by Skipper et al [35] non hospitalized adult population was enrolled with four or fewer days of novel coronavirus disease symptoms or confirmed laboratory test after being exposed to an infected patient within 14-19 days of time. A total of 423 patients were randomized to either intervention or control group in 1:1 ratio using stratified block randomization technique, and the primary outcome was hospitalization, admission to ICU or death. The results showed no significantly improved outcomes among intervention group as compared to placebo group, similarly, no change in symptoms severity was observed in two groups (p=0.117). There were 49/201 (24%) patients with ongoing symptoms in the intervention group as compared to 59/194 (30%) in the placebo group (p=0.21), and no significant difference was observed in hospitalization rate between two groups (4.9% vs 2.1%, p=0.29). Adverse reactions were more frequently reported for patients administered hydroxychloroquine (43% vs 22%, p<0.001).

I. Safety Concerns

Food and Drug Administration, United States, had issued caution against use of the antimalarial drugs, alone or in combination of azithromycin, to treat novel coronavirus disease patients due to potential association with cardiac complications.[36] Azithromycin, chloroquine, and hydroxychloroquine have established risk of prolonging the QT interval and sudden cardiac death.[37] Keeping in view the previous risk profile and current evidences, American College of Cardiology & American Heart Association published an update on arrhythmogenicity associated with co-administration of hydroxychloroquine and azithromycin and suggested a protocol for assessing QT assessment in clinical studies to ensure patient safety.[38] In a randomized, Phase IIb clinical trial conducted by Borba M et al [39] in Brazil 81 patients were enrolled and randomized into two different dosage regimens of chloroquine, a low (450mg) and a high dose (600mg). Preliminary results suggested that higher dose of chloroquine is potential risk factor for prolonged QT interval and death, with 25%

of patients randomized to high dose arm experienced cardiac toxicity. In another study reported by Lane et al [41] showed increased risk of mortality, heart failure and chest pain in patients treated with hydroxychloroquine combined with azithromycin assessed at 30th day. This study included pooled analysis of studies from various countries and a number of drug combinations were considered for their safety among novel coronavirus disease patients.

Conclusion

Despite promising in-vitro results, there is an existing controversy on safety and effectiveness of antimalarial drugs, alone or in combination, to prevent and treat novel coronavirus disease. Evidence from ongoing clinical trials is awaited to draw conclusive results.

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