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Review Article

OLD DRUG WITH NEW MILESTONE: CHLOROQUINE AND HYDROXYCHLOROQUINE IN SARS-COV-2 (COVID-19) WITH MULTIFACETED EFFECTS IN OTHER DISEASES

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ABSTRACT

Hydroxychloroquine is one of the oldest and widely used anti-malarial drug which can be beard easily with cost and well leeway, also these drugs have been greet to have efficacy in autoimmune-related diseases like rheumatoid arthritis and systemic lupus erythematosus. Hydroxychloroquine is known to be a disease-modifying antirheumatic drug, for this, it has been approved firstly in the year 1955 by the United state of food and drug administration. Hydroxychloroquine and chloroquine are recently shown several activities like glucose-lowering effects along with prophylactic use, Dyslipidemia, anticancer, anti-platelet, antithrombotic, antiviral, endothelial dysfunction. Because of the recent outbreak of world has diverted towards these molecules and initiated global clinical trials on Chloroquine and Hydroxychloroquine. So this article focused on the multifaceted effect of Hydroxychloroquine and chloroquine mainly concerning corona. Considering the anti-hyperglycemic potential, anti-inflammatory activity and, pleiotropic effects such as lipid-lowering action, anti-platelet action, antithrombotic action, endothelial dysfunctioning, orbital sarcoidosis, and nephroprotective action, HCQ may emerge as a cost-effective therapeutic option for uncontrolled diabetes patients in alone therapy or combinations. Chloroquine and Hydroxychloroquine have been proved its efficacy towards the recent spread of pandemic disease novel coronavirus.

INTRODUCTIION

Hydroxychloroquine (HCQ) is obtained from the bark of the Cinchona plant and used to treat different desperate conditions including malaria [1]. During 1950, Quinacrine which is derivative of HCQ has shown less retinal toxic effects and more positive usage than CQ, thus further HCQ was commonly used in conditions like RA and SLE. The triple-drug combination of methotrexate and sulfasalazine along with HCQ has always been preferred in RA considering its safety, tolerability, and costing [2,3].

HCQ is also beneficial to improve cardiovascular profile in RA condition since it can lead to further since RA leads to early mortality and morbidity [4]. Several previous studies have established the beneficial effect of HCQ in the treatment of diabetes mellitus [5,6,7,8]. Because of Mortality and morbidity rate due to cardiovascular risk, HCQ is elucidated to have anti-platelet and antithrombotic properties [9,10,11] So there is a strong need of safe and effective drug therapy which can perform multifaceted effects considering the outbreak of global pandemic disease. Currently, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and novel coronavirus (COVID 19) outbreak was identified and firstly reported in Wuhan city of China at

end of 2019 which further rapidly spread throughout the china and countries around the globe. The reported number says that approximately more than 1000 cases have been diagnosed with SARS COV-2 per day. Regrettably, as of now, no drugs have been approved by regulatory agencies for the treatment of SARS-CoV-2 infection. But Chloroquine is a widely used anti-malarial with Immunomodulatory effects [12,13,14,15,16] Currently several global clinical trials have been initiated to elucidate the effect of chloroquine and its category in the therapy of SARS COV-2 (COVID 19). Severe Acute Respiratory Syndrome Corona Virus- 2 (SARS COV 2).

This is the rarest pandemic disease flickered by a coronavirus which has influenced globally with more than 118,000 cases in 114 countries, and more than 4,291 peoples died, and still, thousands of the peoples have hospitalized under surveillance [17]. Coronaviruses (CoVs) are the major faction of viruses belonging to Nidovirales order, among which Coronaviridae, is also one of the family and which all are coated (enveloped), without segmentation positive RNA viruses. This virus has the largest RNA strand genome of 30 kb (approximately) with a cap, huge replicas, and ornament gene [18]. With a different group of species/living organisms, viruses have been identified by their host variety and genomic arrangements (i.e. gene sequencing). Animals like Cats, dogs, swine, cattle, etc and humans (irrespective of age category, it is much risky to all age of groups) can be prone to this coronavirus and can cause rigorous disease of respiratory and GIT system [19,20]. Even an outbreak is spread through seafood [21].

The Novel Coronavirus outbreak is identified in Wuhan, Hubei Province, China, and WHO named this virus as COVID 19. Although being a respiratory disease, it might not spread through blood transfusion [22,23]. However, there is a strong need for therapy that can be globally applicable and which will significantly reduce the influence of this virus since self precaution is not sufficient to fight against this. Hydroxychloroquine is not only an anti-malarial and DMARD drug [24] but also analyzed antiviral effect in model-based pharmacological observed drug concentration and in vitro testing preventive study (prophylactic study) suggested that it could prevent the SARS 2 and enhance viral shedding [25].

In another in vitro study, viral inhibitory action is shown by HCQ & CQ in inhibiting SARS 2 infections [26]. Previously so many cases showed the antiviral effect of Hydroxychloroquine 600 mg/day in reducing viral diseases like AIDS [27]. Ongoing Global Research of Chloroquine & Hydroxychloroquine related to COVID 19. Currently several global trials are ongoing in multiple indications (Source: www.clinicaltrials.gov & www.chictr.org.un (Chinese Clinical Trial Register)]. Among these, the prominent studies are mentioned below:

These Abbreviations used:

ADP: Adenosine Di Phosphate
AIDS: Acquired Immunodeficiency Syndrome
BID: Bis in die (twice)
COVID 19: Corona Virus Disease 19
CoVs: Corona Viruses
CQ: Chloroquine
CRP: C Reactive Protein
DMARD: Disease-Modifying Anti-rheumatic Drugs
FDC: Fixed-Dose Combination
GIT: Gastro Intestinal Track
HbA1c: Haemoglobin A1c test
HCQS: Hydroxychloroquine Sulphate
HDL: High-Density Lipoprotein
LDL: Density Lipoprotein
NA: Not available
RA: Rheumatoid Arthritis
RBC: Red Blood Corpuscles
RNA: Ribo Nucleotide
RT PCR: Real Time Polymerase Chain Reaction
SAA: Serum Amyloid A
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2
SLE: Systemic Lupus erythematosus
SOFA: Sequential Organ Failure Assessment
TC: Total Cholesterol
TTCR: Time to Clinical Recovery
USFDA: United State Food and Drug Administration

Clinical trial Reg. no	Study Design	Dosing schedule (Inventional drug)	Dosing schedule (Comparatives drug)	Primary outcome
ChiCTR2000029868	Randomized controlled, open label, Parallel, multicenter trial	Exp. Group: Oral H3333CQS tablet	Control group: Conventional treatment	Viral nucleic acid test.
ChiCTR2000029542	Prospective cohort, Non randomized control study	0.5 mg of CQ BID for 10 days	Conventional management	Viral negative-transforming time, SOFA, C-reactive protein, inflammatory cytokines
ChiCTR2000029559	Parallel, Double blind., randomized study	A. Exp. Group 1: HCQ 0.1 oral 2/ day B. Exp. Group 2: HCQ 0.1 oral 2/ day	Placebo control group: Starch pill oral 2/ day	The time when the nucleic acid of the novel coronavirus turns negative, T cell recovery time
ChiCTR2000029609	Prospective, open-label, multiple-center, Non randomized control study	1. Mild moderate CQ group: Oral CQ phosphate 2. Mild-moderate combination group: CQ phosphate plus Lopinavir/Ritonavir 3.Severe-CQ group: Oral CQ phosphate	1. Mild-moderate Lopinavir/Ritonavir group: oral Lopinavir/Ritonavir 2. Severe-Lopinavir/Ritonavir group: oral Lopinavir/Ritonavir	virus nucleic acid negative-transforming time
ChiCTR2000029740	Parallel, randomized open-label control clinical trial study	Intervention group: HCQ 0.2 twice a day (Oral)	Control Group: conventional therapy	Maximum respiratory rate, Oxygen index, Count of lymphocytes
ChiCTR2000029741	Prospective, open-label, multicenter randomized controlled clinical comparative study	Intervention group: CQ Phosphate	Control Group: Lopinavir / Ritonavir	Oxygenation index during treatment, Peripheral blood cell count (including white blood cells, lymphocytes, Neutrophils, etc.)
ChiCTR2000029761	Multicenter, randomized, open clinical, parallel study	1. Group with Low-dose of HCQ and conventional therapy 2. Group with Medium-dose of HCQ and conventional therapy 3. Group with high dose of HCQ and conventional therapy	Control Group	This study is cancelled due to lack of patients
ChiCTR2000029975	Single arm study	Experimental Group: CQ phosphate (Aerosol inhalation)	NA	Viral negative-transforming time
ChiCTR2000029803	Prospective, randomized, open-label, controlled, Parallel study	Group A 1: Small dose of HCQ Group A2: High dose of HCQ Group	B1: Small dose of Abidol HCl Group B2: High dose of Abidol HCl	Body temperature, Cough severity classification, Oxygenation index, Chest CT lesion size, Blood routine, CRP, SAA values
ChiCTR2000029826	Randomized, double-blind, parallel, controlled trial	NA	NA	Study was cancelled by investigator
ChiCTR2000029837	Interventional, randomized, double-blind, parallel, controlled trial	Two tablets of Phosphoric chloroquine BID	Two tablets of Placebo BID	Study was cancelled by investigator
ChiCTR2000029988	Parallel study	Exp. Group: CQ phosphate	Control group: No	NA
ChiCTR2000029992	Prospective, randomized, open label, Parallel, controlled trial	Group 1: 1 gm of CQ phosphate for 2 days (for the first dose) & 0.5gm dose for 12 day (from the third day) Group 2: HCQS 0.2gm BID for14 days	Routine Treatment: Recommended Treatment	NA
ChiCTR2000029899	Interventional, comparative, Parallel study	HCQS group: Day1: first dose: 6 tablets（0.1g/table, second dose: tablet of 0.1g after 6h (6 tablets) Day2: 5: 2 tablets 0.1g/table), BID	Phosphate CQ group: Day1-3:500mg BID Day 4-5:250mg BID	TTCR, Transition time of 2019-nCoV nucleic acid detection
ChiCTR2000030031	Randomized, double-blind, parallel,	Two tablets of Phosphoric CQ BID	Two tablets of Placebo	Time of conversion to be negative of novel coronavirus nucleic acid

	comparative controlled trial		BID	& remission time of fever
ChiCTR2000030054	Prospective, open label, randomized Parallel, control trial	Group 1: 0.2 gm of HCQS BID for 14 days Group 2: CQ phosphate 1 mg for 2 days (for the first dose) & 0.5gm dose for 12 day (from the third day)	Control group: Recommended treatment	Time to 2019-nCoV RT-PCR negativity in upper and lower respiratory tract specimens along with clinical recovery time
NCT04261517	Open label, Parallel Randomized study	Exp: HCQ 400 mg per day for 5 days Intervention/treatment: HCQ 400 mg per day for 5 days	No Intervention: Conventional treatments: conventional treatments without HCQ	Schedule analysis of virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions up to 7 days after randomization, The mortality rate of subjects after 14 days of randomization
NCT04303507	Randomized, double blind, Parallel preventiveclinical trial	1. A loading dose of 10 mg base/ kg followed by 155 mg daily (250mg chloroquine phosphate salt or 200mg of or HCQS) will be taken for 3 months 2. Experimental: CQ/HCQ In Europe, the participant will receive HCQ Intervention: Drug: CQ or HCQ	Placebo	Number of symptomatic COVID-19 infections, Drug exposure-protection relationship

This Table 1 based on Ongoing Global Research of Chloroquine & Hydroxychloroquine related to COVID 19 (Current status of clinical trials) HCQ: Hydroxychloroquine, CQ: Chloroquine, NA: Not available, RT PCR: Real-Time Polymerase Chain Reaction, TTCR: Time to Clinical Recovery.

PHARMACOLOGICAL EFFECT

Lowering of blood glucose level (Both prophylactic and treatment) in diabetes mellitus

The exact mechanism of lowering of blood glucose by HCQ (R & S Hydroxy chloroquine) is shown by some preclinical studies and some clinical Pharmacodynamic studies. HCQ inhibits the photolytic enzyme responsible for the degradation of insulin is explained by one of the animal studies conducted by Emami J et al. along with this further sustained availability of insulin is also increased by increasing intracellular PH [28]. Mercer E et al confirmed with a help of human Pharmacodynamic study conducted, that use of hydroxylchloroquine for around 6 weeks in overweight obese non-diabetic subjects, which concluded with a remarkable improvement in insulin sensitivity index and drift towards abridged insulin resistance and insulin secretion [29].

Pareek A *et al,* conducted the preclinical study in alloxan-induced Wistar rats model (36 rats divided into 6 groups) which has been treated with HCQ and Atorvastatin to evaluate the hyperglycaemic effect and hypothesized that anti-hyperglycaemic effects shown by combination may be due to synergistic between HCQ and Atorvastatin [30].

Lupus and Rheumatoid arthritis patients have already been shown glucose-lowering and antihyperlipidemic effects of Hydroxychloroquine [31,32]. Wasko *et al* conducted observational prospective, multi centre study in around 4905 adults in Rheumatoid arthritis patients with more than 20 years follow up (around 21.5 years). Significant preventive differences were observed such as the rate for diabetes 5.2 per 1000 patients years of observation patients with HCQ ever use ($p<0.001$) verses rate for diabetes were 8.9 per 10000 patient-years of observation for patients with never use. Further increased duration of HCQ use shown to significantly reduce the risk of diabetes. Four years' observation clarified that 77 % rate with those who never took Hydroxychloroquine reduction in diabetes with the use of HCQ compared to those who never took Hydroxychloroquine [33].

Fahimeh S *et al,* has studied the effect of Hydroxychloroquine on glucose control and insulin resistance for the pre-diabetes condition in a randomized, double-blinded, controlled trial on 39 successive patients (two groups) for 12 weeks. At the end of the study serum level of insulin significantly improved however changes in other parameters were not significantly changed [34].

Outcome of randomized, double-blind, parallel-arm (placebo vs Hydroxychloroquine 400 mg/day) trial study conducted by Wasko MCM *et al* [35] that included rotund or obese non-diabetic subjects with markers of insulin resistance. Hydroxychloroquine administration improved ß-cell function and elevated the adinopectin level (a positive change in insulin sensitivity with HCQ) after 13±1 weeks of treatment.

These metabolic effects may elucidate a lower risk of type 2 diabetes in correspondence with the treatment of Hydroxychloroquine. A retrospective cohort study conducted by Bili A *et al*, with newly diagnosed non-diabetic rheumatoid arthritis, supported the potential benefit of Hydroxychloroquine in faded the jeopardy of diabetes in rheumatoid arthritis patients (1127 adult patients) [36]. Chan YM et al contemplated cohort study in systemic lupus erythematosus patients and bring to the conclusion that HCQ is consociate in reduction with the risk of incident diabetes mellitus (dose-dependent manner) in systemic lupus erythematosus. Also, Chan YM *et al* accomplished that concomitant co-administration of HCQ decreases the high risk of diabetes caused by a high dose of Glucocorticoids [37].

In a retrospective cohort study among 1,21, 280 patients diagnosed with psoriasis or rheumatoid arthritis, adjusted risk of diabetes mellitus lowering effect for starting the therapy with HCQ compared with other DMARDs [38].

Gerstein *et al*, conducted a study in 135 obese diabetic patients to assess glucose-lowering efficacy in which HCQ for 300 mg for 18 months (two doses in a day) administered with sulfonylurea refractory type 2 diabetes patients decline to take insulin. Patients on placebo were more likely to be withdrawn from study drug because of unacceptable glycemic control than patients randomized to HCQ (P=0.0001). HCQ lowered HbA1c by an around 1.02% more than placebo. With no adverse event, the administration of HCQ reduced total cholesterol, LDL, and triglyceride levels significantly compared with placebo [39]. In a retrospective study, HQC treatment was associated with a reduction in HbA1c significantly as compared to methotrexate among diabetic patients with rheumatoid arthritis [40].

Dyslipidemia

Several studies have confirmed the association between the use of HCQ and improved lipid levels. Rahman P *et al*. suggested ricochet in cholesterol levels when HCQ was discontinued resulted from a retrospective analysis [41]. HCQ resulted in a significant decrease in low-density lipoprotein and cholesterol when a retrospective study was conducted by Morris J *et al*, in 706 RA patients [42]. In one of the Baltimore lupus cohort studies, HCQ for the prevention of hyperlipidemia, diabetes mellitus, and thrombosis was employed. Petri *M et al* run a longitudinal group study including SLE patients and showed a significant serum cholesterol-lowering effect of HCQ treatment with 200 or 400 mg daily [43]. In other Baltimore lupus cohort studies, Petri M *et al* indicated the use of Hydroxychloroquine for the prevention of hyperlipidemia, diabetes mellitus, and thrombosis [44].

Longitudinal evaluative study in 24 SLE patients conducted by E Cairoli *et al*., showed that short term use of Hydroxychloroquine can also contribute to lowering of low-density lipoprotein, total cholesterol along with reduces the cardiovascular risk [45]. Several Antidiabetic studies have been conducted along with antihyperlipidemic agents to prevent cardiovascular risk in diabetic patients. Pareek A *et al* also tested FDC of Atorvastatin and HCQ in a randomized, double-blind comparison study of 24 weeks within 328 Indian patients who have been received either Atorvastatin 10 mg or Atorvastatin 10 mg + Hydroxychloroquine 200 mg (FDC). And the main features of adding HCQ divulge significant reduction in mean LDL-C, TC, and non-HDL-C at week 24 for patients treated with FDC [30].

Anti-platelet and Anti-thrombotic

Historically Packham and Mustard *et al*, has assumed the anti-platelet effect of HCQ with combination through ADP and collagen mechanism [46]. HCQ decreases sludging of erythrocytes and inhibits platelet aggregation that would contribute to its anti-thrombotic activity [47]. Before the use of heparin, in 1970s the famous orthopedician Sir John Charnley found a significant reduction in the incidence of postoperative pulmonary embolism in patients receiving HCQ 600 to 1600 mg daily, beginning the day before surgery and continuing till discharge [48,49]. An article published by Loudon JR *et al*, documents the usefulness of HCQ as a prophylactic agent against thromboembolism after total hip replacement. It mentions that HCQ causes a reduction in red blood cell aggregation and experimentally reduces the size of thrombus [50]. A pre-clinical study conducted by Edwards MH *et al*, demonstrated that HCQ significantly diminished both thrombus size and the total time of thrombus formation in mice [51].

Recently, a human Pharmacodynamic study was conducted on healthy volunteers by Achuthan S *et al*. The results of the study showed that when arachidonic acid is used as an agonist, aspirin + HCQ (97%) leads to significantly ($p<0.001$) more inhibition of platelet aggregation might be through arachidonic acid pathway through downstream to thromboxane A2 production as compared to aspirin alone (60%). A combination of HCQ with aspirin, it also enhances the anti-platelet effect of aspirin which further reduces fibrinogen levels [52]. Long years ago, 22 rheumatoid arthritis patients had been shown retinal veins sludging effect (intravascular aggregation of RBC), but when treated with

Hydroxychloroquine sulfate for the period of 3 months, eternal fade has been observed for slugging recorded in 20 (within 2-8 weeks) [53].

Lupus Nephritis

Guidance document of the American College of Rheumatology (2012) has recommended treatment with a background of Hydroxychloroquine for patients of SLE patients with nephritis [54]. Considering the protective consequence on survival, the recommendation of use for HCQ has been given in patients with SLE [55]. Data from LUMINA, a multiethnic U.S. Cohort, demonstrated that the use of HCQ retards renal damage in lupus nephritis patients [56].

Endothelial dysfunction

The effect of Hydroxychloroquine has been studied in pregnant women for evaluating endothelial dysfunctioning which could be aroused due to Preeclampsia condition (by collecting sera of pregnant women). It might elucidate that definitely HCQ would have been added endothelial protective outcome significantly when added as an adjuvant therapy as a safety parameter [57] which supported findings of Gomez-Guzman and colleagues about the endothelial protective function of HCQ studied on an SLE mice mode [58].

Anticancer effect

Chloroquine and Hydroxychloroquine have been comprehensively studied both *in vitro* and *in vivo* in various types of cancers [59]. Also, several studies indicated the synergistic effect of HCQ in chemotherapy on many tumours identified in ongoing clinical trials and further inhibitory effect on autophagy too [60]. Lin Q. L *et al* concluded that HCQ when collectively treated along with Bevacizumab in Glioblastoma, further it helps to inhibit autophagy, however, further investigation or trials may need to identify the exact mechanism of action [61]. HCQ also plays a major role in lung cancer through elevating drug release from the lysosome into the nucleus when given in combination and in single mono therapy treatment, induces CD8+ cell immunity which further exerts antitumor/anticancer effects [62]. So conclusively HCQ might be promising drug treatment in cancer therapy too.

Orbital Sarcoidosis

Although HCQ shows Humphrey visual field by HCQ toxicity [63] it can also damage the retina of the eyes, which may cause vision impairment, or central vision loss due to Hydroxychloroquine retinopathy (Cystoid macular Oedema) there is some evidence indicating contributing work of HCQ in orbital sera.[64-65] A case study of Orbital Sarcoidosis has been studied which analyzed that oral corticosteroids did not respond to therapy but successful recovery by Hydroxychloroquine has been reported on the same patients [66].

CONCLUSION

Hydroxychloroquine or related antimalarial have shown a wide range of other indications as conditions including diabetes mellitus, malignancy, Dyslipidemia, reducing thrombosis, and many more pleiotropic effects in alone or combination therapy which further helps in reducing cardiovascular events. Considering the global prevalence of diabetes patients and related mortality rates, HCQ has promised hypoglycemic effects through novel mechanisms of action for reducing blood glucose levels. Even it has shown prophylactic blood sugar lowering effect when given in RA or SLE patients. Some studies have revealed antiviral effects also. Considering the current pandemic disease outbreak of COVID 19, USFDA has not approved any therapy for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) but several global studies have been under clinical trials because of reducing viral load. So Hydroxychloroquine has come out as a novel milestone with multifaceted uses, long term experience of use in other diseases, cost-effectiveness, and global easy availability. It will be proved as a magic remedy shortly since HCQ and CQ have obtained unprecedented attention as potential therapeutic agents against COVID 19.

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