Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Life Sciences 254 (2020) 117775

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

A systematic review on use of aminoquinolines for the therapeutic management of COVID-19: Efficacy, safety and clinical trials

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ARTICLE INFO

Keywords:
COVID-19
Aminoquinolines
Chloroquine
Hydroxychloroquine
Safety
Anti-viral mechanism

ABSTRACT

Recent global outbreak of the pandemic caused by coronavirus (COVID-19) emphasizes the urgent need for novel antiviral therapeutics. It can be supplemented by utilization of efficient and validated drug discovery approaches such as drug repurposing/repositioning. The well reported and clinically used anti-malarial aminoquinoline drugs (chloroquine and hydroxychloroquine) have shown potential to be repurposed to control the present pandemic by inhibition of COVID-19. The review elaborates the mechanism of action, safety (side effects, adverse effects, toxicity) and details of clinical trials for chloroquine and hydroxychloroquine to benefit the clinicians, medicinal chemist, pharmacologist actively involved in controlling the pandemic and to provide therapeutics for the treatment of COVID-19 infection.

1. Introduction

Coronavirus disease 2019 (COVID-19 or 2019-nCoV) continues to spread all over the world. The infection has spread over to 213 countries (23,14,621 confirmed cases and 157,847 confirmed deaths) since its outbreak in November 2019 in China (as on 20 April 2020) (Fig. 1) [1–5]. The worldwide pandemic and uncontrolled scenario demands use of efficient drug discovery approaches such as computational chemistry and biology, high throughput screening (HTS), artificial intelligence (AI), drug repurposing etc. for effective control [6–12]. Among these approaches, drug repurposing (or drug repositioning) has been implemented for anti-viral drug discovery (Fig. 2) [13–90]. It has helped to conduct in vitro studies and clinical trials for a dozen of chemical molecules and evaluate their anti-viral efficacy against COVID-19 (Table 1) [91–93].

One of the examples of successful application of drug discovery approaches is drug repurposing of the traditional anti-malarial drugs aminoquinolines namely, chloroquine (CQ) and hydroxychloroquine (HCQ) (Fig. 3). Both are synthetic anti-malarial drugs with rapid absorption. Chloroquine and hydroxychloroquine are water soluble; the latter is more soluble due to presence of hydroxyl group and possesses plasma half-life of 900 h and 1300 h, respectively [94]. During chronic treatment the drugs gets accumulated in tissues [95]. The selected anti-malarial drugs have been used for last 70 years. They are economic, have proven safety profile and are categorized as essential medicines by World Health Organization (WHO) [96]. Aminoquinolines have effectively reduced viral replication in Zika virus, Chikungunya virus, SARS-associated coronavirus (CoV) and MERS-CoV [97–100]. Chloroquine and hydroxychloroquine has shown inhibition of SARS-CoV-2 replication [101]. Clinical trials have demonstrated the effective role of chloroquine phosphate (dose 500 mg/day) against COVID-19 [102]. The N-hydroxyethyl substituted derivative of chloroquine, hydroxychloroquine is less toxic, more soluble and has similar activity towards COVID-19 inhibition. There is continuous requirement to explore the molecular mechanism towards underlying antiviral action and clinical benefits of aminoquinolines and the toxicity profile. The detailed outcomes will help to design the randomized clinical trials [95,103–107]. The present manuscript provides a systematic review of mechanism of action, efficacy, and safety of chloroquine and hydroxychloroquine which are being used as therapeutic measure to cure COVID-19 infection.

2. Mechanism of action

For viral replication, a stable acidic pH of endosomes, lysosomes, Golgi complex of host is required. The bioaccumulation properties of both the selected aimnoquinolines explain the antiviral mechanism of their action [108]. Chloroquine increases the pH of intracellular vacuoles. In lysosomes, it alters the catalysis of the protein degradation pathways through acidic hydrolases. It also alters endosomal

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https://doi.org/10.1016/j.lfs.2020.117775
Received 21 April 2020; Accepted 7 May 2020
Available online 11 May 2020
0024-3205/

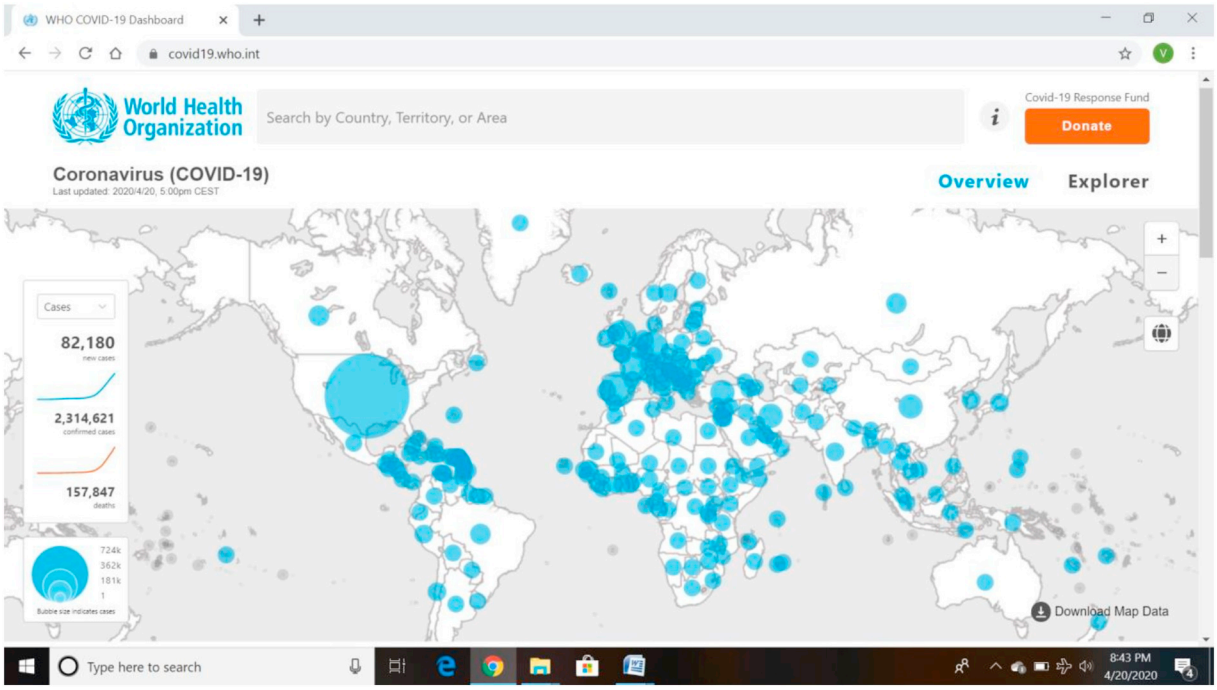

Fig. 1. Global COVID-19 spread showing number of confirmed cases (blue color) (as on 20 April 2020, 8:43 pm). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

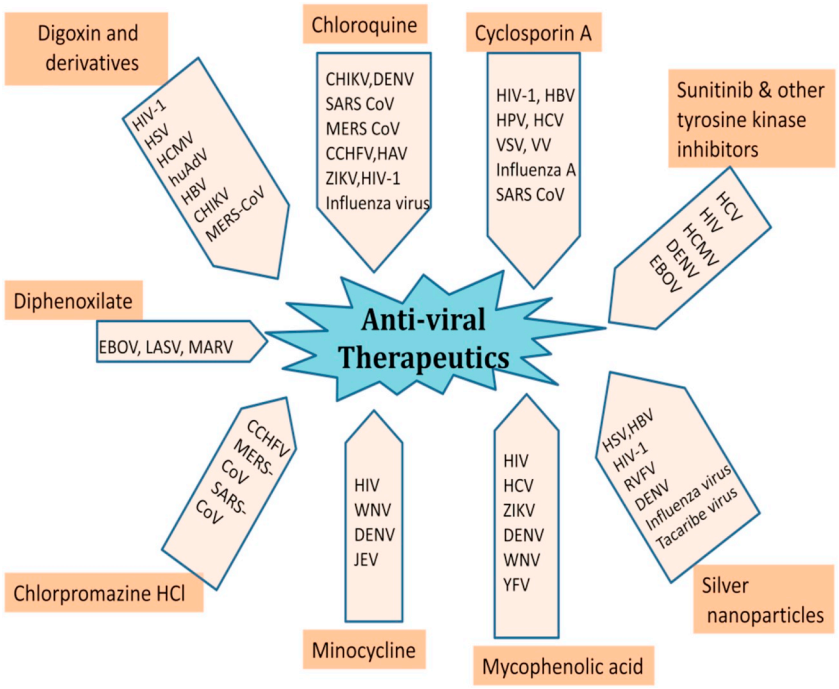

Fig. 2. Examples of drug repurposing for viral inhibition [13–90].

macromolecule synthesis and in Golgi apparatus it affects post-translational modifications. The antirheumatic response is produced by interfering with the immunological process which occurs in macrophages and antigen-presenting cells [109]. The mechanism involved for antiviral action is similar. It decreases the pH and interferes with the viral fusion process. In coronavirus, chloroquine binds to the cellular receptors and changes the glycosylation [110]. Chloroquine possesses selective and reversible immunomodulatory effect through its action on human $CD4^+$ T-cells which is mediated by inhibition of JNK catalytic activity [109].

Hydroxychloroquine exerts similar mechanism of antiviral action and some of the key features are – i) increases the pH, ii) modulation of activated immune cells, iii) downregulation of expression of Toll-like receptors (TLR), iv) downregulation of TLR-mediated signal transduction; v) interleukin-6 formation drops; vi) reduces the formation of pro-inflammatory cytokines and other mediators to control inflammation [105,110,111].

The recent literature review helps to propose the possible mechanism of action of chloroquine and hydroxychloroquine through three ways i.e. immunomodulatory effect, zinc ionophore effect and

Table 1
Clinical trials details for studies going on for use of chloroquine (CQ) and hydroxychloroquine (HCQ) in the treatment of COVID-19 infection [5].

ID	Country	Number of patients	Intervention
NCT04303507	USA	40,000	Drug: CQ or HCQ A loading dose of 10 mg base/kg followed by 155 mg daily (250 mg CQ phosphate salt or 200 mg of or HCQ sulphate) will be taken for 3 months drug: CQ or HCQ A loading dose of 10 mg base/kg followed by 155 mg daily (250 mg CQ phosphate salt or 200 mg of or HCQ sulphate) will be taken for 3 months
NCT04335084	ProgenBiome, US	600	HCQ, vitamin C, vitamin D and zinc (through dietary supplement)
NCT04330586	–	141	Ciclesonide metered dose inhaler; HCQ
NCT04342169	University of Utah, US	400	HCQ, placebo oral tablet
NCT04328012	USA	4000	Lopinavir, HCQ sulfate, losartan, placebos
NCT04333732	Washington University School of Medicine (USA, Australia, Canada, Ireland, South Africa, UK)	55,000	Low dose: CQ/HCQ, mid dose CQ/HCQ, high dose CQ/HCQ, placebo
NCT04343677	11 MDG, US	1450	HCQ, dietary supplement, placebo
NCT04334967	Providence Medical Group Infectious Disease, US	1250	HCQ, dietary supplement of vitamin C
NCT04333225	Baylor Health Care System, US	360	HCQ
NCT04328961	University of Washington, US	2000	HCQ sulfate, ascorbic acid
NCT04318444	Columbia University Irving Medical Centre, US	1600	HCQ, placebo oral tablet
NCT04329832	Intermountain Health Care Inc. US	300	HCQ, azithromycin
NCT04334382	Intermountain Health Care Inc. US	1550	HCQ, azithromycin
NCT04332991	Massachusetts General Hospital, US	510	HCQ, placebo
NCT04328467	University of Minnoesota, US	3500	HCQ, placebo
NCT04336332	Rutgers, The State University of New Jersey, US	160	Combination product HCQ sulfate + azithromycin; drug: HCQ sulfate
ACTRN12620000447954	Australia	150	HCQ is not considered a trial intervention
ACTRN12620000447987	Australia	680	CQ phosphate (tablet, 500 mg, oral) for 10 week trial period followed with plasma CQ levels
NCT04328493	Vietnam	240	CQ will be administered orally, as tablets. For unconscious patients CQ can be crushed and administered as a suspension via a nasogastric tube. A loading dose of 1200 mg CQ phosphate base, administered with food where possible, is given on the first 24 h after randomization. Following, patients will receive a dose of CQ phosphate base of 300 mg once daily for 9 days (unless they are <60 kg, when the dose will be reduced following its pharmacokinetic properties). The total duration of treatment with Chloroquine will be 10 days
NCT04342650	Brazil	210	CQ diphosphate, placebo oral tablet
NCT04329572	Azidus Brasil	400	HCQ sulfate, azithromycin tablets
NCT04321278	Hospital Israelita Albert Einstein, Brazil	440	HCQ + azithromycin, HCQ
NCT04322123	Hospital do Coracao. Brazil	630	HCQ oral product, HCQ _ azithromycin
NCT04333628	HaEmek Medical Center, Israel	210	CQ, standard care
NCT04303507	–	40,000	CQ or HCQ, placebo
EUCTR2020-001345-38-GR	Uni-Pharma Kleon Tsetis Pharmaceutical Lab SA, Greece	60	UNIKINON tablets 200 mg, CQ phosphate
NCT04321993	Canada	1000	Lopinavir/ritonavir, HCQ sulfate, baricitinib, sarilumab
NCT04324463	Population Health Research Institute, Canada	1500	Azithromycin, HCQ
NCT04329611	University of Calgary, Canada	1660	HCQ
NL8490	the Netherlands	950	Standard supportive care, CQ arm (loading dose 600 mg as CQ base followed by 300 mg 12 h later followed by 300 mg twice a day; total treatment duration: 5 days); HCQ arm (loading dose 400 mg twice daily followed by 200 mg twice a day; total treatment duration 5 days); no antiviral treatment arm
NCT04322396	Denmark	226	Azithromycin, HCQ, placebo oral tablet
NCT04334928	Plan Nacional sobre el Side, Spain	4000	Drug: emitricitabine/tenofovir disoproxil, drug: HCQ, drug: placebo: emtricitabine/tenofovir disoproxil placebo; drug: placebo: HCQ
EUCTR2020-001385-11-ES	Spain	4000	HCQ
EUCTR2020-001565-37-ES	ISGlobal, Spain	440	HCQ sulfate, placebo (oral use)
EUCTR2020-001421-31-ES	Delos Clinical, Spain	1530	HCQ sulfate
NCT04332094	Spain	276	Tocilizumab, HCQ, azithromycin
NCT04331834	Barcelona Institute for Global Health, Spain	440	HCQ, placebos
EUCTR2020-001366-11-ES	FIB-HCSC, Spain	1,00,000	Remedesivir, CQ, HCQ sulfate, lopinavir/ritonavir, interferon b 1A
IRCT20100228003449N29	Iran	50	HCQ 400 mg single dose + Oseltamivir 75 mg twice daily + lopinavir/ritonavir 200/50 mg two tablets twice daily for 5 days, sofosbuvir/ledipsavir 400/100 mg daily for 10 days,

(*continued on next page*)

Table 1 (*continued*)

ID	Country	Number of patients	Intervention
IRCT20100228003449N28	Tehran University of Medical Sciences, Iran	30	Intervention 1: concomitant with the national corona treatment recommendation (HCQ + Oseltamivir + Lopinavir/ritonavir), patients will receive interferon B, sub type 1b with dose of 250 μg subcutaneously every other day for 14 days. Intervention 2: control group will receive the national corona treatment recommendation (HCQ + oseltamivir + lopinavir/ritonavir) for at least 5 days
IRCT20100228003449N29	Tehran University of Medical Sciences, Iran	50	Intervention group: tab HCQ 400 mg single dose + cap oseltamivir 75 mg, twice daily + tab lopinavir/ritonavir 200/50 mg two tablets twice daily for at least 5 days and one tablet of Sofosbuvir/ledipasvir 400/100 mg daily for 10 days. Intervention 2 (control group): tab HCQ 400 mg single dose + cap oseltamivir 75 mg, twice daily + tab lopinavir/ritonavir 200/50 mg two tablets twice daily for at least 5 days
NCT04331470	Iran	30	
IRCT20151227025726N12	Shahid Beheshti Unmversity of Medical Sciences, Iran	20	Tab HCQ 400 mg P.O. twice daily for 5 days + tab oseltamivir 75 mg P.O. twice daily for 5 days + tab lopinavir/ritonavir 200/50 mg P.O. two tablets twice daily for 5 days + interferon beta-1a 44 mg every other day S.C. for 10 days
IRCT20100228003449N27	Tehran University of Medical Sciences, Iran	30	Intervention group 1: concomitant with the national corona treatment recommendation (HCQ + oseltamivir + lopinavir/ritonavir), patients will receive Interferon beta-1b with dose of 250 μg subcutaneously every other day for 14 days Intervention 2 (control group): control group will receive the national corona treatment recommendation (HCQ + oseltamivir + lopinavir/ritonavir) for at least 5 days
NCT04343768	Shahid Beheshti University of Medical Sciences	60	HCQ, lopinavir/ritonavir, interferon beta-1A, interferon Beta-1B
NCT04343092	–	50	Ivermectine, HCQ sulfate, placebos
NCT04318015	National Institute of Respiratory Diseases-Mexico	400	HCQ
NCT04340349	Mexico	100	HCQ sulfate, bromhexine (8 mg)
NCT04342221	University Hospital Tubingen, Germany	220	HCQ sulfate, placebo
NCT04340544	Germany	2700	HCQ, placebo
EUCTR2020-000936-23-FR	INSERM, France, Belgium, Luxembourg, Netherlands, Germany, UK, Spain	3100	Lopinavir/ritonavir, HCQ
EUCTR2020-001010-38-NO	Akershus University Hospital, Norway	200	HCQ sulfate
NCT04316377	Akershus University Hospital, Norway	202	HCQ sulfate
ACTRN12620000457943	New Zealand	70	Oral administration of HCQ capsules for 5 days. Day 1- 800 mg (4 capsules) HCQ stat day 2 to 5- 400 mg (2 capsules)
NCT04323631	Rambam MC	1116	HCQ, control group will not receive HCQ
NCT04333654	Sanofi – US, France	210	HCQ SAR321068, placebo
EUCTR2020-001281-11-FR	URCIP-CHU Saint Etienne, France	50	HCQ sulfate
EUCTR2020-001435-27-FR	Centre Hospitalier Universitaire de Bordeaux, Etablissement Public, France	1057	HCQ (200 mg), imatinib (400 mg), favipiravir
EUCTR2020-001281-11-FR	France	50	HCQ
NCT04315948	Hospital Civils de Lyon, France	3100	Remdesivir, lopinavir/ritonavir, interferon beta 1A, HCQ, standard of care
NCT04325893	France, Monaco	1300	HCQ, placebo
NCT04315896	National Institute of Respiratory Diseases, Mexico	500	HCQ, placebo oral tablet
NCT04318015	National Institute of Respiratory Diseases, Mexico	400	HCQ, placebo oral tablet
NCT04341493	Hospital Materno-Perinatal, Mexico	86	Nitazoxanide (500 mg), HCQ
JPRN-jRCTs031190227	Gunma University Hospital, Japan	50	Lopinavir, ritonavir, HCQ with or without oseltamivir (oral)
NCT04328272	Khyber Medical University, Peshawar, Pakistan	75	Drug: HCQ (200 mg oral tablet), drug: azithromycin (500 mg oral tablet), dietary supplement: glucose tablet
NCT04338698	University of Health Sciences, Lahore	500	HCQ, oseltamivir, azithromycin
ChiCTR2000031454	The Fifth Affiliated Hospital of Sun Yat-Sen University, China	Experimental group: 28; Control group: 28	Experimental group: rabeprazole + CQ Control group: lopinavir + rabeprazole
ChiCTR2000030417	Harbin Peiyou Jiandi Biotechnology Co Ltd., China	Experimental group: 15; Control group: 15	Experimental group: combined standard therapy of CQ phosphate aerosol inhalation solution Control group: water for injection atomization inhalation combined with standard therapy
ChiCTR2000030054	Zhongshan Hospital Affiliated to Xiamen University, China	HCQ sulfate group: 40 CQ Phosphate Group: 40 Control group: 20	HCQ sulphate group: HCQ sulfate 0.2 g twice daily for 14 days CQ phosphate group: day 1 and 2 – CQ phosphate 1 g; day 3 to 12 – CQ phosphate 0.5 g Control group: recommended treatment plan for novel coronavirus pneumonia diagnosis and treatment plan
ChiCTR2000030031	The Sixth Affiliated Hospital of Guangzhou Medical University, China	Phosphoric chloroquine: 80; Placebo: 40	Phosphoric chloroquine: two tablets twice daily + recommended therapy Placebo: 2 tablets placebo twice daily + recommended therapy

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Table 1 (*continued*)

ID	Country	Number of patients	Intervention
ChiCTR2000029992	Zhongshan Hospital Affiliated to Xiamen University, China	CQ phosphate group: 40 HCQ sulfate group: 40 Routine treatment group: 20	CQ phosphate group: Day 1 and 2 – CQ phosphate 1 g Day 3 to 12 – CQ phosphate 0.5 g HCQ sulfate group: HCQ sulfate 0.2 g twice daily for 14 days Routine treatment group: recommended treatment plan for novel coronavirus pneumonia severe and critical cases
ChiCTR2000029988	Zhongnan Hospital of Wuhan University, China	Experimental group: 40; Control group: 40	Experimental group: CQ phosphate Control group: no
ChiCTR2000029935	HwaMei Hospital, University of Chinese Academy of Sciences, China	Case series: 100	Conventional treatment combined with CQ phosphate
ChiCTR2000029899	Peking University Third Hospital, China	HCQ sulfate: 50; CQ phosphate: 50	HCQ sulfate: day 1- first dose of 6 tablets (0.1 g/tablet); second dose after 6 h of 6 tablets (0.1 g/tablet) Day 2 to 5- two tablets (0.1 g/tablet) twice daily CQ phosphate: day 1 to 3–500 mg twice daily; day 4 to 5–250 mg twice daily
ChiCTR2000029898	Peking University Third Hospital, China	HCQ sulfate: 50; CQ phosphate: 50	HCQ sulfate: day 1- first dose of 6 tablets (0.1 g/tablet); second dose after 6 h of 6 tablets (0.1 g/tablet) Day 2 to 5- two tablets (0.1 g/tablet) twice daily CQ phosphate: day 1 to 3–500 mg twice daily; day 4 to 5–250 mg twice daily
ChiCTR2000029868	Ruijin Hospital, Shanghai Jiaotong University School of Medicine, China	Experimental group: 180; Control group: 180	Experimental group: HCQ sulfate oral tablets; Control group: conventional treatment meet the Guideline
ChiCTR2000029837	Jingzhou Central Hospital, China	Phosphoric chloroquine: 80; Placebo: 40	Phosphoric chloroquine: 2 tablets twice daily + recommended therapy; Placebo: 2 tablets twice daily + recommended therapy
ChiCTR2000029826	Jinhzhou Central Hospital, China	Phosphoric chloroquine: 30; Placebo: 15	Phosophoric chloroquine: two tablets twice daily + recommended therapy Placebo: 2 tablets twice daily
ChiCTR2000029803	Renmin Hospital of Wuhan University, China	A1:80; A2:80; B1:80; B2:80	A1: HCQ, small dose A2: HCQ, high dose B1: abidol hydrochloride, small dose B2: abidol hydrochloride, high dose
ChiCTR2000030987	Beijing Chao-yang Hospital, China	Experimental group 1: 50; Experimental group 2: 50; Control group: 50	Experimental group 1: oral trial drug favipiravir tablet + CQ phosphate tablet Experimental group 2: oral trial drug favipiravir tablet Control group: oral placebo treatment
ChiCTR2000029762	The First affiliated Hospital of Chongqing Medical University, China	Experimental group: 30; Control group: 30	Experimental group: conventional treatment and HCQ Control group: conventional treatment
ChiCTR2000029760	Chongqing Medical University, China	Experimental group: 120; Control group: 120	Experimental group: HCQ Control group: lopinavir/ritonavir
ChiCTR2000029761	The First affiliated Hospital of Chongqing Medical University, China	Low-dose group: 60; Medium-dose group: 60; High-dose group: 60; Control group: 60	Low-dose group: HCQ low dose + conventional therapy Medium-dose group: HCQ medium dose + Conventional therapy High-dose group: HCQ high dose + conventional therapy Control group: conventional therapy
ChiCTR2000029741	The Fifth Affiliated Hospital Sun Yat-Sen University, China	Experimental group: 56; Control group: 56	Experimental group: CQ phosphate; control group: lopinavir/ritonavir
ChiCTR2000029740	The First Hospital of Peking University, China	HCQ group: 54; Control group: 24	HCQ group: Oral intake HCQ 0.2 twice a day; Control group: conventional therapy
ChiCTR2000030718	Zhongnan Hospital of Wuhan University, China	Experimental group: 40; Control group: 40	Experimental group: CQ phosphate Control group: none
ChiCTR2000029975	China	10	CQ phosphate dissolved in 5 ml of normal saline, q 12 h, inhaled by atomization for one week
ChiCTR2000029939	China	100	CQ phosphate, Standard treatment
ChiCTR2000029609	China	205	Mild-moderate CQ group: oral CQ phosphate; Mild-moderate combination group: CQ phosphate plus lopinavir/ritonavir; severe CQ group: oral CQ phosphate
ChiCTR2000029559	China	300	Group 1: HCQ 0.1 g oral twice a day Group 2: HCQ 0.2 g oral twice daily
ChiCTR2000029542	China	20	Oral CQ 0.5 g twice daily for 10 days
ChiCTR2000029826	China	45	Two tablets CQ phosphate twice daily Two tablets placebo twice daily
ChiCTR2000031204	Beijing Institute of Pharmacology and Toxicology, China	Treatment group: 150 Control group: 150	Treatment group: oral CQ phosphate tablets Control group: oral placebo group
NCT04342156	Tan Tock Seng Hospital	3000	HCQ sulfate 200 mg tablet
NCT04261517	China	30	HCQ
NCT04319900	China	150	Favipiravir tablets + CQ phosphate tablets, favipiravir tablets, placebo
NCT04307693	Korea	150	Lopinavir/ritonavir, HCQ sulfate
NCT04332835	Universidad del Rosario, Cambodia	80	Plasma, HCQ, azithromycin
NCT04338906	–	334	Camostat mesilate, placebo, HCQ
NCT04336748	–	440	HCQ

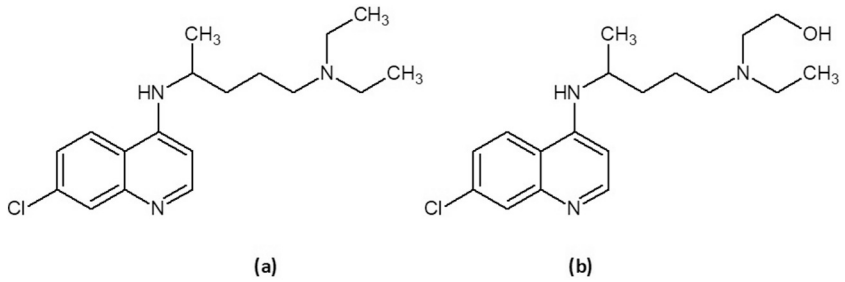

Fig. 3. Chemical structures of (a) Chloroquine and (b) Hydroxychloroquine.

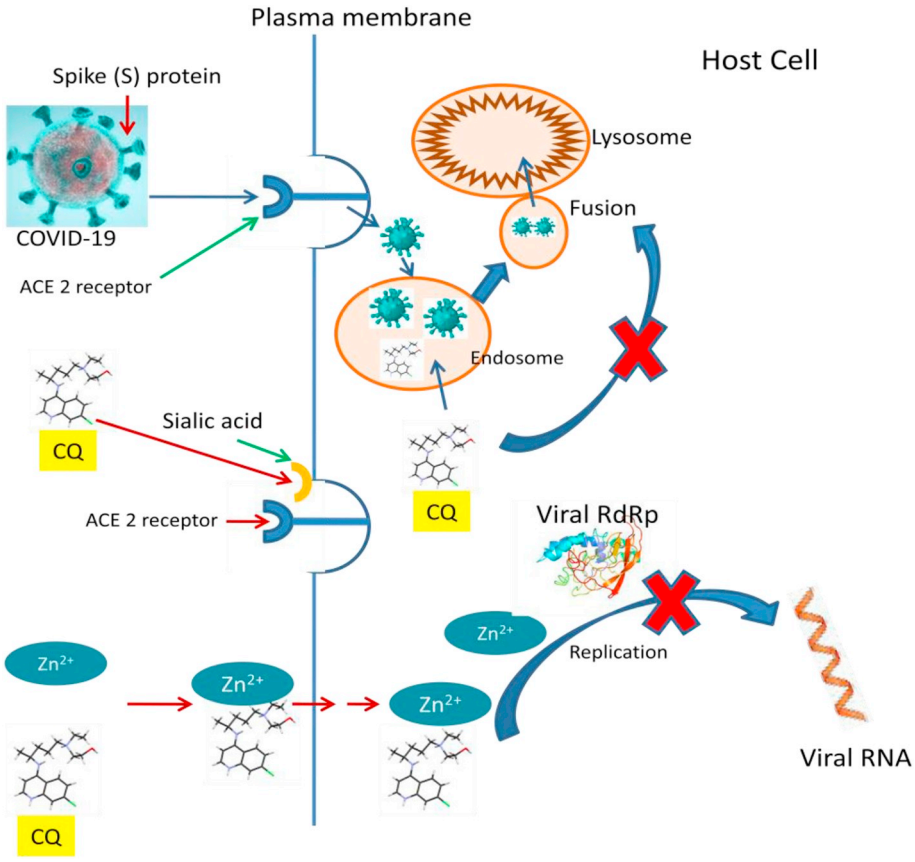

Fig. 4. Proposed mechanism of action for aminoquinolines (CQ: Chloroquine; RdRp: RNA dependent RNA polymerase; Green color arrow: names; Red color arrow: Zn2+ ionophore action of CQ; Blue color arrow: COVID-19 entry into host cell, endosome and lysosome; X: Site of action for CQ). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

binding with Sialic acid [112–114]. The three mechanisms are illustrated in Fig. 4.

3. Chloroquine vs. hydroxychloroquine

When compared for pharmacological profile, chloroquine and hydroxychloroquine possess equivalent anti-malarial activity. The latter is preferred due to lower ocular toxicity [115]. Theoretically, the antiviral activity for chloroqunie and hydroxychloroquine are similar but the reported clinical details for chloroquine are more in number [116]. Use of chloroquine is less due to some associated adverse effects and lack of availability in some countries. In patients with COVID-19 infection hydroxychloroquine is preferred as chloroquine when used in combination with lopinavir or ritonavir shows prolongation of the QT interval. Some of the other antiviral therapeutics that does not interfere with hydroxychloroquine is oseltamivir, lopinavir/ritonavir, robavirin, interferons, and immunoglobulins (intravenous) [117].

4. Safety and adverse effects

The toxicological properties reported with use of chloroquine and hydroxychloroquine are retinopathy, neuromyopathy and cardiomyopathy. Both these drugs possess affinity for melanin and affect the macular cones. The phagocytic activity of lysosomes is declined on the photoreceptors and they migrate towards central and peripheral regions as well as induces epithelial atrophy and irreversible alterations in photoreceptors [106]. In the lysosomes, hydroxychloroquine is protonated and accumulated due to its basic nature. It inhibits the activity of lysosomal phospholipases causing vacuolization of cardiac and skeletal muscle cells [118]. Prolong use of hydroxychloroquine produces – i) toxicity to retina tissue which may lead to unrepirable retinopathy [119,120]; ii) Cardiotoxicity and CNS toxicity with neuromyopathy symptoms and alterations in gastrointestinal tract [121]; toxicity to liver cells (genetic material) [122]; and genotoxicity [123,124]. Studies have shown substantial increase in retinal toxicity with chronic treatment based on the hypothesis of bioaccumulation [125]. Some investigators report $<2\%$ incidences of retinopathy and more common in Asian patients [126,127]. Some studies failed to report cardiac

complications and neuromyopathy and may be rare after long-term treatment [128,129]. The monitoring of side effects need to be continued even after discontinuation of treatment due to prolong half-life of chloroquine and hydroxychloroquine. The side effects (keratopathy, maculopathy) may be delayed. The current anti-COVID-19 therapeutic regimen suggests longer duration of treatment with chloroquine than that as anti-malarial drug. Thus close monitoring of the adverse reactions, pharmacological effects, poisoning and toxicological mechanisms to provide help to the worldwide clinical work [110].

Consideration of clinical outcomes is essential to be monitored to design safe and effective protocol with prevention of toxicological effects for therapeutic use of the antiviral aminoquinolines (chloroquine and hydroxychloroquine).

5. Outcomes of in vivo, in vitro studies and clinical trials

WHO has framed a collective protocol to conduct randomized clinical trials for investigating the clinical role and safety of therapeutics for the treatment of COVID-19 infection [130]. As on 14 April 2020, approximately 961 clinical trials which are carrying on worldwide have been reported to WHO. The essential ethical requirement is use of chloroquine in COVID-19 patients with ethical trial approval or off-label. Timely availability of the clinical outputs to the biomedical fraternity is important considering the evolving outbreak and growing number of COVID-19 infected patients with availability of any specific licensed drug. The use of chloroquine in the treatment of COVID-19 infection is considered by WHO as experimental. In this regard use of chloroquine is associated with various concerns such as patient safety, close monitoring of drug use, etc. The repurposing of the anti-malarial drugs need to follow ethical approaches and may raise concern about shortage of such drugs. The outcomes of some of the reported in vivo, in vitro and clinical studies carried globally have been documented here one by one. Approximately 100 clinical trials are in recruiting or pending approval and are ongoing at single or multiples centers with satisfactory primary outcomes but final outcomes/results are pending. These are summarized in Table 1 for ease of access to medical fraternity.

- In vitro study of chloroquine were performed in Vero E6 cells infected with SARS-CoV with a multiplicity of infection (0.05) demonstrated effective reduction of viral replication (EC_{90} = 6.90 μM). The antiviral effects are reproducible with standard dose with favorable tissue and lung penetration. The proposed mechanism of viral inhibition involves increased pH in endosomes, altered glycosylation of SARS-CoV cellular receptor and the synergistic action of immunomodulation properties [131].
- The Department of Science and Technology (Guangdong Province and Health Commission of Guangdong Province) reported a multicentric collaborative in vitro and clinical study, use of chloroquine phosphate (dose 500 mg twice a day for 10 days) in mild, moderate and severe SARS-CoV-2 pneumonia [132]. The study included some advisories to monitor for history of drug contraindication, blood testing for anemia, thrombocytopenia or leucopenia, serum electrolyte disturbances, tests for hepatic and renal functioning, routine electrocardiography and monitoring for visual and mental disturbances. Concurrent administration of some drugs should avoided including drugs which can prolong QT interval (examples: quinolones, macrolides, ondansetron), anti-arrhythmic, anti-depressant and antipsychotic drugs.
- The Italian Society of Infectious and Tropical disease, Lombardy section suggests administration of chloroquine (500 mg, twice a day) or hydroxychloroquine (200 mg per day for 10 days) (5 to 20 days treatment depending on clinical severity) [133].
- Another guideline as documented by the Dutch Center of Disease Control (CDC) recommended use of chloroquine to treat severe infections with requirement of oxygen therapy and optimal supportive care [134]. The recommended dose for chloroquine base is 600 mg followed by 300 mg after 12 h (on day 1) and 300 mg twice a day (for 2–5 days) and discontinuation of the treatment at day 5 to reduce the side effects (30 h half-life of chloroquine) (500 mg of chloroquine phosphate = 300 mg of chloroquine base).
- In China, more than two dozen clinical trials have been carried out for evaluating efficacy various anti-viral drugs in different disease severity to investigate dose and duration of treatment. The studies have been coordinated by the Chinese authorities through a prescribed regulating guideline [135]. These trials are the first to report the characteristics and management of COVID-19 infected patients but no details on use of chloroquine [136–140].

6. Conclusion

For therapeutic use of aminoquinolines (chloroquine and hydroxychoroquine) the important aspects are – i) it will be administered to millions of infected patients with COVID-19, ii) It will be administered to medical workers as preventive measure, iii) during acute approach against COVID-19 higher dose will be administered as compared to use during the treatment of chronic rheumatic diseases [141]. Following points can be concluded and to be considered during the use of aminoquinolines (chloroquine and hydroxychloroquine) for the treatment of COVID-19 infection –

i) History of previous or ongoing use of chloroquine and hydroxychloroquine in malaria, amebiasis, rheumatoid arthritis, and systemic lupus;
ii) Higher risk of development of retinopathy in Asian patients;
iii) Periodical monitoring of patients with vision problems, cardiovascular problems;
iv) To measure central and peripheral visual acuity;
v) Drug interaction with Kaolin clay and antacids reduces antiviral and anti-inflammatory action;
vi) Regular monitoring for symptoms like ocular pruritus and cardiac arrhythmias;
vii) Aminoquinolines decreases activity of immunosupressants and antibiotics;
viii) Other aminoquinoline analog, Mefloquine is associated with increased risk of convulsion;
ix) The toxicity is associated with the dose calculated by real weight and therefore dose should be suitable for patients with potential high risk of adverse effects. Cumulative dose >203 mg/kg body weight/day is under high risk category. [142].

In the absence of sufficient clinical data, detailed information on safety, adverse effects, dose of aminoquinolines (chloroquine and hydroxychloroquine), etc. should be made available among health professionals who will dissipate it among patients. The successful application of available resources needs to be grounded in practices to minimize risk of rigorous screening and dose calculation.

Acknowledgment

Authors acknowledge the resources provided by KIET Group of Institutions (Delhi-NCR), Lala Lajpat Rai Memorial Medical College (Meerut) and Dr. A. P. J. Abdul Kalam Technical University (Lucknow), India for the completion of work.

Funding

The work is not supported by any funding agency.

Declaration of competing interest

Authors declare no potential conflict of interest.

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