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

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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) [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 [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 get 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 aminoquinolines 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
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 anti-viral action.

**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].
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: Drug | Intervention: Details |
|------------------|---------|--------------------|--------------------|-----------------------|
| NCT04303507      | USA     | 40,000             | 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 |
| NCT04335084      | ProgenBiome, US | 600          | HCQ, vitamin C, vitamin D and zinc (through dietary supplement) | Ciclesonide metered dose inhaler; HCQ, placebo oral tablet |
| NCT04324169      | University of Utah, US | 400          | HCQ, placebo oral tablet | Low dose: CQ/HCQ, mid dose CQ/HCQ, high dose CQ/HCQ, placebo |
| NCT04328012      | USA     | 4000               | HCQ, placebo oral tablet | Low dose: CQ/HCQ, mid dose CQ/HCQ, high dose CQ/HCQ, placebo |
| NCT04337332      | Washington University School of Medicine (USA, Australia, Canada, Ireland, South Africa, UK) | 55,000         | - | - |
| 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 | Combination product HCQ sulfate + azithromycin; drug: HCQ sulfate |
| NCT04334382      | Intermountain Health Care Inc. US | 1550         | HCQ, azithromycin | - |
| NCT04322991      | Massachusetts General Hospital, US | 510          | HCQ, placebo | - |
| NCT04328467      | University of Minnesota, 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          | QP phosphate (tablet, 500 mg, oral) for 10 week trial period followed with plasma QP 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. | 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 | - |
| NCT04336328      | Holon Medical Center, Israel | 210          | CQ, standard care | - |
| NCT04303507      | EUCR2020-001345-38-GR Uni-Pharma Kleon Tsetis Pharmaceutical Lab SA, Greece | 40,000         | CQ or HCQ, placebo | UNIKINON tablets 200 mg, CQ phosphate |
| NCT04321993      | Canada | 1000         | HCQ | - |
| 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 | Azithromycin, HCQ, placebo oral tablet |
| NCT04322396      | Denmark | 226          | Azithromycin, HCQ, placebo oral tablet | - |
| NCT04334928      | Plan Nacional sobre el Sida, Spain | 4000         | Drug: emtricitabine/tenofovir disoproxil; drug: HCQ, drug: placebo: emtricitabine/tenofovir disoproxil placebo; drug: placebo: HCQ | - |
| EUCR2020-001385-11-ES Spain | 4000         | HCQ sulfate, placebo (oral use) | - |
| EUCR2020-001565-37-ES Spain | 440          | HCQ sulfate | - |
| EUCR2020-001421-31-ES Spain | 1530         | HCQ sulfate, placebo | - |
| NCT04332094      | Spain | 276          | HCQ | - |
| NCT04331834      | Barcelona Institute for Global Health, Spain | 440          | HCQ, placebo | - |
| EUCR2020-001366-11-ES Spain | 1,00,000       | Remedesivir, CQ, HCQ sulfate, lopinavir/ritonavir, interferon b 1 A | - |
| 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/ledipasvir 400/100 mg daily for 10 days, | - |

(continued on next page)
| 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/ledipivir 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                 | 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 |
| NCT04318015         | Pakistan, University of Health Sciences, Lahore, Pakistan | 20                 | 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. |
| NCT043768           | Shahid Beheshti University of Medical Sciences | 60                 | HCQ, lopinavir/ritonavir, interferon beta-1A, interferon Beta-1B |
| NCT0434092          | National Institute of Respiratory Diseases-Mexico | 50                 | Ivermectine, HCQ sulfate, placebo |
| NCT04318015         | Iran                                         | 400                | HCQ |
| NCT04340349         | Mexico                                       | 100                | HCQ sulfate, bromhexine (8 mg) |
| NCT04342221         | University Hospital Tubingen, Germany        | 220                | HCQ sulfate, placebo |
| NCT04340544         | Germany                                      | 2700               | HCQ, placebo |
| EURCTR2020-000936-23-FR | INSERM, France, Belgium, Luxembourg, Netherlands, Germany, UK, Spain | 3100              | Lopinavir/ritonavir, HCQ |
| EURCTR2020-001010-38-NO | Akershus University Hospital, Norway       | 200                | HCQ sulfate |
| ACTRN12620000457943 | New Zealand                                  | 202                | HCQ sulfate |
| EURCTR2020-001128-11-NO | Akershus University Hospital, Norway     | 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) |
| EURCTR2020-001135-27-FR | Centre Hospitalier Universitaire de Bordeaux, Etablissement Public, France | 1057           | HCQ, control group will not receive HCQ |
| EURCTR2020-001128-11-NO | Hospital Civils de Lyon, France           | 50                 | HCQ SAR321068, placebo |
| EURCTR2020-001128-11-NO | Hospital Civils de Lyon, France           | 3100           | HCQ |
| NCT04326831         | Rambam MC                                    | 1116               | HCQ, control group will not receive HCQ |
| NCT04333654         | Sanofi - US, France                         | 210                | HCQ sulfate, placebo |
| EURCTR2020-001281-11-NO | URCP-GHU Saint Etienne, France           | 50                 | HCQ sulfate |
| EURCTR2020-001435-27-FR | Centre Hospitalier Universitaire de Bordeaux, Etablissement Public, France | 1057           | HCQ (200 mg), imatinib (400 mg), favipiravir |
| EURCTR2020-001281-11-NO | Hospital Civils de Lyon, France           | 50                 | HCQ |
| EURCTR2020-001281-11-NO | Hospital Civils de Lyon, France           | 3100           | Remdesivir, lopinavir/ritonavir, interferon beta 1A, HCQ, standard of care |
| NCT04325893         | France, Monaco                               | 1300               | HCQ, placebo |
| NCT04315886         | 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 |
| JPJN-jRCTs031190227 | Gunna 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 | 500         | Experimental group: rabeprazole + CQ |
| ChiCTR2000030417     | Harbin Poyou Jiandi Biotechnology Co Ltd., China | 150         | Control group: lopinavir + rabeprazole |
| ChiCTR2000030054     | Zhongshan Hospital Affiliated to Xiamen University, China | 20              | Experimental group: combined standard therapy of CQ phosphate aerosol inhalation solution |
| ChiCTR2000030031     | The Sixth Affiliated Hospital of Guangzhou Medical University, China | 40              | Control group: water for injection atomization inhalation combined with standard therapy |
|                    |                                              |                    | HCQ sulfate 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 14 – CQ phosphate 0.5 g |
|                    |                                              |                    | Control group: recommended treatment plan for novel coronavirus pneumonia diagnosis and treatment plan |
|                    |                                              |                    | Phosphoric chloroquine: two tablets twice daily + recommended therapy |
|                    |                                              |                    | Placebo: 2 tablets placebo twice daily + recommended therapy |

(continued on next page)
| ID                  | Country                                                                 | Number of patients | Intervention                                                                                                                                                                                                 |
|---------------------|-------------------------------------------------------------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ChiCTR2000029992    | Zhonghan Hospital Affiliated to Xiamen University, China               | CQ phosphate group: 40; HCQ sulfate group: 40 | 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; Low-dose group: 60; Medium-dose group: 60; High-dose group: 60; Placebo: 40 | Experimental group: conventional treatment meet the Guideline Phosphoric chloroquine: 2 tablets twice daily + recommended therapy; Placebo: 2 tablets twice daily + recommended therapy Phosphoric chloroquine: two tablets twice daily + recommended therapy Placebo: 2 tablets twice daily |
| ChiCTR2000029826    | Jinhzhou Central Hospital, China                                        | Phosphoric chloroquine: 30; Placebo: 15 | Phosphoric 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 | Experimental group 1: oral trial drug favipiravir tablet + CQ phosphate tablet Experimental group 2: oral trial drug favipiravir tablet Control group: oral placebo treatment |
| 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 | HCO 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                  | QC phosphate dissolved in 5 ml of normal saline, q 12 h, inhaled by atomization for one week                                                                                                               |
| ChiCTR2000029939    | China                                                                   | 100                 | QC phosphate, Standard treatment                                                                                                                       |
| ChiCTR2000029609    | China                                                                   | 205                 | Mild-moderate CQ group: oral QC phosphate; Mild-moderate combination group: QC phosphate plus lopinavir/ritonavir; severe CQ group: oral QC 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 QC 0.5 g twice daily for 10 days                                                                                                                   |
| ChiCTR2000029826    | China                                                                   | 45                  | Two tablets QC phosphate twice daily                                                                                                                     |
| ChiCTR2000031204    | Beijing Institute of Pharmacology and Toxicology, China                | Treatment group: 150 | Two tablets placebo twice daily                                                                                                                        |
| NCT04342156         | Tan Tock Seng Hospital                                                  | 3000                | Treatment group: oral QC phosphate tablets                                                                                                               |
| NCT04326517         | China                                                                   | 30                  | Treatment group: oral placebo group                                                                                                                     |
| NCT04319500         | China                                                                   | 150                 | HCQ sulfate 200 mg tablet                                                                                                                                |
| NCT04307693         | Korea                                                                   | 150                 | Lopinavir/ritonavir, HCQ sulfate                                                                                                                         |
| NCT04332835         | Universidad del Rosario, Cambodia                                      | 80                  | Plasma, HCQ, azithromycin                                                                                                                                |
| NCT04338906         | --                                                                     | 334                 | Canostat mesilate, placebo, HCQ                                                                                                                        |
| NCT04336748         | --                                                                     | 440                 | HCQ                                                                                                                                                    |
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 chloroquine 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 unreparable 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 (EC50 = 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 hydroxychloroquine) 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 immunosuppressants 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.

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Declaration of competing interest

Authors declare no potential conflict of interest.
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