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HYDROXYCHLOROQUINE (HCQ) AS AN EMERGING AND PROMISING DRUG CANDIDATE IN COVID-19 PANDEMIC - A SYSTEMATIC REVIEW

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Keywords:

Hydroxychloroquine, 4-aminoquinolines, COVID-19, Coronavirus, SARS-COV-II

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ABSTRACT: Hydroxychloroquine (HCQ) belongs to the class of 4-aminoquinolines. It is a hydroxylated version of chloroquine with a similar mechanism of action but rather a safe profile. It is primarily an antimalarial drug but has been extensively used for treating rheumatoid arthritis, porphyria, discoid and systemic lupus erythematosus as well. Most recently, this drug has found a place in the treatment of COVID-19 with successful results. It is relatively a safer drug to treat COVID-19 in pregnant ladies, diabetic and hypertensive patients. This molecule has found its successful and safer use as a pediatric drug. The World Health Organization (WHO) has listed hydroxychloroquine as an investigational drug for efficacy against SARS-COV-II. COVID-19 is spreading at a tremendous rate, and we need a less expensive drug against the virus, especially in countries with high poverty. The production cost of this drug is very low, and so is its retail cost. These collective advantages of hydroxychloroquine make it a suitable, effective, safer, and readily available drug candidate for COVID-19 patients.

INTRODUCTION: In December 2019, a new type of pneumonia was observed in Wuhan, China, with unique respiratory symptoms. Initially, everyone considered it as normal seasonal flu, but then researchers found that they were dealing with an entirely new strain of coronavirus, which is highly contagious in nature. Later on, this infectious disease and the virus were termed as COVID-19 and SARS-COV-II, respectively, by World Health Organization. COVID-19 was declared as a pandemic in March 2020. Till 20th May 2020, this virus has infected more than five million people worldwide across 213 countries and territories.

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The authorities are struggling to control this outbreak but with little luck. At present major part of the world is under lockdown to minimize human to human transmission. By practicing social distancing, the chances of the viral spread can be reduced. COVID-19 is a highly contagious viral infection, and a person can get this infection by any of the following ways:

a. By having a travelling history of country with active cases.
b. From an infected person to his/her family members.
c. By community spread (highly dangerous).

Out of these three modes, community spread is highly dangerous as nobody knows when and where the virus invaded the body.

What are Coronaviruses? Coronaviruses (CoV) are a large family of viruses that cause infections like the common cold to many more severe

diseases. Before COVID-19, several coronaviruses have caused serious problems in humans and animals in the past two decades.

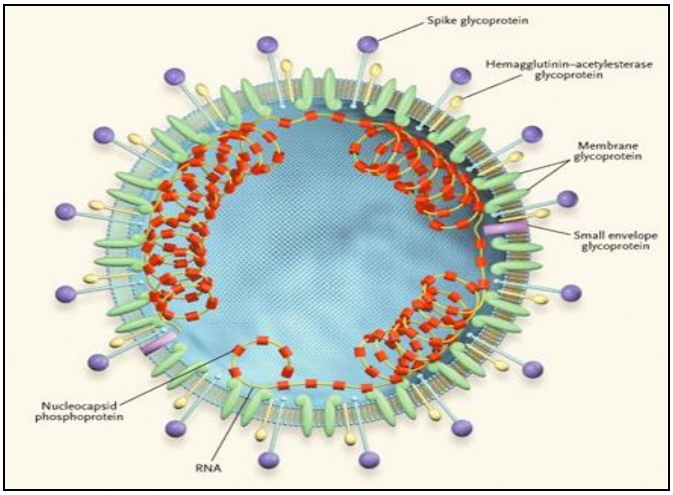

FIG. 1: CELL STRUCTURE OF CORONAVIRUS

For instance, severe acute respiratory syndrome coronavirus (SARS-CoV), middle east respiratory syndrome coronavirus (MERS-CoV) and porcine epidemic diarrhea virus (PEDV). Earlier SARS-CoV was known for its ability to transmit from animals to humans [1]. Likewise, SARS-COV-II is highly capable of such transmission. Some researchers have found that this virus is modified genetically several times, and there are many new strains of coronavirus spreading throughout the world.

Hydroxychloroquine in COVID-19: According to an in vitro study in China, it has been reported that hydroxychloroquine is far more potent than chloroquine in inhibiting SARS-COV-II.[2] More research is being done worldwide to validate these findings. Hydroxychloroquine is a potent and cheapest candidate among the other suitable drugs available. It has been found to produce reliable results against SARS-COV-II, and these facts are likely to cause its shortage throughout the world. Hydroxychloroquine is frequently used for the treatment of systemic lupus erythematosus and rheumatoid arthritis. Now it is used for COVID-19 also; therefore, its shortage is highly anticipated. The pharmaceutical world is working really hard in order to maintain a balance between demand and supply of hydroxychloroquine. At present, India is the largest manufacturer of hydroxychloroquine, with its global manufacturing share of 70%. The Indian government has directed its top Pharmaceutical companies to manufacture this drug even on a larger scale than usual.

Philippe *et al*., conducted an uncontrolled, non-comparative, observational study in a group of relatively mildly infected patients and gave them a combination of hydroxychloroquine and azithromycin for at least three days. During this study, one 86 year-old patient died, and another patient of age 74 was kept in intensive care unit. The health of all the other patients was improved significantly. After this treatment, 83% of cases were reported negative on 7th day and 93% of cases on the 8th day of the study. Recovered patients were rapidly discharged with an average stay of five days. Thus, using this drug is a cheaper and effective way to fight the coronavirus [3].

Zhaowei Chen *et al.*, studied sixty-two patients who were diagnosed with COVID-19 and admitted to Renmin Hospital of Wuhan University. Thirty-one patients were given hydroxychloroquine (400 mg/day) for five days. Factors like time to clinical recovery, clinical characteristics, and radiological results were observed. Out of sixty-two COVID-19 patients, twenty-nine patients were male, and thirty-three were female with a mean age of 44.7 years. The pattern of distribution was the same for both the control group and the hydroxychloroquine group. They observed that the body temperature recovery time and the cough remission time were significantly reduced in the hydroxychloroquine group. Also, a major part of patients was found with improved pneumonia in the hydroxychloroquine treatment group (25 out of 31) compared with the control group (17 out of 31). Four patients got severe illnesses in the control group. It has been reported that the use of hydroxychloroquine could shorten the time to clinical recovery and cure pneumonia faster in patients with COVID-19 [4].

Chen Jun *et al*., performed a study on thirty COVID-19 patients at Shanghai Public Health Clinical Center. The patients were equally distributed in the hydroxychloroquine group and the control group. Patients in hydroxychloroquine group were given hydroxychloroquine 400 mg per day for 5 days along with other conventional treatments, while those in the control group were given conventional treatment. The nucleic acid of

throat swabs was found negative in 13 (86.7%) cases of hydroxychloroquine group after day seven. The median time for body temperature to normalize in hydroxychloroquine group was 1 day after hospitalization, and only four cases of this group developed transient diarrhea and abnormal liver function. Thus, the prognosis of COVID-19 moderate patients was found to be good in this study [5].

The use of hydroxychloroquine needs to be promoted due to its safety and efficacy. This drug could save many lives with critical conditions if administered on time. It will help with the fast recovery of COVID-19 patients and will reduce the mortality rate. Xiaobo Yang *et al*., studied a group of fifty-two adult patients suffering from SARS-CoV-II pneumonia and were admitted to the intensive care unit (ICU) of Wuhan Jin Yin-tan hospital (Wuhan, China). The data collected was observed and compared between survivors and non-survivors. The mean age of the fifty-two patients was 59.7 years, thirty-five were men, twenty one had a chronic illness, and fifty one had a fever. Thirty-five patients died within 28 days after being admitted to ICU. Most of the patients had organ function damage, including acute kidney injury, cardiac injury, liver dysfunction, and pneumothorax. The mortality of critically ill patients with SARS-CoV-2 pneumonia is quite high [6].

Hydroxychloroquine is Better Choice than Chloroquine: Some clinical trials have shown that aminoquinolines are effective against COVID-19. Chloroquine has been found capable of inhibiting the in vitro replication of several coronaviruses. Chloroquine can improve the clinical outcome of patients infected by novel coronavirus [7].

Studies have proved that both hydroxychloroquine and chloroquine exhibit their broad-spectrum antiviral effects via interfering with the fusion process of these viruses by decreasing the pH. Moreover, these drugs also alter the glycosylation of the cellular receptors in coronaviruses. On the other hand, Hydroxychloroquine is considered a less toxic aminoquinoline and consists of an N-hydroxyethyl side chain instead of the N-diethyl group of chloroquine. The presence of hydroxyl group in the hydroxychloroquine molecule is responsible for its better results than chloroquine.

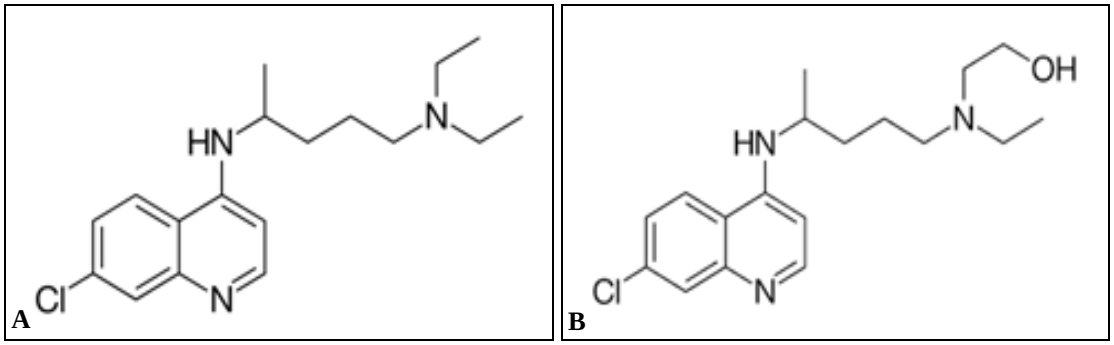

FIG. 2: STRUCTURES OF (A) CHLOROQUINE AND (B) HYDROXYCHLOROQUINE

This structural modification makes hydroxy-chloroquine more soluble than chloroquine. In patients with COVID-19, chloroquine can interact with Lopinavir or Ritonavir. Thus hydroxy-chloroquine is safer to use rather than chloroquine as the latter has drawbacks while treating COVID-19 patients. Hydroxychloroquine can be recommended in countries having a shortage of chloroquine. Other antiviral agents (oseltamivir, lopinavir/ritonavir, ribavirin, *etc*.), interferons, and intravenous immunoglobulins do not interfere with hydroxychloroquine, hence are currently under investigation [8].

Hydroxychloroquine was first synthesized in 1946 by introducing a hydroxyl group into chloroquine. Being a safe drug, it is used to treat various autoimmune diseases. Since both drugs share similar chemical structures and mechanisms of action, hydroxychloroquine is a potent drug candidate to treat COVID-19 due to its fewer side effects [9].

Hydroxychloroquine has a lower level of tissue accumulation as compared to chloroquine. Due to no teratogenic effects, it is strongly recommended for pregnant patients with an autoimmune disease.

The maximum tolerable dose for hydroxy-chloroquine is 1200 mg, which has an antiviral effect equivalent to 750 mg chloroquine (for which the maximum tolerable dose is 500 mg). This indicates that hydroxychloroquine can be administered at a higher dosage and may therefore achieve a more powerful antiviral effect [10].

Hydroxychloroquine could serve as a better therapeutic approach than chloroquine for the treatment of SARS-CoV-II infection. Hydroxy-chloroquine inhibits the cytokine storm by reducing CD154 expression in T cells; therefore, it can control the severe progression of COVID-19. It exerts a similar antiviral effect at both pre- and post-infection stages, as found with chloroquine. Given the fast-growing number of COVID-19 patients and the urgent need for effective and safe drugs in the clinic, it is more practical to identify reliable candidates by screening currently available drugs. We herein strongly urge that clinical trials are performed to assess the preventive effects of HCQ on both infection and malignant progression [11].

Hydroxychloroquine in Pregnant and Lactating COVID-19 Patients: Hydroxychloroquine crosses the placenta, but no fetal toxicity was evident in subsequent studies and no congenital abnormalities were seen in pregnant patients treated with hydroxychloroquine during the first trimester of pregnancy. If a lactating woman uses the drug, then the amount of hydroxychloroquine transferred to the infant is very low and apparently does not confer any risk of toxicity to the child. HCQ is safe during pregnancy, and there's no evidence against breastfeeding during treatment [11].

A study was done on pregnant women who were treated with hydroxychloroquine. The women received 200 mg of hydroxychloroquine either once or twice daily. Maternal blood and cord blood were collected at the time of delivery. Even the concentration of hydroxychloroquine in breast milk was measured one week after delivery. Drug assay was done in whole blood and in breast milk by high-performance liquid chromatography with fluorimetric detection. This study revealed that the concentration of hydroxychloroquine in cord blood, as well as maternal blood, was quite similar. This indicates that during pregnancy, the exposure level of hydroxychloroquine is similar in mother as well as the fetus.[12]

Another study involved experiment on pregnant ladies who were on hydroxychloroquine for the treatment of lupus. These ladies took this drug throughout their pregnancy. All of those pregnancies resulted in live births and no congenital abnormalities were observed even during the first few years of the developmental stages [13].

In 2001, Levy *et al*., performed a study on twenty patients who were diagnosed with systemic lupus erythematosus or biopsy proven discoid lupus erythematosus and received hydroxychloroquine or placebo during pregnancy. After the gestational period was over, results were observed. No patient in the hydroxychloroquine group had toxemia while in the placebo group three patients had toxemia and one delivered at 25 weeks of gestation and the newborn died. The children born were examined at ages of 1.5 ± 3 years but no health issue was found. All the children achieved percentiles above 50 in the National Center for Health Statistics Percentiles curve for height and weight. They were able to perform the normal activities expected for their age group. In those nineteen children, clinical examination was found normal and no auditory defect was observed. Even ophthalmoscopic examination of both eyes was normal in all children [14].

Mario *et al.,* performed a prospective observational study on forty infants. They were born from mothers who used hydroxychloroquine during their pregnancy for treating rheumatic disease. The study was done to detect any incidence of prematurity, congenital malformations, and neonatal infections. No significant congenital malformations or neonatal infections were detected. All infants, including those who were breast-fed, had normal visual function and development of neurons. Thus, using hydroxychloroquine during gestation and lactation was considered safe [15].

Hydroxychloroquine in Diabetic COVID-19 Patients:: Hertzel *et al*., performed a study on one hundred and thirty-five obese patients with type II diabetes and an average age of 57.5 years. They were given sulfonylureas along with hydroxy-

chloroquine (up to 300 mg bid) or placebo and followed for up to eighteen months. Various factors like glucose tolerance, lipids, and quality of life were also assessed during this time period. Researchers observed that those who were on placebo were more likely to be withdrawn from the study drug because of unacceptable glycemic control than patients randomized to hydroxychloroquine. During the first 6 months, hydroxychloroquine decreased glycated hemoglobin more than placebo did. Glucose tolerance and low-density lipids were also improved during the first three months of therapy. No significant adverse effects were noted. Factors that predicted responsiveness included initial glycated hemoglobin lesser than 13.5%, early responsiveness to study drug, and no prior metformin use. Lower glycated hemoglobin levels at baseline predicted a better response. Thus according to this study, hydroxychloroquine improves glycemic control in sulfonylurea-refractory patients with poorly controlled type II diabetes [16].

Anil Pareek *et al.,* performed a double-blind study on randomized two hundred and sixty-seven patients with uncontrolled type II diabetes after thre e months of treatment with glimepiride/gliclade and metformin, to additionally receive hydroxy-chloro-quine (400 mg/day) or pioglitazone (15 mg/day) for 24 weeks. Fasting and post-prandial blood glucose levels were measured at week twelve and week twenty-four. The blood glucose levels were found to be reduced significantly in both groups. The mean reduction in glycemic parameters at week twelve was not significantly different between the hydroxychloroquine and pioglitazone groups. Triglycerides were significantly reduced in both groups at week twenty-four. Study treatments were well tolerated; therefore hydroxychloroquine may be considered as a safe and effective therapeutic option for COVID-19 patients with type II diabetes [17].

In 2015, Chen *et al.,* studied eight thousand six hundred twenty-eight subjects having systemic lupus erythematosus out of which two hundred and twenty-one newly diagnosed diabetes mellitus patients were identified (6795 patients had taken hydroxychloroquine and 1833 patients had never taken hydroxychloroquine), with an average follow up period of 5.6 years. Compared with patients without hydroxychloroquine treatment, the hazard ratio of diabetes mellitus in patients taking hydroxychloroquine at a cumulative dose of 5129 g was found to be reduced. Daily glucocorticoid 510 mg prednisolone-equivalent dose was associated with an increased risk of developing diabetes mellitus, which was minimized by concomitant hydroxy-chloroquine use at a cumulative dose of 5129 g. It is safe to use hydroxychloroquine as it is associated with reduced risk of incident diabetes mellitus in a dose-dependent manner [18].

Mercer *et al.,* recruited 13 obese, non-diabetic subjects without systemic inflammatory conditions for an open-label longitudinal study of hydroxy-chloroquine 6.5 mg per kilogram per day for six weeks. Subjects underwent an oral glucose tolerance test at three-time points: 0 weeks (pre-treatment with hydroxychloroquine), 6 weeks (at the end of the hydroxychloroquine treatment), and 12 weeks (6 weeks post hydroxychloroquine - treatment). Hydroxychloroquine use for 6 weeks in non-diabetic obese subjects was associated with a significant increase in insulin sensitivity index and trends toward reduced insulin resistance and insulin secretion. These data suggest that hydroxy-chloroquine, a common medication used to treat rheumatoid arthritis, possesses beneficial effects upon insulin sensitization. Further study of the insulin-sensitizing effects of hydroxychloroquine in patients with rheumatoid arthritis is warranted [19].

Daniel *et al.,* performed a sixteen-week double-blind crossover study on twenty-three rheumatoid arthritis subjects who were not using hydroxy-chloroquine. The mean patient age was 56 years, with 96% women, and the median body mass index was 26.0. The subjects were randomly given hydroxychloroquine (6.5 mg/kg/day) or placebo for the first eight weeks, followed by crossover for the next eight weeks. During this study, oral glucose tolerance testing and fasting lipid measurements were done at eight weeks and sixteen weeks. Standard deviation from baseline in insulin sensitivity index, homeostatic model assessment for insulin resistance, and lipid parameters were compared between placebo and hydroxy-chloroquine using linear regression. Small decreases in total cholesterol and low-density lipoprotein (LDL) cholesterol were observed during the hydroxychloroquine treatment periods.

The researchers concluded that using hydroxychloroquine in patients without diabetes mellitus with stable rheumatoid arthritis caused no significant change in insulin resistance. They observed significant improvements in total and LDL cholesterol levels during the treatment [20].

Sara *et al.*, studied a group of non-diabetic women with systemic lupus erythematosus or rheumatoid arthritis for a cross-sectional evaluation of cardiovascular risk factors by using the hydroxychloroquine. Their mean fasting glucose, median insulin, and insulin resistance were compared among hydroxychloroquine users and nonusers for disease-specific groups. More women with systemic lupus erythematosus were taking hydroxychloroquine than those with rheumatoid arthritis. For women with systemic lupus erythematosus or rheumatoid arthritis, after adjustment for age, waist circumference, disease duration, prednisone dosage, C-reactive protein, menopausal status, non-steroidal anti-inflammatory drugs, and disease-specific indicators, serum glucose was lower in hydroxychloroquine users than in nonusers. The results were assessed by the homeostasis model assessment (HOMA-IR) calculation.

In women with systemic lupus erythematosus, hydroxychloroquine use also was associated with lower logHOMA-IR, whereas in those with rheumatoid arthritis, no differences in logHOMA-IR were seen. Hydroxychloroquine usage was not associated with fasting insulin levels in either patient group but was associated with lower fasting glucose in women with systemic lupus erythematosus or rheumatoid arthritis and also lower logHOMA-IR in the systemic lupus erythematosus group. The use of hydroxychloroquine may be beneficial for reducing cardiovascular risk by improving glycemic control in such patients [21].

A 77-year-old man with type II diabetes taking a stable dose of subcutaneous, twice daily human insulin developed symmetrical, inflammatory, rheumatoid factor positive polyarthritis. Within 2 weeks of starting therapy with prednisone 5 mg daily and hydroxychloroquine 400 mg daily, he had two episodes of severe hypoglycemic coma requiring emergency care. His blood glucose became controlled again when his insulin was decreased by 37%. There are no reported cases of hypoglycemia in diabetic or non-diabetic patients treated with hydroxychloroquine. Hydroxychloroquine has been reported to reduce insulin requirements in refractory type II diabetes by an average of 30%. When hydroxychloroquine is initiated for the treatment of polyarthritis in type II diabetic requiring insulin or sulfonylurea treatment, blood glucose levels should be monitored closely and the insulin dose may need to be reduced [22].

Mary Chester *et al.*, performed a randomised, double-blind, parallel-arm (placebo *vs.* hydroxychloroquine 400 mg/day) trial at the University of Pittsburgh. Randomization was conducted by a computer system, and duration of treatment was about 13 weeks. Randomized non-diabetic, overweight or obese participants with age more than eighteen years and having one or more markers of insulin resistance were given either hydroxychloroquine (n=17) or placebo (n = 15). All participants were included in the intention-to-treat analysis. Results were found in the form of changes in insulin sensitivity and beta-cell function which were measured by intravenous glucose tolerance tests and minimal model analysis. There was a significant positive change in insulin sensitivity and an improvement in beta-cell function with hydroxychloroquine but not with placebo. No serious or unexpected adverse effects were found.

According to this study, hydroxychloroquine improves both beta-cell function and insulin sensitivity in non-diabetic individuals. Additionally they observed that hydroxychloroquine also improves adiponectin levels, possibly being a mediator of the favourable effects on glucose metabolism [23].

Safe Dose of Hydroxychloroquine: Anna *et al*., performed a study on 123 child patients, out of which 119 children were suffering from juvenile rheumatoid arthritis (JRA) and 4 with systemic lupus erythematosus (SLE). Sixty patients were treated with chloroquine diphosphate and sixty-three patients with hydroxychloroquine sulphate. After treatment, some ADRs were found in thirty-six patients taking chloroquine, and in twenty-three patients taking hydroxychloroquine. No correlation between the occurrence of side effects and the duration of treatment or total drug dose was

observed. They found that maximum safe dose of chloroquine diphosphate is 4 mg/kg/day (100 mg/m^2/day), and that of hydroxychloroquine sulphate is 5 to 7 mg/kg/day (120 to 150 mg/m^2/day) in the treatment of children with juvenile rheumatoid arthritis. Both chloroquine and hydroxychloroquine show almost equal side effects with a dosage of 4 mg/kg/day of either, but at higher dosages, chloroquine is apparently more toxic. According to this study, the maxima of safe serum concentrations are considered to be 250 to 280 μg/1 during chloro-quine therapy and 370 to 470 μg/l during hydroxychloroquine therapy. Despite the same dose in mg/kg of body weight or in mg/m^2 of body surface area, significant individual variations in serum concentrations of chloroquine and hydroxy-chloroquine were observed. When these drugs were used for a longer duration, even large variations were seen [24].

Xueting *et al.*, tested the pharmacological activity of chloroquine and hydroxychloroquine using SARS-CoV-2 infected Vero cells. They implemented physiologically based pharmacokinetic (PBPK) models for both drugs separately by integrating their in vitro data. Simulations were used showing hydroxychloroquine concentrations in lung fluid under five different dosing regimens to explore the most effective regimen while considering the drug's safety profile. In general, hydroxychloroquine was found to be more potent than chloroquine *in-vitro*. Based on PBPK model results, a loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days, is recommended for SARS-CoV-2 infection. This regimen has the potency of chloroquine phosphate thrice when given 500 mg twice daily 5 days in advance. Hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-CoV-2 *in-vitro* [25].

Levy *et al.*, conducted a randomized, controlled study to assess the need for hydroxychloroquine during lupus pregnancy and to assess safety. They performed their study on twenty pregnant patients with similar characteristics. The hydroxychloroquine group included eight patients with systemic lupus erythematosus and two with discoid lupus erythematosus. The placebo group included nine patients with systemic lupus erythematosus and one with discoid lupus erythematosus. The hydroxychloroquine group showed no flare-ups, and even one patient had improvement of skin lesions and another of arthritis, resulting in the reduction of prednisone dose. No retinal effects were observed. On the other hand, three patients in the placebo group flared up, two with skin rashes, one also with arthritis and uveitis, and one with hemolytic anemia, polyserositis, and anti-dsDNA antibody. Even toxemia was diagnosed in three patients in the placebo group. They observed a significant decrease in prednisone dosage in the hydroxychloroquine group and an increase in the placebo group. The delivery age was also higher in the hydroxychloroquine group. No congenital abnormalities were observed even after 1.5–3 years of age [14]. This research alone shows that hydroxychloroquine is a relatively safer pediatric drug.

CONCLUSION: In a nutshell, I would like to say that hydroxychloroquine is quite safer than any other aminoquinoline. It exerts an antiviral effect at both pre- and post-infection stages. It can be used for the treatment of COVID-19 patients who are pregnant or breastfeeding, having hypertension, diabetes, systemic lupus, erythematosus, and rheumatoid arthritis. It is not associated with any risk of congenital defects, spontaneous abortions, or fetal death, and with its low cost and high availability, it can be really considered as a boon for mankind.

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