International Journal of Engineering Sciences & Research Technology

(A Peer Reviewed Online Journal)
Impact Factor: 5.164

IJESRT

RESEARCHERID
THOMSON REUTERS
[Tyagi *et al.*, 9(7): July, 2020]
IC™ Value: 3.00
ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

IJESRT
INTERNATIONAL JOURNAL OF ENGINEERING SCIENCES & RESEARCH TECHNOLOGY

THE ROLE OF HYDROXYCHLOROQUINE IN THE TREATMENT OF HIV AND COVID-19: A REVIEW

Abhishek Tyagi[1] & R S Dubey[*2]
Department of Chemistry, Amity Institute of Applied Science, Amity University, NOIDA, UP, India

DOI: https://doi.org/10.29121/ijesrt.v9.i7.2020.3

ABSTRACT

Hydroxychloroquine (HCQ) which is an antimalarial drug also used widely in the treatment of rheumatoid arthritis and systemic lupus erythematosus. It is less toxic and more soluble metabolite of chloroquine. HCQ is widely available and affordable drug. Potential mechanism of action of HCQ against COVID-19 have been postulated. According to the collected data of activities of HCQ, there are the indications of treatment of infectious disease such as COVID-19 and in the improvement of insulin sensitivity because these drug have effect on some cellular process that impact on viruses. A number of clinical trials are undergoing HIV treatment with arthritis case study is also included in the report. In this review we present a case report of hydroxychloroquine overdose. Precaution which may be taken during the treatment with HCQ are included. Overdose effect of the drug are rare, but lethal. Toxic effects such as retinopathy and genotoxicity are also listed.

KEYWORDS: hydroxychloroquine, metabolisation, pharmacodynamics and pharmacokinetics, ratinopathy, toxicity and overdose, effect in pregnancy, HIV, COVID-19.

1. INTRODUCTION

Hydroxychloroquine (hcq) is a disease modifying anti rheumatic drug (dmard) that was first used to treat malaria where malaria remains sensitive to chloroquine, and has been beneficial for patient with lupus, rheumatoid arthritis. Also been studied as a treatment for COVID-19 (CORONA VIRUS INFECTIOUS DISEASE-2019).On 18 may, 2020 American president Donald Trump publicly stated that he was taking HCQ during covid-19 pandemic.

The drug belongs to 4-aminoquinoline class with immunosuppressive, antimalarial, and antiautophagy activities. It is a mixture which consists of R and S enantiomers. Hydroxychloroquine and chloroquine both are used for treating acute form of malaria caused by P. vivax. Drugs sold under the trade name quensil, plaquenil, toremonil etc. HCQ is made by a similar way of making of chloroquine. HCQ was approved for use in the United State in 1994. Hydroxychloroquine can be prescribed to all ages children or adults, and safely taken by nursing mother and pregnant women. People with psoriasis should not take hydroxychloroquine. CDC has no limit on use of HCQ for prevention of malaria, but when used in high doses for many years, retinopathy has occured.
Hydroxychloroquine was invented during world war II to provide an alternate with fewer side effects. In the early 1950s it began to use in the treatment or SLE (systematic lupus erythematosus), and now in 2020 it is found to be effective against SARS-CoV-2. Hydroxychloroquine drug used in the form of sulfate salt or hydroxychloroquine sulfate which is known as the trade name PLAQUENIL. These tablets of HCQ sulphate contain 200 mg of HCQ-sulfate and 155 mg of base in equivalent and used orally.

ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

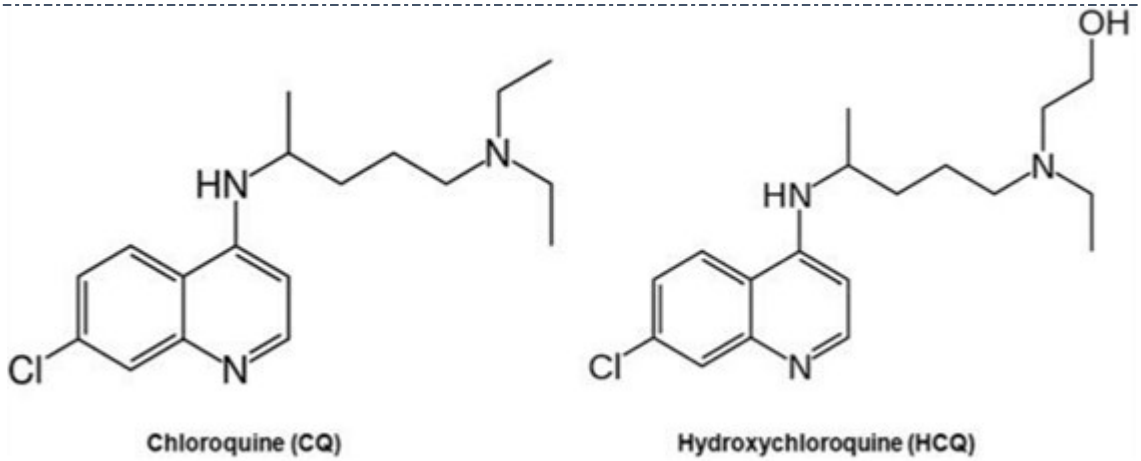

Fig.-A (STRUCTURE OF CQ AND HCQ)

2. PHARMACOLOGY OF HYDROXYCHLOROQUINE

The antimalarial drug CQ and HCQ have been also used for treatment of arthritis and SLE.

Pharmacokinetics

In the past antimalarial regimens have not been based on pharmacokinetics, but that information is now available. HCQ is 67-74% bioavailable [19]. HCQ and CQ both are weak bases due to basic side chain and have a deep volume characteristic of distribution. HCQ and CQ have similar pharmacokinetics with rapid gastrointestinal absorption, elimination by kidneys. HCQ is administered as sulfate and CQ is administered as phosphate salt. The Cytochrome P450 enzyme metabolize HCQ to N-desethylhydroxochloroquine. The pharmacokinetic interaction studies of chloroquine are limited. HCQ and CQ both are given orally and well absorbed [23]. Both have low blood clearance and prolonged half-lives between 40-50 days, but these drugs have notably different renal clearance rate. Chloroquine (CQ) has been used for treatment of malaria and porphylaxis. It acts on the rings form of parasite. CQ exerts its effect directly on hemoglobin digestive pathway of parasite.Hydroxychloroquine is an analogue of chloroquine in which one of the N-ethyl substituent of CQ is β-hydroxylated. After oral administration HCQ is completely and rapidly absorbed. About 50% of HCQ in plasma is bound to plasma protein.

Table-The boundation of Hydroxychloroquine with protein in Plasma.

Plasma protein	R(37%)-S(64%) enantiomers boundation
Serum albumin	R(29%) S(50%)
Alpha-1 acid glycoprotein	R(41%) S(29%)

In total, HCQ is 50% protein bound in plasma, but as shown in table, R-enantiomers are 37% bound and S-enantiomers are 64% bound to protein in plasma. In R-enantiomers, it is 29% bound to serum albumin and 41% bound to alpha-1 acid glycoprotein. In the same way R-enantiomers are 50% bound to serum albumin and 29% to alpha-1 acid glycoprotein. After 3-4 hours Peak plasma levels of HCQ were seen.

The hepatic metabolism in liver generate three active metabolites as shown in fig.1 [31] –

- Bisdesethylhydroxychloroquine (BDCQ)
- Desethylhydroxychloroquine (DHCQ)
- Desethylchloroquine (DCQ)

ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

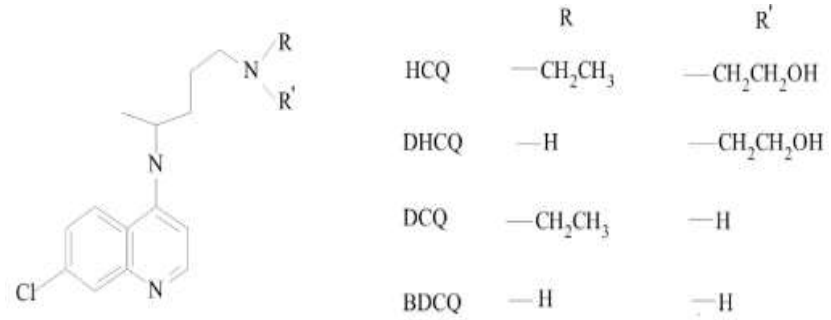

FIGURE 1- HCQ and its metabolites.

The metabolism and properties of HCQ is not well known. Cytochrome P450 enzyme mediate dealkylation of CQ and HCQ. DCQ is an immediate downstream product of Cytochrome P450 mediated dealkylation of these drugs. And DHCQ is a metabolite of only HCQ, BDCQ is downstream metabolite of both drugs. 40-50% of HCQ is excreted renally and only 16-21% of unchanged drug excreted in the urine.

Pharmacodynamics and Mechanism of Action:

The precise mechanism for hydroxychloroquine exhibition against plasmodium is not known. It increases pH as protein degradation by acidic hydrolases in lysosome within antigen-presenting cell [4]. HCQ and CQ both are weak bases and both may concentrate in acid vesicles of the parasite to give the effect and inhibiting polymerization of heme, and can also inhibit certain enzymes by interaction with DNA. Plasmodium has a food vacuole that used to digest food nutrient. The food vacuole has a proton pump and surface has a H^+ ions. HCQ is alkaline in nature and when HCQ entered in food vacuole, it alkalinize it, it also inhibit proton pump functioning and increase the pH of food vacuole, this is how HCQ treat plasmodium protozoa [3]. Pharmacokinetic factors may be accountable for the slow action of the drug in rheumatic disease [19]. HCQ is now the reference therapy for chronic Q fever with impact of restore intracellular pH. Glycosylation inhibition and modification or change of new synthesized proteins is the impact which described in vitro with HIV virus [27].

HCQ is a slow acting anti-rheumatic drug which is administered as racemic mixture. HCQ can improve hyperglycaemia and hyperlipidaemia and reduce rate of atherosclerosis and protect patient with infection of rheumatic disease. It decreases the production of cytokine [4].

HCQ in treatment of Human Immunodeficiency Virus (HIV):

Hydroxychloroquine medicine has been used widely to treat autoimmune disease such as HIV. A person's immune system become overactive due to HIV infection. This is called immune hyperactivation. By using HCQ it is possible to inhibit HIV type-1(>75%) as measured in the main T cells and monocytes with reverse transcript activity [28]. HCQ a weak base inhibits the posttranslational modification of glycoprotein in monocytes and T cells [2, 27]. HCQ cannot prevent virus to enter into the cell. The effect of HCQ on HIV is less than ZDV (ZIDOVUDIN) drug. There are fewer trials and case reports available for HIV treatment with HCQ. In a case report of 44-year old man who suffered HIV with arthritis for many years without opportunistic infections [29]. He had been treated with indomethacin with a dose of 50 mg three times a day. After failing to respond to indomethacin, doctors prescribed him to start HCQ with a dose 600 mg/day with combination of Didanocin (DDI). After some time HCQ dosage decreased to 400 mg/day and dosage of DDI remains constant. After one year of medication the blood samples shows decrease in CD4 count to 90/mm^3. After a time of treatment unfortunately he feels the development of urticarial rash, so advised to stop the HCQ. After recovery with other medication he resumed treatment with narcotics. In the time period of HCQ treatment the laboratory values before and during treatment are as follows-

ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

Table 2: Laboratory values. PHA- phytohemagglutinin. IL-6: interleukin-6 [29].

Test components of patient	Before HCQ	During HCQ
HIV RNA (copies/ml)	10,000	1,000
CD4+cells /mm^3	180	90
PHA	63	125
IL-6 (pg/ml)	40	0
Tetanus	1.8	2.5
%CD4+Cells	7	7

The patient results a reduction of active arthritis with HCQ therapy while taking HCQ he had a reduction in (IL-6) level. Decrease in IL-6 levels will improve the immune response. Thus HCQ may suppress the inflammatory cytokines common to both arthritis and HIV, so the medication used for both the disease. The amount of HIV RNA decreased 10,000 to 1,000 after one year of HCQ therapy. PHA which is a protein that cause red blood cells to clump together, increased 63 to 125 as shown above. The reported data shows HCQ as an anti-HIV-1 agent and suggested as immune-supportive agent in patient with HIV [17]. It is also important to note here that rashes developed during the therapy as side effect.

Hydroxychloroquine in COVID-19:
Chloroquine and Hydroxychloroquine both have been found to be effective on SARS-CoV-2 or COVID-19.

COVID-19 is an infectious disease caused by a newly discovered coronavirus. In dec.2019 an outbreak of an emerging disease due to the novel corona virus started in china, which named as SARS-CoV-2 or COVID-19. The virus is transmitted through droplets generated by an infected person's cough or sneeze. WHO declared COVID-19 as a pandemic on 12th March 2020. No vaccines are available for the treatment of COVID-19, many drugs and vaccines are under development. Presently, social distancing, good hygiene and good immunity are only available ways to avoid infection. In view of recent studies and discussion on Hydroxychloroquine and chloroquine shows that these drugs may have role in the treatment of COVID-19. There is a limited data which shows the support of HCQ for COVID-19. As of April,6th 2020 over 3.66 M cases have been confirmed worldwide, including 257K deaths. Such huge numbers of infected people call for effective and affordable drug with urgent demand to control this situation.

Effectiveness of HCQ in inhibiting SARS-CoV-2 infection.
The drug HCQ was initially developed as an antimalarial drug. This drug becomes a topic of discussion when researcher says that it become useful in corona treatment. A case report in US showed that by the treatment of infection of SARS-CoV-2 with CQ, the clinical condition of the patient improved. This drug potentially blocks the spike protein of this coronavirus, from getting into cytoplasm of cell. CQ has the capacity of inhibiting the DNA replication of intracellular micro-organisms including corona viruses. In light of clinical data, clinical trials of CQ has been started for the treatment of COVID-19 published by Chinese National Health Commission. Chloroquine influences immune system activity by means of mediating an anti-inflammatory response, which would possibly minimize damage due to exaggerated inflammatory response. Since CQ has the similar chemical structure and mechanism of action to HCQ, it is easy to ask about the idea that HCQ may be an effective drug in treatment of infection by COVID-19. So data shows that HCQ may be less potent compared to CQ against COVID-19, and called the drug as unproven coronavirus drug [14,13].

There is evidence available for antiviral effect of HCQ against SARS-CoV-2 infection. HCQ/CQ has been shown to kill the COVID-19 virus in laboratory dish. French studies suggested that HCQ could reduce the viral load in

ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

patient with virus, and CQ and HCQ has been prescribed to patient to reduce the length of hospital stay and improve the chances of disinfection of COVID-19. These drugs appear to work through two mechanisms. One is, they make it harder for the virus to attach itself to the cell, inhibiting the virus from entering the cell and multiplying within it. The other is, if the virus enters the cell, the drug kill it before it can multiply [11]. Chloroquine also increases endosomal pH and interferes with the glycosylation of cellular receptors of COVID-19 and it has the potential to block viral infection. It also seems that both HCQ and CQ blocked the way of transport of the virus from early endosomes (EEs) to endolysosomes (ELs), which seems to be a need to release the viral genome as in the case of SARS-CoV.

Studies on patients tells that 2.8% of patient died within 7 days who treated with HCQ, while 4.6% of patient died who didn't treat with HCQ. In the outcome of transferred patients to the ICU 20.2% of total patients transferred to the ICU who were treated with HCQ while 22.1% of total patients transferred to the ICU who were not treated with HCQ [12, 14].

In the treatment of COVID-19 it has been suggested to take with azithromycin and may increase the risk of prolonged QT syndrome. Patients who are already on medication of heart rhythm problems, after addition of HCQ/CQ can cause fatal dysrhythmia. Still this drug needs to undergo further clinical trials on COVID-19 [11]. In many researches it is showed that treatment with HCQ may increase the mortality rate or increase the risk of death in the hospitalized patients [21].

Caution needed on the use of Hydroxychloroquine:
Hydroxychloroquine uses can lead to complication. Drugs can only be taken under the supervision of doctor. Serious poisoning and deaths have been reported after inappropriate dosage of hydroxychloroquine or chloroquine. There are many reports which mentions about cautions in the recommendation of these drugs. The treatment of malaria in adults recommends the doses 13mg/kg which not exceed 800 mg and should not be used to treat patient with weight less than 31 kg. In the treatment of rheumatoid arthritis (RA) it may take 400-600 mg daily, and with a good response dosage may reduce to 50%. Many gastrointestinal disorders like nausea, vomiting, abdominal pain may happen after improper consumption routine [25]. Patients who have blood disorder and sensitivity to quinine use the drug with cautions seriously. Irregularity in heartbeat, and liver disease may concern with taking of HCQ. Antacids may decrease the absorption of HCQ, so antacids give effect on the medicinal effects of HCQ. It should be taken minimum after 4 hour interval between intakes of both agents. For the patient with hepatic impairment the dose of drug may be decreased HCQ has been widely excite as miracle drug against covid-19. In the time of COVID-19 (FDA) food and drug administration (US) has issued a caution against the use of hydroxychloroquine in the treatment of the viral-disease because of not showing safe and effective treatment of covid-19, corona-patients being treated with the combination of other drug as azithromycin or other medicines. Indian Council of Medical Research (ICMR) advised not to take the drug below the age of 15 and above the age of 60 and the patient with cardiovascular disease. In the treatment of covid-19 higher dose of HCQ or CQ should not be given specially when interact with azithromycin as this combination raises the potential regarding QT prolongation [30, 13].

There are many drug which gives adverse effect when interact with HCQ such as-

- Digoxin (used to treat heart failure)- increased serum digoxin level.
- Drug that prolong QT interval- increased the risk of ventricular arrhythmias.
- Insulin (anti-diabetic drug)– enhance the effect of hypoglycemic treatment.
- Methotrexate (used to treat cancer, ectopic pregnancy)- may increase the frequency of side effects.
- Cycloporin (used for RA, nephrotic syndrome)- increased plasma cycloporin level.
- Antacids- reduced the rate of absorption.

Toxicity and Side Effects of Hydroxychloroquine:
Only limited preclinical data are available for HCQ therefore chloroquine data is considered due to similarity of pharmacological properties and structure between two products. HCQ is efficacious for various disease and widely used for long term treatment of autoimmune conditions but can produce toxic effect. The main reason for stopping the treatment of HCQ is toxicity but in case of antimalarials, absence of clinical reaction is main reason for

ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

stopping treatment. HCQ drug can increase plasma concentration of penicillamine which is the reason for development of many side effects. Patients who are under medication of HCQ may experience vomiting, head-ache, nausea, dizziness and change in mood have also been reported. There are many contraindication and precautions required if patient have heart condition, psoriasis and diabetes. If giving without physician's prescription to children, it would be very dangerous. Even a single pill can be lethal to life.

- **Retinopathy-**

The mechanism of HCQ retinopathy is not well understood. Hydroxychloroquine ocular toxicity include keratopathy, lens opacities, ciliary body involvement and retinopathy. One of the most important concerns is toxic effect or side effect is retinopathy [7]. It generally takes place with chronic use. People who take less dose generally have low or negligible risk. The risk begins to go up when a patient takes the medication over 5 years or taking more dose [18]. HCQ retinopathy is estimated 0.33% incidence before 5-7 year and is increased to 2.1% by 15 years. Histologic examination and animal experiments shown that retinopathy can occurred due to boundation of HCQ to melanin in the retinal pigmented epithelium as well as direct toxicity to retinal ganglion cells. The risk increased by 1% every year with continue medication. To control this, eyes monitoring is applicable. The good thing is patient who treated with HCQ have a lower chance to develop diabetes in comparison to who never took this medicine.

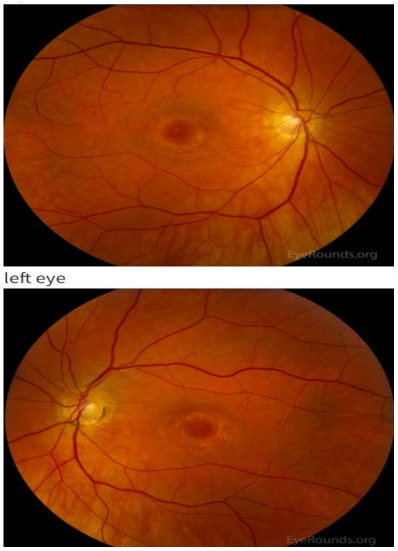

Figure:- The photograph of classic Retinopathy of hydroxychloroquine toxicity.

Image credit- university of lowa healthcare. (eyerounds.org)/bull's eye maculopathy due to hydroxychloroquine toxicity.

The major pathogenic effect of HCQ is the induction of lysosomal dysfunction in photoreceptors and RPE cells which leads to the accumulation of lipofuscin in RPE.
If patient has sign and symptoms of poisonous such as rash/visual changes then it is important to informed early to his/her physician.

- **Genotoxicity-**

Genotoxicity is a toxic effect which describe the properties of chemical agent that damage the genetic information (DNA/RNA). Limited data is available on hydroxychloroquine genotoxicity, but Chloroquine is reported as a weak genotoxic agent [22]. These drugs produce weak genotoxic effect through the catalytic inhabitation of DNA repair enzyme. Cytochrome P450 inherited macular disease may confer high susceptibility to toxicity. If there are chances of toxic effects then HCQ therapy may be stopped. A genetic predisposition also known as genetic susceptibility is an increased developing of disease based on genetic makeup. And the patient who has genetic disorder as G6PD deficiency may have a serious reaction to HCQ and should be used with proper precautions.

ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

Discussion of a case study of HCQ overdoses:
HCQ overdose can manifest rapidly with severe cardio-toxicity. HCQ is less toxic than CQ. As HCQ and CQ have similar structure and properties of pharmacology, so most of the discussion are based on chloroquine toxicity. Gastrointestinal upset has been reported with HCQ intake. Some side effect of HCQ may occur that usually do not need medical attention, but overdose of HCQ can also kill a person. Drowsiness, increased thirst, loss of appetite, no pulse or blood pressure etc. are the first symptoms of overdose. After HCQ overdose life threatening hypotension, hypokalemia, and conduction problem can occur within half an hour after ingestion. Usually adult dose of HCQ for malaria is 400 mg orally every week. And each dose should be taken with a glass of milk or meal. Hydroxychloroquine has effects of cardiac sodium and potassium channel blocking which is related to dose and resulted in delayed repolarization and slow intraventricular conduction. This results in widened QRS and ventricular dysrhythmias and hypotension. Due to intracellular movement of potassium on cell membrane Hypokalemia appears. The mechanism is related to reduce potassium efflux from the membrane channels blockade [26]. Treatment of overdose need further study but current recommendations for treatment are-

- Replacement of potassium with close monitoring of levels [10].
- Charcoal for gastrointestinal decontamination within an hour of ingestion.
- Mechanical ventilation and early intubation [10].
- Reduce level of HCQ in the blood by using exchange transfusion.

At home or before admission to hospital overdose may treated with evacuation of the stomach by emesis or gastric lavage until the stomach get empty [18].
The conclusion of Hydroxychloroquine overdose is that HCQ poisoning is very rare but because of its rapid progression to life threatening symptoms, it is very poisonous [10].

Proper Dosage:
In the case of heavy doses, it is important to take the drug with a meal or glass of milk. HCQ mainly used in malaria, SLE and RA.

- In case of *malaria* prophylaxis 400 mg once a weak or 6.5 mg/kg is the proper dosage for adult patient.
- The patients effected with coronavirus (COVID-19) recommends 400 mg. once every week for seven weeks.
- 600 mg or 6.5 mg/kg per day,[4] or whichever lower is proper dosage in the case of *RA*. Retinopathy has been occurred in the patients when dose is exceeded [6].

Hydroxychloroquine During Pregnancy:
Use of HCQ during pregnancy has remained controversial. Malaria and lupus may increase the chance of premature delivery. HCQ don't increase the chance of premature delivery [7, 8]. HCQ may benefit pregnancies by reducing active disease of lupus without harming baby [5], also HCQ reduce the chance of a specific heart problem in new born baby. Studies doesn't show the chances of miscarriage related to HCQ [7]. It may take six to eight weeks to eliminate completely. HCQ binds less rapidly in comparison of CQ to the tissues. In studies on pregnant women, both retinal and ototoxicity have been reported in children born to women treated with CQ/HCQ. Some amount of HCQ found in the breast milk of the mother who breastfed while taking HCQ, that have no harmful effect in infants [9].

3. CONCLUSION
HYDROXYCHLOROQUINE which is derivative of CHLOROQUINE is mainly used in the treatment of malaria and arthritis. HCQ have pharmacokinetics with rapid gastrointestinal absorption, elimination by kidneys and administered as sulfate salt and metabolized by enzyme named Cytochrome P450. The drug has a toxic side effect known as retinopathy. Poisoning cases of HCQ are very rare but because of rapid progression to life threatening symptoms, it is very poisonous in overdose. Studies and clinical trials proved the role of HCQ in the treatment or prevention of COVID-19, but it is also true that overdose of the drug may cause of death. Demand of HCQ has increased a lot in all over world after these trials. But some researches says that the use of HCQ in treatment of covid-19 may increase the mortality rate. Further studies need to elucidate how these drugs or derivatives may be used in the disease that currently have no treatment. There are so many precautions which are taken during the

ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

medication with HCQ, and with the interaction the drug gave inverse effect in the time of COVID-19. HCQ may be used as an anti-HIV-1 drug with antiviral effect against HIV and arthritis. The patient who was studied had 1-log decrease in HIV-RNA and a decrease in IL-6 levels which improved immune response.

Future Aspect:

- Repurposing is the process of finding new therapeutic indication for currently available drugs. HCQ/CQ are currently among the most studied drugs. After use of Hydroxychloroquine in treatment of COVID-19, repurposing of this drug is growing. These drugs (CQ/HCQ) have antitumoral properties, and also antimutagenic, antiproliferative capacities. Due to these properties it can be a possible option of tumors' treatment with chemotherapy. For many neurological disease, repurposing of Hydroxychloroquine is under examination. In future it is possible to treat neuro-disease with HCQ. Neoplasm treatment is also under trials. Cutaneous and gastrointestinal manifestation are not serious but retinal toxicity and cardiac toxicity are classified as serious effect, all these effects are under clinical trials with HCQ and trying to overcome it. Hydroxychloroquine can also be used in cancer which gives effect as immune response modulation. Recently a role of HCQ has been postulated in the treatment of multiple sclerosis (MS). There are so many trials of HCQ which undergoing in non-neoplastic disease [16]. Some are mentioned below-

- For the treatment of hidradenitis suppurativa.
- Prevention of recurrent miscarriage (pregnancy loss).
- Prevention of congenital heart block.
- In pediatric interstitial lung disease.
- Dose reduction in rheumatoid arthritis.
- Metabolic effect of HCQ.
- Treatment of type-2 diabetes mellitus.
- PK studies of Drug administration to children.

Abbreviations	Meaning
CQ/HCQ-	Chloroquine/Hydroxychloroquine
COVID-19-	Corona Virus Infectious Disease-2019
DMARD-	Disease Modifying Anti-Rheumatic Disease
DNA-	Deoxyribonucleic acid
HIV-	Human Immunodeficiency Virus
IL-6-	Interleukin-6
PHA-	Phytohemagglutinin
RA-	Rheumatoid Arthritis
RPE-	Retinal Pigment Epithelium
SARS-CoV-2-	Severe Acute Respiratory Syndrome Coronavirus-2
SLE-	Systematic Lupus Erythematosus

REFERENCES

[1] N.J. Olsen, M.A. Schleich and D.R. Karp. "Multifaceted effects of hydroxychloroquine in human disease." seminar in arthritis and rheumatism vol.43, issue 2, 264-272, 2013.
[2] Ben Zvi, Kivity S, Langevitz P, Shoenfeld Y. "Hydroxycholroquine; from malaria to autoimmunity." Clinical reviews in allergy & immunology 42 (2), 145-153, 2012.
[3] Scgrezenmeir, Eva; Dorner T. "mechanism of action of hydroxychloroquine and chloroquine implication for rheumatology." Nature reviews rheumatology.16, 155-166(2020).
[4] Rynes RI: "antimalarial drugs in the treatment of rheumatological disease." Br J Rheumatol, 36(7), 799-805, 1997.

ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

[5] G Ruiz-Irastorza, M Ramos-Casals, P Brito-Zeron, M A Khamashta. "Clinical efficacy and side effects of antimalarial in systemic lupus erythematosus: a systematic review." Annals of the rheumatic disease 69 (01), 20-28, 2010.
[6] James Odell, Claire Haire, N Erikson, W Drymalski, William Palmer, P James Eckhoff, Vernon Garwood, Pierre Maloley, Lynell W Klassen Steven Wees, Harry Klein, Gerald F Moore. "Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine, and hydroxychloroquine or a combination of all three medications." The England journal of medicine. 334(20), 1287-1291, 1996
[7] Crispin Abarientos, MD, Kirk Sperber,MD, Deborah L Shapiro, Wilbert S Aronow, Chun Peng Chao & Julia Y Ash. "Hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy." expert opinion on drug safety 10 (5), 704-714, 2011.
[8] Buchanan NM, Elias Toubi, Munther A Khamashta, Fernanda Lima, Sian Kerslake, GR Hughes. "Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases." Annals of rheumatic disease 55(7), 486-488, 1996.
[9] Frassi M, C. Biasini, M. Taglietti, E. Danieli, D. Faden, A. Lojacono, et al. "Hydroxychloroquine in pregnant patient with rheumatic disease: a case control observation of 76 treated pregnancies (abstract)". lupus 13 (9) 755, 2004.
[10] Kathy Marquardt, Timothy E. Albertson. "Treatment of hyroxychloroquine overdose." The American journal of emergency medicine. 19 (5), 420-424, 2001.
[11] Lai C C, Liu Y.H., Wang C.Y., Wang Y.H., Hsueh S.C., Yen M.Y. "Drug treatment option for the 2019-new coronavirus (2019-nCoV)." Bioscience Trends 14 (1), 69-71, 2020.
[12] Wang M., Cao R., Zhang L., Yang X., Liu J., Xu M. "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro." Cell Research 30 (3), 269-271, 2020.
[13] Gautret P, Lagier J-C, Parola P, Jean Christophe Lagier, Line Meddeb, Morgane Malihe, Barbara Doudier, Johan Courjon, Vera Esteves Vieira, Didier Roult et al. "hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non randomized clinical trials." international journal of antimicrobial agent, 105949, 2020.
[14] Colson P., Rolain J.M., Lagier J.C., Brouqui P., Raoult D. "chloroquine and hydroxyhloroquine as available weapons to fight COVID-19." International Journal of Antimicrobial Agent 105932 (10.1016), 2020.
[15] Shi TT, Yu XX, Yan LJ, Xiao HT. "research progress of hydroxychloroquine and autophagy inhibitors in cancer." Cancer chemotherapy and pharmacology 79 (2), 287-294, 2017
[16] Ongoing Trials based on HCQ. (www.clinicaltrials.gov)
[17] Sperber K, Louie M, Proner J, Kraus T, Sapira E, Lin S, Mayer L. "hydroxychloroquine treatment of patient with human immunodeficiency virus type-1." Clinical therapeutics 17 (4) 622-636, 1995.
[18] Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patient hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A randomized clinical trial. 2020.
[19] S E Tett, Dj Cutler, RO Day, KF Brown: "bioavailablity of hydroxychloroquine tablets in healthy volunteers." British journal of clinical pharmacology, vol.27 1989
[20] Micheal F. Marmor, Fredrick Wolfe. "Rates and predictors of hydroxychloroquine retinal toxicity in patient with rheumatoid arthritis and systemic lupus erythematous." arthritis care and research 62 (6), 775-784, 2010.
[21] Liang Chen, Shuoyan An, Guangyu Yao, Jiasheng Xiong, Haiyan xiong, Ping Zhao, Lufang Jiang, Wei Hua, Firat Duru, Qingwu Jiang. "lack of benefit in COVID-19 patients treated with hydroxychloroquine or chloroquine: a systemic review and meta analysis. 2020.
[22] Taraknath Chatterjee, Kalim A. Khan, Ashok K. Giri, Amitabh Muhkopadhyay. "comparative mutagenic and genotoxic effects of three antimalarial drugs, chloroquine, primaquine and amodiaquine." Mutgenesis 13 (6), 619-624, 1998.
[23] Evan W. MeChesney "animal toxicity and pharmacokinetics af hydroxychloroquine sulphate." the American journal of medicine 75 (1), 11-18, 1983.
[24] Mohamad A El,Shistawy, Khodor Haider Hassan, Ragaee Ramzy, Fadwa Berri, Mohamad Ezzedine, Salam Najreddin. "comaparative toxicity study of chloroquine and hydroxychloroquine on adult albino rats." 2nd mediterranean interdisciplinary forum on social science and humanities: MFS 2014, 399, 2014.

ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

[25] Tephan D. Fihn, Eli Perencevich,Steven M. Bradley. "caution needed on the use of chloroquine and hydroxychloroquine for coronavirus disease." jama network open 3(4) e209035-e209035, 2020.
[26] HT Fung, KK Lam, OF Wong, B Lau, CW Kam. "A Case of fatal hydroxychloroquine overdose." Hong-kong journal of emergency medicine.14(1), 53-57, 2007.
[27] Jean-Marc Rolain, Philippe Colson, Didier Roult. "recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and vial infection in the 21st centuary."International journal of antimicrobial agents 30 (4), 297-308, 2007.
[28] kirk Sperber, Thomas H Kalb, Vera J. Stecher, Ranjit Banarjee, Lloyd Mayer. "inhibition of human immunodeficiency virus type 1 replication by hydroxychloroquine in T cells and monocytes." AIDS research and human retrovirus 9(1), 91-98 1993.
[29] Matthew H. Ornstein and Kirk Sperber. "the antiinflammatory and antiviral effects of hydroxychloroquine in two patients with acquired immunodeficiency syndrome and active inflammatory arthritis." Arthritis & Rheumatism:official journal of the american college of rheumatology 39 (1), 157-161, 1996.
[30] Catherine Marcucci, Neil B. Sandson, Matt V. DeCaro, Wayne T. Nicholson. "summary of chloroquine and hydroxychloroquine drug-drug interaction." march 27, 2020.
[31] wey, Y.; NYGARD, G.A.; ELLERTSON, S.L.;KHALIL, S.K. stereoselective disposition of hydroxychloroquine and its metabolites in rats. Chirality, v.7,n.8, p.598-604, 1994.