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A SYSTEMATIC REVIEW ON CLINICAL & STRUCTURAL EFFICACY OF HYDROXYCHLOROQUINE IN TREATMENT OF COVID-19 & RHEUMATOID ARTHRITIS

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Abstract: COVID 19 has affected humans in every possible way. According to the WHO Globally, as of 10:34am CEST, 9 July 2020, there have been 11,841,326 confirmed cases of COVID-19, including 544,739 deaths. Most affected regions include America followed by Europe. Chloroquine and hydroxychloroquine are commonly prescribed worldwide. When used for malaria prophylaxis, chloroquine is generally administered at a dose of 500 mg per week starting 2 weeks before and continuing for up to 8 weeks following endemic exposure. Long-term use can be considered for the treatment of chronic autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. Hydroxychloroquine is typically prescribed as a 400 mg weekly dose when used for malaria chemoprophylaxis and as a 200 to 400 mg daily dose in patients with systemic lupus erythematosus or with rheumatoid arthritis on 17 June 2020, WHO announced that the hydroxychloroquine (HCQ) arm of the Solidarity Trial to find an effective COVID-19 treatment was being stopped. This review article discusses historical perspective and development of chloroquine analogues, current research work on chloroquine analogue, advance treatment used for the treatment of the COVID19 and new drugs as well as various test available for the COVID 19.

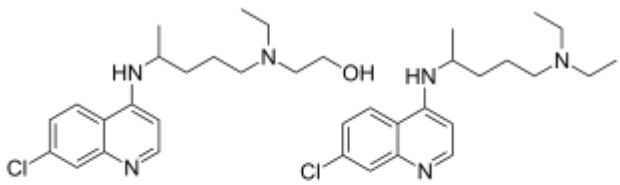
Index Terms: Chloroquine, Hydroxychloroquine, COVID19, Rheumatoid Arthritis

I. INTRODUCTION

Historical perspective and development of chloroquine analogues

Chloroquine was discovered by Hans Andersag in 1934.[6] The safety profile is excellent and well established over time. Chloroquine can be prescribed to adults, children of all ages, pregnant women, and nursing mothers. It has milder adverse effects when taken as prescribed. Milder and frequent adverse effects include gastrointestinal intolerance, i.e. nausea, vomiting, and epigastric pain. A higher dose can lead to retinal toxicity, seizures, pruritus, and photosensitivity. [7–10]

In 2014, Stevens–Johnson syndrome (SJS) was added as an adverse drug reaction into the prescribing information leaflet of chloroquine in India. SJS is a rare and serious disorder of the skin and mucous membranes. [11]



hydroxychloroquine (1) chloroquine (2)

Hydroxychloroquine (HCQ) sulfate, was first synthesized in 1946 by adding hydroxy group within chloroquine. Hydroxychloroquine is a synthetic antimalarial drug derived from 4-aminoquinolone. [13]Since CQ and HCQ share similar chemical structures and mechanisms of acting as a weak base and immunomodulator, it is easy to conjure up the idea that HCQ may be a potent candidate to treat infection by SARS-CoV-2. Actually, as of February 23, 2020, seven clinical trial registries were found in Chinese Clinical Trial Registry (http://www.chictr.org.cn) for using HCQ to treat COVID-19.

Both CQ and HCQ are weak bases that are known to elevate the pH of acidic intracellular organelles, such as endosomes/lysosomes, essential for membrane fusion.[14] In addition, CQ could inhibit SARS-CoV entry through changing the glycosylation of ACE2 receptor and spike protein.[15] oral absorption of CQ and HCQ in humans is very efficient. In animals, both drugs share similar tissue distribution patterns,

with high concentrations in the liver, spleen, kidney, and lung reaching levels of 200–700 times higher than those in the plasma.[16] It was reported that safe dosage (6–6.5 mg/kg per day) of HCQ sulfate could generate serum levels of 1.4–1.5 μM in humans.[17]
The antimalarial drugs hydroxychloroquine and chloroquine are DMARDs introduced serendipitously and empirically for the treatment of various rheumatic diseases. [18]
The antimalarial drug chloroquine and its analogue hydroxychloroquine, which is used for the treatment of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.[19–20] The combination of hydroxychloroquine with a second-generation macrolide, such as azithromycin (or clarithromycin), has also been advocated, despite limited evidence for its effectiveness.[21] treatment with chloroquine, hydroxychloroquine, or either drug combined with a macrolide can have the cardiovascular adverse effect of prolongation of the QT interval, which could be a mechanism that predisposes to ventricular arrhythmias.[22] In addition to having direct immunomodulatory effects, chloroquine and hydrochloroquine can reduce rates of atherosclerosis, improve hyperglycaemia and hyperlipidaemia and protect against infections in patients with inflammatory rheumatic diseases.[23–24]

II Pharmacokinetics Consideration

Chloroquine analogues are water soluble and almost completely absorbed from the gastrointestinal tract. Both chloroquine and hydroxychloroquine reach the peak plasma concentration 4–12 h after an individual dose and achieve equilibrium plasma levels after 4–6 weeks of constant daily dosing, although there is considerable inter-individual variation. The half-lives of chloroquine and hydroxychloroquine are prolonged, ranging between 40 and 50 days. In addition, a major fraction of chloroquine analogues in the plasma is bound to plasma proteins, mainly albumin and α-acid glycoprotein, and also avidly bound to several tissues in the body when given at therapeutic doses. small amounts are excreted in bile, sweat and saliva, the major elimination route of chloroquine analogues is via the renal system, and elimination may thus be affected by the pH of urine.[25-27]

III 3.1 Indications for chloroquine[28]

Chloroquine analogues have been shown to have potent beneficial effects in many non-malarial diseases.

Summary of indications for chloroquine analogues

FDA-approved and FDA-labelled indications
Malaria (except resistant *P. falciparum* and *P. vivax* causing malaria)
Lupus erythematosus in different forms, such as discoid, systemic; also effective in pregnant SLE patients
RA, act as first-line disease-modifying antirheumatic drugs
Chloroquine analogues in clinical research trials
Lupus erythematosus (discoid and cutaneous) in different adjunct therapies
RA in combination with other drugs
Psoriatic arthritis
Prostatic cancer
Additional research trials
Local metastatic melanoma, chronic lymphocytic leukemia and diffuse large B cell lymphoma
Unapproved but first-line uses include
PCT and chronic ulcerative stomatitis
Hepatic amoebic abscess
Refractory chronic urticaria[29–30]

Quinacrine is used as an effective contraception. [31]

Second- and third-line treatments

Non-infectious skin diseases such as dermatomyositis, sarcoidosis, polymorphous light eruption and disseminated granuloma annulare

Miscellaneous conditions

Sjogren's syndrome, granuloma annulare, erosive lichen planus, frontal fibrosing alopecia[32], necrobiosis lipoidica, chronic actinic dermatitis, actinic reticuloid, actinic prurigo, epidermolysis bullosa, Kikuchi–Fujimoto disease, graft-versus-host disease, chronic erythema nodosum, morphea and systemic sclerosis, pemphigus vulgaris, pemphigus foliaceus and pemphigoid gestationis[33]

Chloroquine analogues and current research

Bone diseases, different forms of cancers, hyperglycaemia, dyslipidaemia, thrombosis and severe infectious diseases

Chloroquine analogues as investigational drugs

AIDS and severe acute respiratory syndrome (SARS)

Human prion diseases (CJD) and LAM

3.2 MOA

In addition to having direct immunomodulatory effects, chloroquine and hydrochloroquine can reduce rates of atherosclerosis, improve hyperglycaemia and hyperlipidaemia and protect against infections in patients with inflammatory rheumatic diseases. [34–35] The mechanisms of action of hydroxychloroquine and chloroquine remain under continuous study in modern molecular medicine [36–37],using advanced tools in computational biology[38], synthetic biology[39–41], immunology[42–43], structural biology[44–45] and 'big data'-driven public health science.[46–47]Detailed studies on the mode of action of hydroxychloroquine are needed to better understand dose–response relationships and safety-related aspects. Hydroxychloroquine is metabolised in the liver by dealkylation to desethyl chloroquine and bisedesethyl chloroquine. [48]

I. Rationales for lysosome tropic amines

Chloroquine is a diprotic weak base (pK_{a1}=8.1, pK_{a2}=10.2 at 37°C) that can exist in both protonated and unprotonated forms Unprotonated chloroquine can diffuse freely and rapidly across the membranes of cells and organelles to acidic cytoplasmic vesicles (late endosomes and lysosomes). chloroquine analogues are known as lysosomotropic agents (i.e. they are taken up selectively into lysosomes).[49] For optimal activity of hydrolases, pH is maintained at ~5.0 by the action of lysosomal H^+-ATPases.[50] an irreversible accumulation of chloroquine in lysosomes to >100-fold excess concentration and causes an elevation of pH due to trapping of H^+ ions by chloroquine.[51] The increased pH induced by chloroquine in lysosomes also causes decreased activities of the aspartyl protease cathepsin D and the cysteine protease cathepsin B, which are responsible for early and late cleavage of invariant chains from the MHC class II molecule.[52–54]

3.1 Anti-inflammatory and immunomodulatory effects[28]

Chloroquine analogues have well-recognized anti-inflammatory and immunomodulatory actions[55], but their specific mechanisms in individual diseases are not clear.

Anti-inflammatory and immunomodulatory actions of chloroquine analogues

1.Inhibition of antigen processing and presentation

2.Inhibition of stimulation of TLR9 cells, which participate in immune responses

3.Inhibition of cytokine production and release by T cells: IL1, 2, 6 or 18, TNFα and IFNγ

4.Increase in Treg activity and up-regulated levels of IFNα and IL2 and 10 cytokines

5.Inhibition of activity of cytotoxic T lymphocytes and self-reactive CD4+ lymphocytes

6.Reduced levels of chemokines CCL2 and CXCL10 in SLE

7.DNA binding: competitive inhibition of anti-DNA antibodies

8.Inhibition of phospholipase A2 and thereby antagonizing the effects of prostaglandins and leukotrienes

9.Decreased DNA, RNA and protein synthesis in thymocytes

10.Blockade of the actions of endogenous as well as exogenous histamine

11.Inhibition of nitric oxide formation by macrophages and induced production of reactive oxygen species in astroglial cells

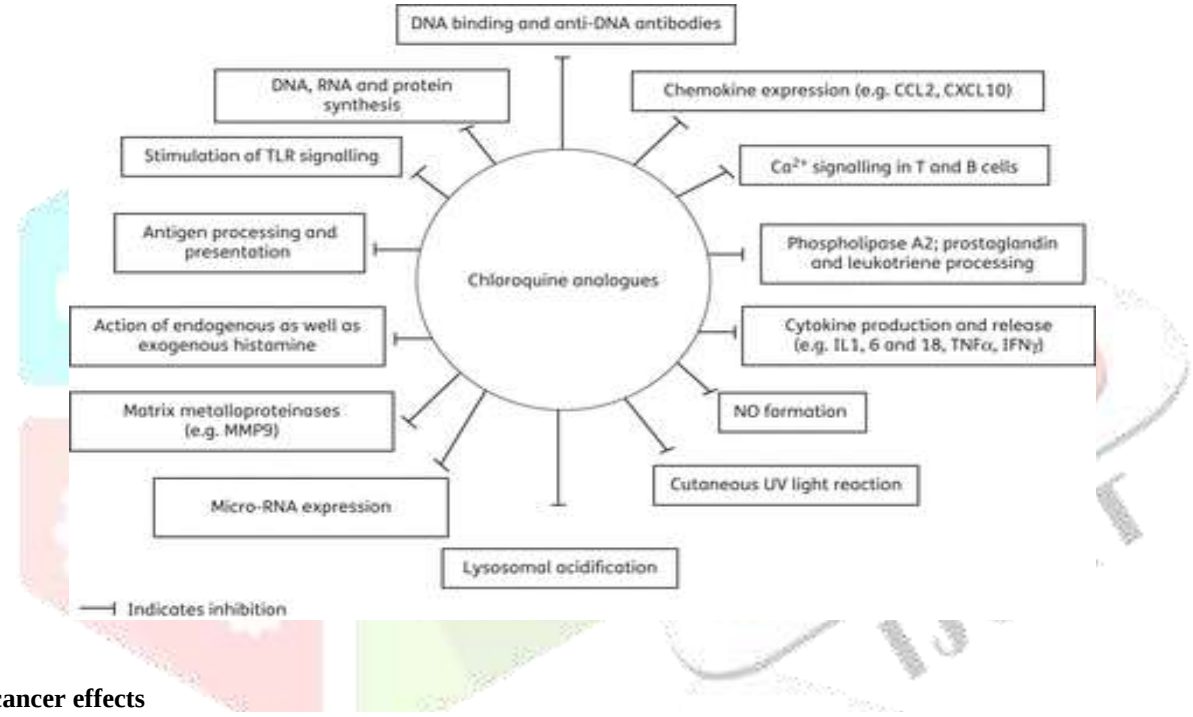
12.Absorption and blocking of cutaneous reactions to UV light

13.Inhibition of T and B cell receptor calcium signaling

14.Inhibition of matrix metalloproteinases

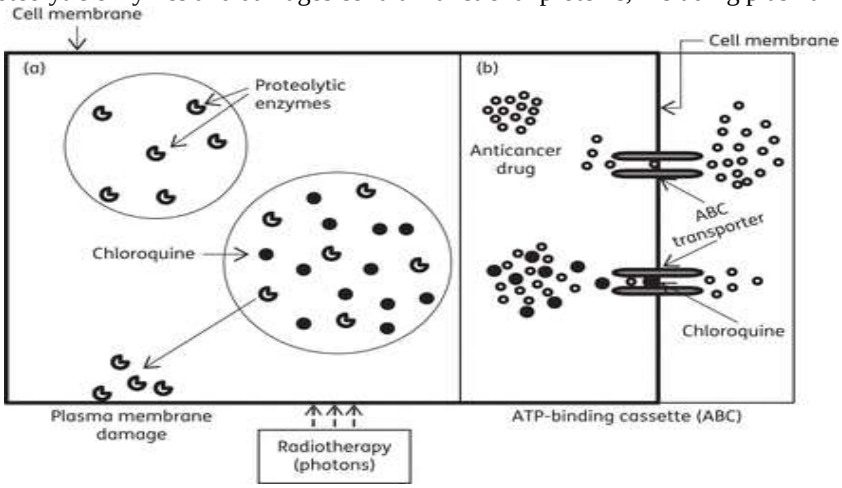
15.Inhibition of micro-RNA expression

16.Decreased T_H17-related cytokines



3.2 Anticancer effects

The anticancer mechanisms of chloroquine analogues are more complex, with many potential cellular targets. The most common approach in cancer therapy is the inhibition of autophagy and sensitization of malignant cells to radiation and chemotherapeutic agents by chloroquine analogues. [56–57] The lysosome tropic properties of chloroquine analogues are their most important characteristics for alteration of the malignant progression of cancer cells. the analogues can damage tumor cells when lysosomal permeability is also increased by radiation, which causes the release of proteolytic enzymes and damages cellular functional proteins, including plasma membrane-associated proteins



The ATP-binding cassette (ABC) family of transmembrane proteins and the multidrug resistance proteins extrude chemotherapeutic drugs from targeted cancer cells. Chloroquine analogues, used at clinically achievable concentrations, are also known to sensitize cells to radiation and anticancer drugs.

Chloroquine analogues, used at clinically achievable concentrations, are also known to sensitize cells to radiation and anticancer drugs. [58] The other main actions of chloroquine analogues responsible for most intracellular actions are (i) the molecular intercalation of chloroquine into DNA. [59](ii) the inhibition of lysosomal enzymes, particularly phospholipase A2. [60]

3.3 HCQ in nephrology

The mechanistic rationale for the use of CHQ analogues in renal diseases are primarily driven by immunological properties discussed hereinbefore in the rheumatologic disorders and CVD. The glomerular mesangial cells are derived from the monocyte/macrophage lineage and play a prominent role in the pathogenesis and progression of the autoimmune damage in primary glomerular diseases. [61]

Due to its inhibitory effects on a series of steps critical to the process of autoimmunity, that is, self-peptide recognition, its antigenic presentation and the resultant short-term and long-term downstream responses with the generation of cytotoxic cytokines and Th-1 type cellular immune response, respectively. [62]

A number of investigators in recent times have focused on the potentials of HCQ to affect the pathophysiological basis of the IgA nephropathy. Activation of the TLR-9 pathways by the common antigens has been shown to affect the severity of IgA nephropathy and HCQ is a potent inhibitor of this pathway. [63]

3.4 CHQ in oncology

There is growing research of CHQ is important for the treatment of neoplasms. CHQ and HCQ have been tested in many cancer tumors including gliomas, breast cancer, metastatic cancer, multiple myeloma, lymphomas, head and neck cancers, and gastrointestinal cancers.

Recent research suggests that CHQ is used as a antineoplastic effects are likely independent from its autophagy-inhibiting activities as the autophagy-related pathways were found to inhibit cholesterol biosynthesis and thereby induce cell death. [64]

There is evidence that CHQ can profoundly influence cell metabolism through multitude of pathways such as inhibition of glyconeogenesis, mitochondrial metabolism, and amino acid metabolism. [65]

The CHQ property against T cell multiplication evoked in response to foreign antigens and major histocompatibility complex antigens in conjunction with reduced T cell cytokine production is leveraged for inhibition of graft-*versus*-host disease in patients who receive bone marrow transplantation. [66]

3.5 Chloroquine analogues and current research

3.5.1 Bone diseases

In RA and SLE patients, Administration of chloroquine or hydroxychloroquine reportedly results in a slowing or even arrest of joint destruction as well as increased bone mineral density (BMD).[79] The effect of hydroxychloroquine which is used on insulin sensitivity and lipid parameters in non-diabetic patients with rheumatoid arthritis: a randomized blinded cross-over trial.[80–81]

For type II diabetic mellitus the hydroxychloroquine also emerges as a well-tolerated therapeutic option. When hydroxychloroquine was combined with insulin for the treatment of diabetes mellitus, glycated hemoglobin decreased significantly compared with patients receiving placebo, and the insulin dose had to be reduced by 30% in the hydroxychloroquine group. [82]

3.5.2 Anti-lipidaemic effects

The plasma lipid-lowering effects in RA, SLE, dyslipidaemia and diabetes mellitus that are therapeutically relevant in Chloroquine analogues due to the increased risks of premature atherosclerosis in these diseases.[83–86] So the mechanism is responsible for altered lipid profiles with chloroquine analogue treatment include a significant increase in lipid clearance rate and up-regulation of LDL receptors.[87]

3.6 Rheumatoid Arthritis

RA is a chronic inflammatory disease which results in bone damage as well as cartilage damage. Regarding the etiology of the disease, a possible risk factor for the onset or worsening of RA is cigarette smoking. Early diagnosis is key to optimal therapeutic success, particularly in patients with well-characterized risk factors for poor outcomes such as high disease activity, presence of autoantibodies, and early joint damage. [67]

Rheumatic diseases are considered major public health problem which affect millions of people worldwide resulting in high & rising health-care costs.[68–70] Approximately 0.5-1% of the world population are affecting with RA[71–72], it is common in women than in men & ages between 40 & 60 years.[73]

Both chloroquine and hydroxychloroquine inhibit the antigen presentation in dendritic cells, cytokine production in macrophages, and calcium and Toll-like receptor (TLR) signaling in B, T and other immune cells. Hence, chloroquine analogues have become the most commonly prescribed drugs in the treatment of many rheumatic diseases, including RA, palindromic arthritis, psoriatic arthritis and juvenile idiopathic arthritis.[74–77] Hydroxychloroquine is usually a component of medication combinations, including triple-drug therapy with methotrexate and sulfasalazine, a regimen that has been advocated as a safe, well-tolerated alternative to more expensive biological therapies which is used to treat RA.

There are various diagnostic tests are carried out[78]

1. Anti CCP antibody (second generation)
2. Anti MCV antibody
3. MRI
4. Ultrasound

3.6.1 Newer molecules for treatment of RA

It is now well validated that biologic therapies & medication have changed the way rheumatoid arthritis is managed. The target specific therapies which are act on the cytokines or its receptors; thus, modify immune mediated damage during the "window of opportunity". There are various examples of potential targets in RA include cytokines such as TNFa, IL1 and IL6, B cells, molecules that cause interaction between antigen presenting cells and T cells, RANK ligand (receptor activator of nuclear factor kB ligand), and small molecules that mediate intracellular signaling. [78]

IV. DISCUSSION

4.1 COVID-19

Many Scientist and physicians are working at heightened pace to research the treatment of current coronavirus infection (COVID-19). There are several potential repurposed candidate drugs have been tried in COVID-19. From these list of candidate drugs, two anti-malarial drugs came into limelight for following reasons. According to Initial studies found both chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) inhibits SARS-CoV-2 effectively *in vitro.* [88–90]

As per the Initial studies on hydroxychloroquine and chloroquine it was found that they inhibit covid in vitro and also a Chinese commentary, mentioning 15 trials, reported that, "Thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to control the treatment in inhibiting the exacerbation of pneumonia,[91] Advocates, including Donald Trump, have argued that hydroxychloroquine is widely used and safe for COVID-19. Its use is now permitted by the US Food and Drug Administration[92] and advocated by the Indian Council for Medical Research(ICFMD).[93] If it is permitted by USFDA but no drug is guaranteed to be safe, and wide use of hydroxychloroquine will expose some patients to rare but potentially fatal harms, including serious cutaneous adverse reactions **.**[93]

4.2 What is Corona Virus?

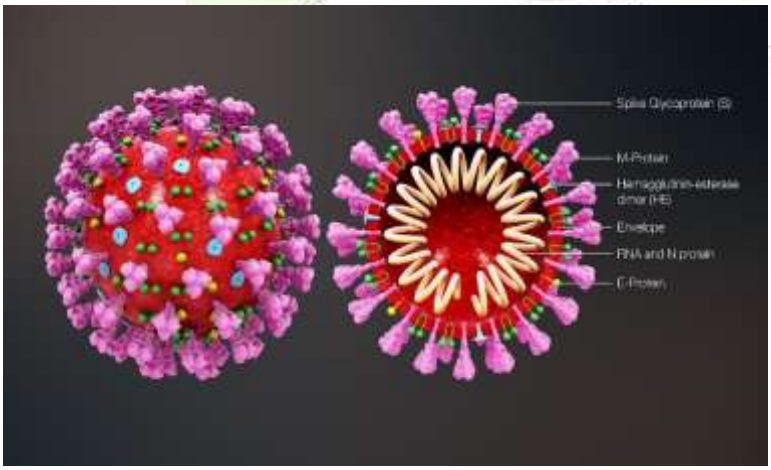
In the 1930's coronaviruses were first discovered when an acute respiratory infection of domesticated chickens was shown to be caused by infectious bronchitis virus (IBV).[94] In the 1940s, two more animal coronaviruses like mouse hepatitis virus (MHV) and transmissible gastroenteritis virus (TGEV) were isolated.[95] In the 1960s Human coronaviruses were discovered.[96–97] In late December 2019, an outbreak of an emerging disease (COVID-19) started in Wuhan, China and rapidly spread in China and outside due to a novel coronavirus (named SARS-CoV-2 latter). [98—99]

So basically, **Coronaviruses** are a group of related viruses that cause diseases in mammals and birds. In case of humans, coronaviruses results in respiratory tract infections. In some cases of the common cold (which maybe cause by rhinoviruses), while more lethal varieties can cause SARS, MERS, and COVID-19. Symptoms of covid varies from species to species like in case of chickens, they cause an upper respiratory tract disease, and in cows, pigs they cause severe diarrhoea. There are as yet no vaccines or antiviral drugs to prevent or treat human coronavirus infections. [100–101] The viruses can make people sick, usually with a mild to moderate upper respiratory tract illness, similar to a common cold, & Breathing Problem.

4.3 Structure

The structure of **Coronaviruses** are large pleomorphic spherical particles with bulbous surface projections. [102]The diameter of the virus particles is around 120 nm (12 μm), diameter of the envelope is ~80 nm (08 μm) and the spikes are ~20 nm (.02 μm) long. The envelope i.e. Outer covering of the virus if we see in electron micrographs it appears as a distinct pair of electron dense shells. [103]

The following structure of Coronavirus:



The viral envelope contains lipid bilayer in which the membrane (M), envelope (E) and spike (S) structural proteins are attached. .[104] the members of beta coronavirus subgroup A also have a shorter spike-like surface protein called hemagglutinin esterase (HE),therefore it is also called as a spike like structure.[105] Inside the envelope, there nucleocapsid, build using multiple copies of the nucleocapsid (N) protein, which are bound to the positive-sense single-stranded RNA genome in a continuous beads-on-a-string type conformation.[106–107] The lipid bilayer envelope, membrane proteins, spike and nucleocapsid protect the virus when it is outside the host cell.[108]

4.4 Prevalence of SARS-CoV-2

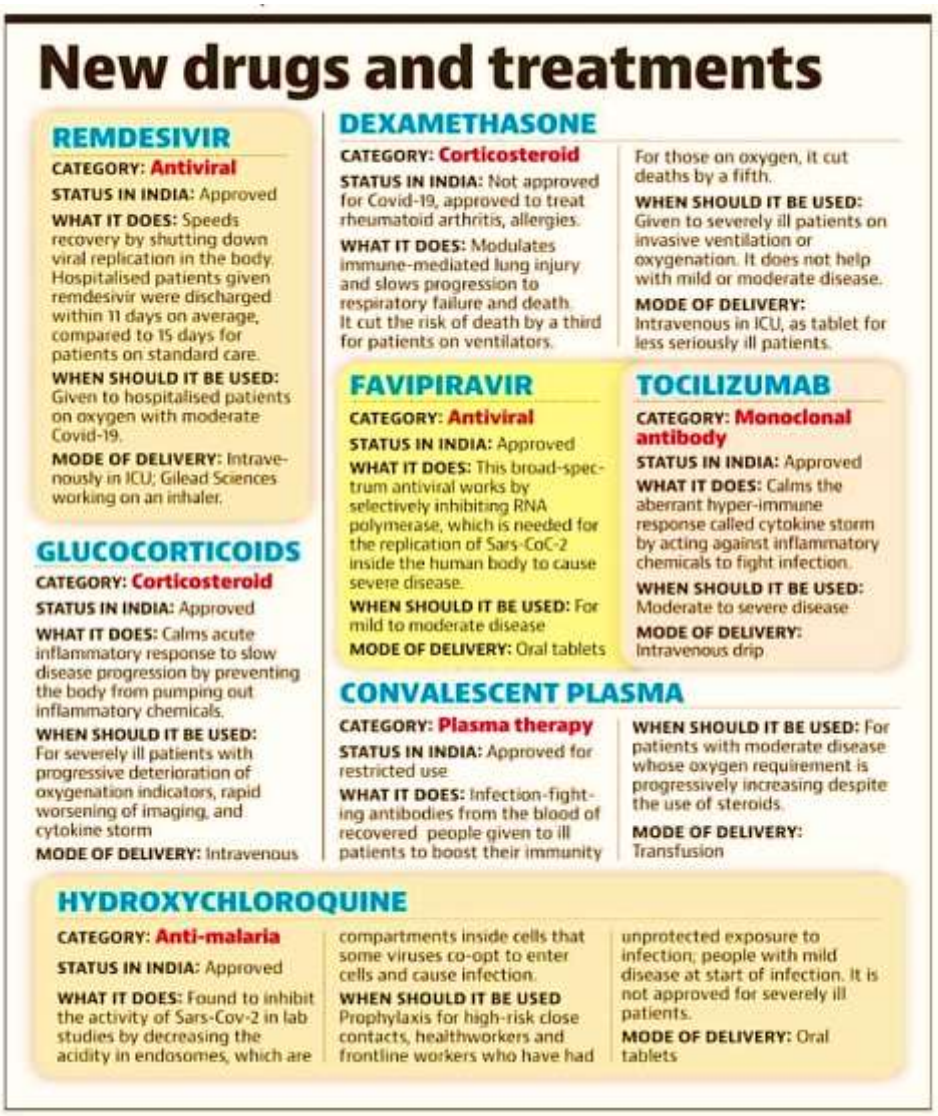
The average number of secondary infections that patients may cause in a completely susceptible population without intervention is represents the basic reproduction number (R_0). [109] Estimation of R_0 varies between research teams and is updated as more information becomes available. Using the SEIR model, according to Wu et al. estimated the R_0 of SARS-CoV-2 to be 2.47–2.86.[110] according to Majumder et al. used the IDEA model and reported R_0 of 2.0–3.3.[111] The estimated R_0 values 2.2–3.6 is for other β-coronaviruses, such as SARS-CoV.[112] The estimated R_0 value 2.0–6.7 is for MERS-CoV.[113] According to these results indicate that SARS-CoV-2 has relatively high transmissibility. Large studies from China reported that the median age of cases was 47 years (interquartile range 35–58 years), 87% of cases were aged 30–79 years and 3% were aged ≥80 years, and the number of female patients was 41.9%.[114–115] Most cases were diagnosed in Hubei Province, China (75%). 81% of cases were classified as mild, 14% were classified as severe and 5% were classified as critical. The overall case-fatality rate (CFR) was 2.3%; however, among cases aged 70–79 years and ≥80 years, the CFR was 8.0% and 14.8%, respectively.[115] This indicates that elderly males are more susceptible to SARS-CoV-2 compared with other groups, and this virus is more likely to affect elderly males with chronic underlying diseases like diabetes, hypertension, heart disease, etc.[116] In summary, the prevalence of COVID-19 is very high, the population is generally susceptible to SARS-CoV-2 and COVID-19 spread rapidly from a single city (Wuhan) to the entire country in just 30 days. Prompt measures are clearly needed to control the spread of the disease.

4.5 Treatment of SARS-CoV-2

4.5.1 Antiviral Western medical treatment

1. Remdesivir is a promising antiviral drug against a wide array of RNA viruses. Holshue et al. reported that treatment of a patient with COVID-19 with remdesivir achieved good results. [117] Xiao et al. found that remdesivir was effective in the control of COVID-19 in vitro. Meanwhile, chloroquine has been found to have immunomodulatory activity and could effectively inhibit SARS-CoV-2 in vitro.[118] Clinical controlled trials have shown that chloroquine was effective in the treatment of patients with COVID-19.[119] Remdesivir is undergoing a large number of clinical trials in several hospitals; the efficacy of the drug is uncertain at present. Arbidol, a small indole derivative molecule, was found to block viral fusion of influenza A and B viruses and hepatitis C viruses[120], and to have an antiviral effect on SARS-CoV in cell experiments[121]; as such, it may be a possibility for treatment of patients with COVID-19. A randomized controlled study on the treatment of COVID-19 with Arbidol and Kaletra showed that Arbidol had a better therapeutic effect than Kaletra and could significantly reduce the incidence of severe cases. In addition, lopinavir/ritonavir, nucleoside analogues, neuraminidase inhibitors, remdesivir and peptide EK1 could also be possibilities for the treatment of COVID-19. [122]-

2. As we know the chloroquine (CQ) and its less toxic derivative hydroxychloroquine (HCQ) are well known for their immunomodulating effects in rheumatology. For decades, these drugs have been used for the treatment of systemic lupus erythematosus and rheumatoid arthritis. Because of based on their intracellular action the justification for their use in COVID-19 .[123] The drug may disrupt the virus replication and subsequent cytokine storm therefore it is used in severe COVID-19.[124–125]CQ has proved efficient against the virus in COVID-19 pneumonia in Chinese clinical trials, justifying the inclusion of the drug in the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19.[126] An open-label non-randomized clinical trial by Gauret et al. showed that HCQ reduces viral load in most COVID-19 patients and that its efficacy is enhanced in combination with azithromycin.[127] HCQ has low costs and relative safety profile may secure its place in the strategy against COVID-19.[128]



4.5.2 Convalescent plasma therapy

Convalescent plasma therapy could be an effective way to alleviate the course of disease for severely infected patients because of there are no sufficient vaccines or specific drugs are introduced in the market .[129] Convalescent plasma therapy is more effective than severe doses of hormonal shock in patients with severe SARS, reducing mortality and shortening hospital stays in a retrospective analysis.[130] A prospective cohort study by Hung et al. showed that for patients with pandemic H1N1 influenza virus infection in 2009, the relative risk of death was significantly lower in patients treated with convalescent plasma.[131] Moreover, from the perspective of immunology, most patients who recover from COVID-19 will produce specific antibodies in there body against the SARS-CoV-2, and their serum could be used to prevent re-infection of COVID-19. At the same time, antibodies can limit viral reproduction in the acute phase of infection and help clear the virus, which is make to rapid recovery from the disease.[132] During the first week of most viral infections theoretically viraemia peaks, and it should be more effective to give convalescent plasma early in the disease course.[133] Therefore, patients who have recovered from COVID-19 could be collected to prepare plasma globulin specific to SARS-CoV-2 with the help of plasma of that patient. However, the safety of plasma globulin products specific to SARS-CoV-2 deserves further consideration.

4.5.3 Auxiliary blood purification treatment

At present, for severe NCP extracorporeal blood purification technology is used in the treatment of patients. [134] According to the latest study, the key receptor ACE2 of SARS-CoV-2, is highly expressed in human kidney (nearly 100 times higher than in lung). Kidney might be the main target of attack for SARS-CoV-2. continuous blood purification treatment could reduce renal workload in the body and help to promote the recovery of renal function. [135] the most severe cases of COVID-19 may suffer from a cytokine storm. The imbalance of pro-inflammatory factors and anti-inflammatory factors may cause immune damage. Therefore, blood purification technology could be used to remove inflammatory factors, eliminate cytokine storms, correct electrolyte imbalances and maintain acid–base balance to control patients' capacity load in an effective manner. [136] in this way, patient symptoms could be improved and blood oxygen saturation could be increased. [137]

4.5.4 Faecal test for SARS-CoV-2

Substantial evidence from previous studies of SARS supported the gastrointestinal tract tropism of SARS-CoV, which was verified by viral detected in biopsy specimens and stool.[138] Similarly, in the United States SARS-CoV-2 was first reported in stool samples of the first case.[139] Yang et al[140] found that even after a negative throat swab test the stool specimens of three out of seven patients remained positive. The proportion of patients in whom stool samples tested positive was between 36% and 53% of all confirmed cases. Zhang et al[142] reported that in stool samples high accuracy of nucleic acid was detected. The comparison of stool test results to clinical manifestations as well as disease severity suggested that the positive rate of the faecal test was not differentially related to disease activity or digestive symptoms. The age of the patients ranged between 10 months and 78 years with positive stool tests, and the test lasted positive for approximately 1-16 days.[141–142], Available studies also demonstrated a time window in positive tests of specimens from different tissues.[140–141] The faecal nucleic acid was often positive 2-5 days after the respiratory specimens were found to be positive, and 23%-82% patients continued to have positive faecal tests while their respiratory specimens were negative.[140–141] The faecal test for patients treated with corticosteroids remained positive longer.[141] Recently, the isolation of infectious SARS-CoV-2 viruses from stool samples of COVID-19 patients[143] has directly proven that SARS-CoV-2 could be spread *via* faeces.

After a decade why hydroxychloroquine in such high demand

Researchers from worldwide have promoted chloroquine as well as hydroxychloroquine for treatment and prevention of illness cause due to SARS-CoV or C.[144]

Hydroxychloroquine can inhibit replication of SARS-CoV-2 in vitro. [145]

Some observational studies have suggested benefits of hydroxychloroquine for the treatment of Covid-19[146]

Hydroxychloroquine (an analogue of chloroquine) has been demonstrated to have an anti-SARS-CoV activity *in vitro.* [147]

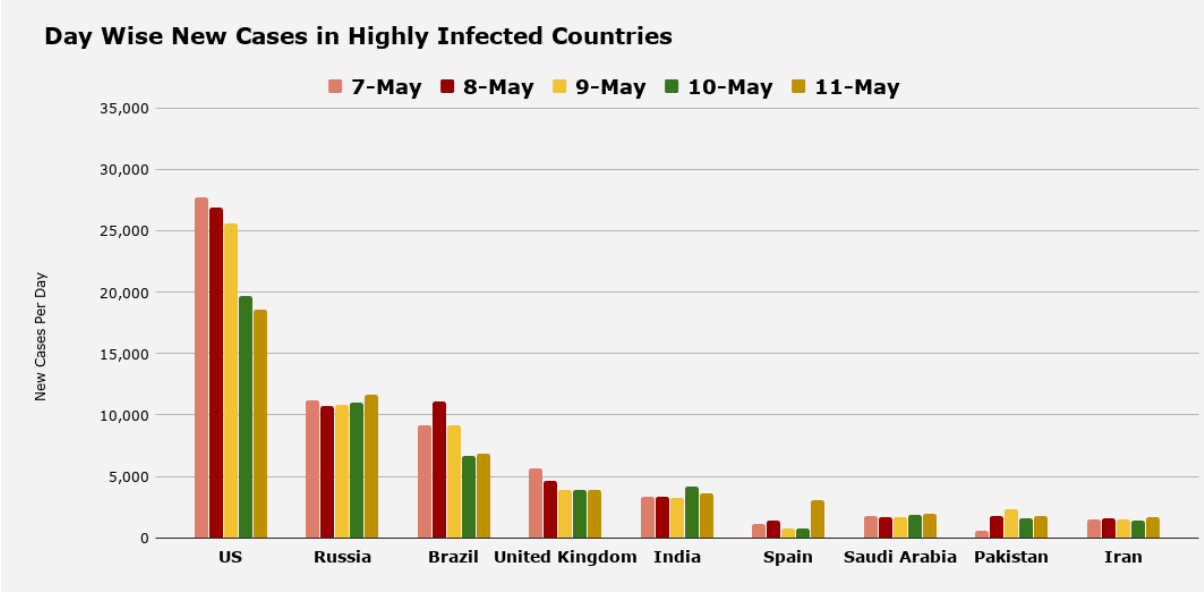
Hydroxychloroquine clinical safety profile is better than that of chloroquine (during long-term use) and allows higher daily dose[148] and has fewer concerns about drug-drug interactions. [149]

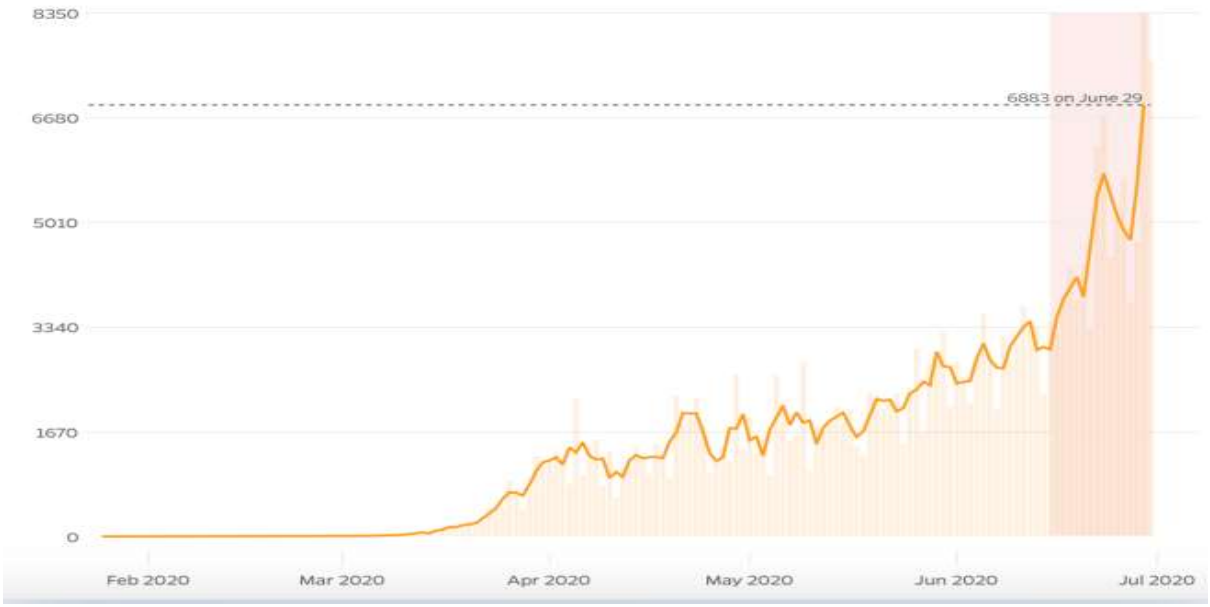
Hydroxychloroquine and azithromycin to cure the infection of COVID-19 patients and to limit the transmission of the virus to other people in order to curb the spread of COVID-19 in the world. [150]

Hydroxychloroquine dosage

Mean hydroxychloroquine serum concentration was 0.46 µg/ml±0.2 (N=20).

Covid-19 cases graph:





V Conclusion:

In the above review, although hydroxychloroquine the derivative of chloroquine are well-known DMARDs that have been used for the treatment of patients with rheumatic diseases for many years. But after a decade the hydroxychloroquine being in such a high demand.
The important factor like pharmacokinetic, pharmacodynamics & the toxic properties of these drugs is their ability to accumulate in acidic compartments such as lysosomes, as well as inflamed (acidic) tissues. [151]
For the metabolic benefit of these drug, combining HCQ with other DMARDs could provide some clinical improvement in patients with RA. Hydroxychloroquine (HCQ) the derivative of chloroquine improves metabolic as well as cardiovascular outcomes in patients with rheumatoid arthritis (RA). The aim of our study was to assess that the current review on the clinical & structural efficacy of hydroxychloroquine in treatment of COVID-19 & Rheumatoid Arthritis. Chloroquine and hydroxychloroquine have antiviral characteristics in vitro. They are used to treat the malaria. Many researchers from worldwide have promoted chloroquine as well as hydroxychloroquine for treatment and prevention of illness cause due to SARS-CoV. The findings support the hypothesis that these drugs have efficacy in the treatment oCOVID-19. [152] Currently there is no specific treatment for coronavirus (COVID-19). People with COVID 19 should receive supportive care to relieve symptoms.

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