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A REVIEW ON HYDROXYCHLOROQUINE AND ITS SIGNIFICANCE

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Abstract:

Hydroxychloroquine [HCQ] belongs to the group of antimalarial agents with immunosuppressive, anti-autophagy, anti-inflammatory and anti-rheumatologic activities. In addition to reducing the manifestations of inflammatory disorders, Hydroxychloroquine is especially also associated with the prevention of disease and prevention of treatment-induced complications that include hyperlipidemia, diabetes mellitus, liver function test elevation and thrombosis [1].

Hydroxychloroquine has shown promising results In-Vitro against SARS-CoV-1 [SARS- related Corona Virus strain 1], that caused the 2002-2004 SARS [Severe Acute Respiratory Syndrome] outbreak. Late 2019 and early 2020 has seen a rapid spread of the novel Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) that caused COVID 19 pandemic. The US-FDA [Food and Drug Administration] has approved Hydroxychloroquine as potential treatments to COVID 19 [or SARS-CoV-2] coronavirus.

However Hydroxychloroquine is linked to several side effects like retinal toxicity, neuromyotoxicity, ocular toxicity and retinopathy. Uncertainty in the mode of action, specificity and risks of Hydroxychloroquine against coronavirus makes it extremely unclear whether it is a viable medication for treatment or not. Nevertheless, the drug is gaining notability like never before in the existing state of affairs.

In this review, we discuss the current literature on the structural characteristics, pharmacokinetics and pharmacodynamics data, benefits and novel applications of Hydroxychloroquine, its immunomodulatory mechanism with respect to each application and the potential side effects associated with it. The present scenario compels critical care physicians and researchers worldwide to undertake several studies emphasising the role of Hydroxychloroquine as a potential drug.

KEYWORDS: *Antiinflamatory, Antimalarial, Chloroquine, Hydroxychloroquine, Quinine, Treatment.*

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INTRODUCTION:

Quinine was universally the first antimalarial drug that proved to be effective against malaria and other inflammatory diseases in 1894 as reported by Payne in his studies. It is a well -established fact that around the year 1630 the value of cinchona bark was well known in Peru and was used to cure malaria. Cinchona bark and its clinical significance started to be spread quickly all over Europe. By 1669 the bark was described in early German pharmacopoeias and in 1677 it appeared even in the London pharmacopoeia. In 1738, the French explorer De la Condamine identified the tree from which the bark was taken and named it quinquina. Carl von Linne in his Genera plantarum of year 1742 classified it as a representative of a new genus and renamed it Cinchona [2]. The bark was used to extract the phytochemicals in 1820, and named by Pierre Joseph Pelletier and Joseph Caventou as Quinine that replaced the bark as the standard treatment for malaria [3]. Quinine remained the forerunner of malaria treatment until the 1920s, when more effective synthetic anti-malarials like Chloroquine came to use in the 1940's [4]. With resistance developed against Chloroquine in some parts of the world, a new derivative Hydroxychloroquine was introduced in 1955 and differs from Chloroquine only by a hydroxyl group, decreasing its toxicity while conserving its efficacy.

Hydroxychloroquine is a well-established antimalarial approved in 1950's. Sold under the brand name **Plaquenil**, it is used as a treatment to wide spectrum of diseases. Chloroquine and Hydroxychloroquine are the two important antimalarial derivatives of Quinine. These have been used since the 1950s for the treatment of various inflammatory, rheumatic diseases like Lupus erythematous, infections with intracellular miccroorganisms and several other dermatologic diseases [5]. They are used as primary treatments in viral infections lacking drugs [6]. These antimalarial agents Chloroquine and Hydroxychloroquine lead to improvement of clinical and laboratory parameters, but their slow onset of action distinguishes them from glucocorticoids and nonsteroidal antiinflammatory agents (NSAID) [7].

Hydroxychloroquine possess an immunomodulatory mechanism of action to target the diseases. It has an established efficacy against Systemic Lupus Erythematous, Rheumatoid Arthritis, Palindromic rheumatism, Eosinophilic fasciitis, Dermatomyositis, Sjögren's syndrome, Porphyria cutanea tarda, Polymorphous light eruption, Granuloma annulare, Lichen planus, Lupus panniculitis and Discoid lupus [8]. It is reported that patients with quiescent lupus erythematous taking Hydroxychloroquine are less likely to have clinical manifestations if they are maintained on the same drug [9]. Hydroxychloroquine is also recommended to pregnant women with Lupus erythematous as it does not possess foetal toxicity [10].

There are many proposed mechanisms of action of Hydroxychloroquine such as increase in PH of the cellular components, interference with DNA stabilisation and cell signalling, activation of immune cells and inhibition of proteases. However, the specific mechanism in individual disease is not very clear. Uncertainty in the mode of action, specificity and risks of Hydroxychloroquine questions its viability as a potential treatment. In this review we discuss the structural characteristics of Hydroxychloroquine and its novel applications.

STRUCTURE OF HYDROXYCHLOROQUINE:

Hydroxychloroquine is a derivative of Chloroquine belonging to the 4-aminoquinoline family of medication and is chemically a 7-Chloro-4-(4-(N-ethyl-N-beta-hydroxyethylamino)-1-methylbutylamino)-quinoline [see **FIG-1]** with immunosuppressive, anti-autophagy, anti-inflammatory, anti-rheumatologic and antimalarial activities. It has a chemical Formula as $C_{18}H_{26}ClN_3O$ with Molar mass 335.872 g/mol. It is also sold as Hydroxychloroquine sulphate. It is an orally administered prescribed medication with a commercial name 'Plaquenil'.

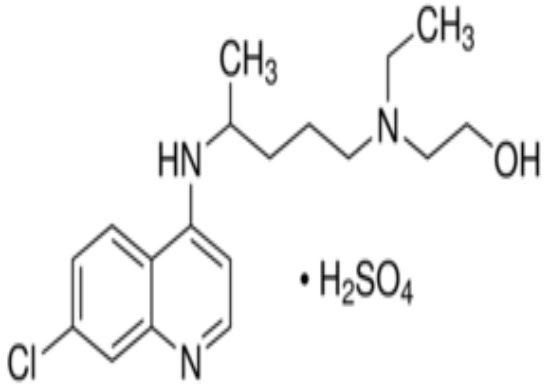

FIG-1: Structure of Hydroxychloroquine [11].

STEREOCHEMISTRY OF HYDROXYCHLOROQUINE:

Hydroxychloroquine is an important chiral drug with symbolic optical activity. The pharmacokinetic and pharmacodynamic properties of the molecule are stereoselective. Animal studies and other In-vitro studies indicate that the several metabolic pathways could express stereoselectivity of Hydroxychloroquine [12]. Hydroxychloroquine is a racemic mixture consisting of an R and S enantiomer [13]. The enantiomers of hydroxychloroquine have very long terminal phase

half-lives [14]. A sequential achiral—chiral high-performance liquid chromatographic system has been developed for the determination of the enantiomers of hydroxychloroquine, (+)-HCQ and (−)-HCQ [15]. (R)- (−)-hydroxychloroquine (the stereochemical 'rectus' configuration of hydroxychloroquine) is present at higher concentrations in the blood than (S)-(+)-hydroxychloroquine (the stereochemical 'sinister' configuration of hydroxychloroquine), suggesting the existence of stereoselective processes in the deposition and metabolism of this drug [16]. (S)-(+)-HCQ enantiomer undergoes more rapid elimination compared to the (R)- (-)-HCQ, probably due to more rapid hepatic metabolism and excretion [17]. The efficacy and safety of the drug enantiomers might also differ and needs to be studied further [18].

MECHANISM OF ACTION:

Hydroxychloroquine can be summarised to have an immunomodulatory effect on the host cell. The major proposed mechanism of the molecule on the immune system involves its intervention in lysosomal acidification [19] , chemotaxis and phagocytosis. It increases pH within intracellular vacuoles and alter processes such as protein degradation by enzymes like acidic hydrolases in the lysosome. It inhibits proteolysis in immune cells by targeting metalloproteinases [20, 21]. This in turn influences the assembly of macromolecules in endosomes and posttranslational modification of proteins within Golgi apparatus. Hydroxychloroquine reduces the production of interleukins and other cytokines [22]. It behaves as a potent antagonist to prostaglandins and inhibits key enzymes like phospholipase A2 [23]. It hinders UV light absorbtion and there by blocks subcutaneous reactions [24]. It interferes in the calcium mediated cell signalling pathways involved in the inhibition of T- cell and B- cell receptors [25]. Hydroxychloroquine is attributed to interfere with the 'antigen processing' in macrophages and other antigen presenting cells. Acidic cytoplasmic compartments are usually required for the antigenic protein to be digested and for the peptides to assemble with the α and β chains of MHC class II proteins. Hydroxychloroquine increases the acidity of lysosomes and diminishes the formation of peptide-MHC protein complexes required to stimulate CD4+ T cells. This results in down-regulation of the immune response against autoantigenic peptides [7].

Hydroxychloroquine has also a strong binding to melanin. This reflects the ocular toxicity and dermatological properties Hydroxychloroquine. The occurrence of any ocular adverse reactions can however be minimised by paying close attention to the dose (based on a body weight) with regular retinal examination [26].

HYDROXYCHLOROQUINE as an ANTIMALARIAL agent

Malaria is one of the most wide spread parasitic disease in the world with about 3 million deaths being attributed to this disease [27]. The causative agent for malaria is a unicellular eukaryote called Plasmodium. There are four species of plasmodium that cause malaria namely P. falciparum, P. malariae, P. ovale and P. vivax. Of the four species of Plasmodium, malaria caused by P.vivax is far more threatening [28]. Chloroquine that is chemically 4-aminoquinoline compound had been used for the prophylaxis and treatment of malaria against Quinine resistant forms of plasmodium until 1960 [29]. With the onset of resistant plasmodium strains to Chloroquine, its N-ethyl substituted analogue Hydroxychloroquine was used as treatment to malaria since then. Hydroxychloroquine is preferred over Chloroquine when high doses are required because of low Ocular toxicity of Hydroxychloroquine over Chloroquine [30]. Hydroxychloroquine is known to actively attack the heme polymerization process to disrupt the life cycle of the parasite. It is also viewed to passively interfere with the parasite's haemoglobin digestive pathway [31]. This mechanism however is similar to the antimalarial activity of Chloroquine.

HYDROXYCHLOROQUINE as an ANTIRHEUMATOLOGIC agent

Antimalarial drugs like Hydroxychloroquine and Chloroquine are most popular treatments for Rheumatologic disorders like Rheumatoid arthritis and Systemic Lupus Erythematous over seven decades. Hydroxychloroquine and Chloroquine in combination with other medications are used as treatments to several severe complications and have shown to reduce the risk of Adult onset Diabetes Mellitus in patients with Rheumatologic conditions. An important factor associated with Hydroxychloroquine and Chloroquine affecting pregnancy outcome is that they are beneficial in controlling Systemic Lupus Erythematous disease activity in the foetus and the mother without causing any harm. Chloroquine though, is associated with side effects like gastrointestinal adverse reactions and ocular toxicity. Hydroxychloroquine on the other hand has an edge over Chloroquine with lower incidence reported of these side effects while being used as treatment for Rheumatoid Arthritis and Systemic Lupus Erythematous. Hydroxychloroquine is also associated with reduction of Dermatological complications in Systemic Lupus Erythematous and reduction of atherosclerosis and cardiovascular diseases in Rheumatoid Arthritis [32].

Hydroxychloroquine reduces the rate of accumulation and specificities of autoantibody in Systemic Lupus Erythematous [33]. Hydroxychloroquine is associated with reduction in cytokine mediated cartilage reabsorption in treating Osteoarthritis [32]. Studies indicate that reduction in Interferon and Interleukins and inhibition of activation of Toll like receptors can be correlated to the mechanism of Hydroxychloroquine in treatment of Rheumatologic conditions [34]. In-vivo and Ex-vivo studies are required to establish the exact relationship of Hydroxychloroquine to its clinical efficacy as anti-rheumatologic agent.

HYDROXYCHLOROQUINE as an ANTIINFLAMATORY agent

Hydroxychloroquine is associated with blocking pro-inflammatory pathways that correlates with its anti-rheumatologic activity. Studies provide evidence that hydroxychloroquine down-regulates the promoter genes and/or decreases the secretion of monocyte derived pro-inflammatory cytokines like TNF α (Tumour Necrosis Factor alpha), IL6 (Interleukins 6) and IL10 (Interleukins 10). The exact mechanism by which these occur need to be fully defined [35, 36, 37].

HYDROXYCHLOROQUINE as an IMMUNOSUPPRESIVE agent

Hydroxychloroquine has many immunomodulatory effects. One proposed mechanism is that it interferes with the Toll-like Receptors. Toll-like receptors (TLRs) are a class of proteins that play crucial roles in the innate immune system by recognizing pathogen-associated molecular patterns derived from various microbes. TLRs signal through the recruitment of specific adaptor molecules, leading to activation of the transcription factors NF-κB and IRFs, which dictate the outcome of innate immune responses [38]. Hydroxychloroquine blocks the activation of intracellular Toll like receptors (TLR-3, TLR-7, TLR-9) and their subsequent signalling pathways [39,40].

Another mechanism of Hydroxychloroquine which is slightly basic in nature is that it enters the lysosomes and other subcellular acidic compartments of immune cells thereby altering the PH of the medium. This considerably influences PH dependent physiological subcellular activities like lymphocyte proliferation, autoantibody production, recycling of receptors and secretion of inflammatory components [41, 42].

HYDROXYCHLOROQUINE as an ANTIAUTOPHAGY agent

Autophagy is a complicated cellular mechanism that maintains cellular and tissue homeostasis and integrity through degradation of senescent, defective subcellular organelles, infectious agents, and misfolded proteins [43]. Autophagy is significant for survival and healthy well-being of an individual. However recent studies have linked to autophagy to cancer development. The neoplastic lessions formed during the tumour progression causes adaptive changes resulting in positive roles for autophagy in malignant progression and in subsequent tumour maintenance. Autophagy critically enables continued growth of some tumours, by reducing oxidative stress and providing key intermediates to sustain cell metabolism. Autophagy also limits drug efficacy as a survival mechanism of cancer cells in response to cancer therapies [44]. Hydroxychloroquine is one such moderately potential immunomodulatory molecule that targets the lysosomes to produce measurable autophagy inhibition [19]. The mechanism involved needs further scientific validation.

HYDROXYCHLOROQUINE as an ANTIVIRAL agent

Antimalarials such as Chloroquine and Hydroxychloroquine have long since been adopted to treat viral diseases. Studies have proved its efficacy on viruses like HIV, Influenza, SARS-CoV and members of Orthomyxoviridae. Chloroquine and hydroxychloroquine also are a valuable option to be tested in low-cost antiretroviral combinations, but correct dosages should be used, considering regularly monitoring to prevent retinopathy.

The antiviral effects of Hydroxychloroquine are attributed to the reduction in interleukins and inhibition of glycosylation of viral particles by specific interactions with glycosyltransferases [45]. Studies have proved that Hydroxychloroquine inhibits replication of the SARS coronavirus1 and Orthomyxoviridae [46]. Hydroxychloroquine has recently been shown to inhibit quinone reductase which is involved in sialic acid biosynthesis [47]. This effect explains the effects of hydroxychloroquine on HIV and SARS coronavirus as sialic acid is an integral part of HIV glycoproteins and SARS coronavirus receptor. It also explains the in-vitro effects of Hydroxychloroquine on orthomyxoviruses which use sialic acid moieties as receptors [48].

The broad-spectrum antiviral effects of Hydroxychloroquine deserve particular attention especially at a time like now in which the world is threatened by the possibility of a new Corona virus pandemic, and the availability of effective drugs would be fundamental during evaluation of an effective vaccine.

OTHER EFFECTS OF HYDROXYCHLOROQUINE:

1. **ANTITHROMBOTIC EFFECT:** Hydroxychloroquine exhibits antithrombotic effect by inhibition of platelet aggregation and adhesion, increasing endothelium dependent vasodilation and artery elasticity, reducing vascular stiffness and vascular resistance [49].

2. **ANTI-NEOPLASTIC EFFECT:** Clinical studies on cancer patients reveal with chronic lymphatic leukaemia that Hydroxychloroquine induces apoptosis of malignant B-cells, by activating caspase-3 and modifying Bcl-2/bax ratio [50, 51]. An In-vitro study using biodegradable nanoparticle drug delivery system revealed that Hydroxychloroquine has a strong apoptotic effect on B-lymphocytes [52]. Hydroxychloroquine has demonstrated In-vitro antiproliferative effect on breast cancer cell and mouse colon cancer cell lines [8].

3. **DERMATOLOGIC EFFECT:** Hydroxychloroquine blocks UV light absorption by skin. This is viewed to inhibit subcutaneous light sensitive reactions or polymorphic light eruptions and reduce skin symptoms like rash [24].

PHARMACOKINETIC DATA of HYDROXYCHLOROQUINE:

Hydroxychloroquine is almost completely and rapidly absorbed after oral administration. It has a 45% protein binding capacity that is metabolised in liver and excreted biliary [<10%] and largely through kidneys [>25%]. It has a bioavailability [Tmax] of 2 to 4.5 hours and a half-life of 32-50 days.

Hydroxychloroquine is metabolized in the liver into three active metabolites: desethylchloroquine, desethylhydroxychloroquine, and bisdesethylhydroxychloroquine [53].

CONCLUSION:

Hydroxychloroquine and other antimalarial drugs since the first use nearly a century ago, have exhibited protracted effects on diseases in nearly all major branches of medicine including immunology, oncology, hematology, dermatology, cardiology, and infectious diseases. This drug hydroxychloroquine works partially by inactivating the body's immune response like inflammation, oedema, pain, fever and disrupts critical cell processes. Recent Clinical study reports from China and France have associated Chloroquine, Hydroxychloroquine in combination with antiviral drug like azithromycin to reduction in fever, decrease in lung lesions, delayed disease progression and reduction in the viral load in patients with COVID-19. The exact mechanism however, by which this drug works to resolve malaria and other diseases is largely unknown. *In-Vitro* studies have shown that hydroxychloroquine inhibits SARS-CoV-2 transmission through alkalinisation of the intracellular phagolysosome, which prevents virion fusion and uncoating and therefore curbs the viral spread.

Though hydroxychloroquine is effective, it is associated with the potential of causing numerous side effects, like headache, loss of appetite, nausea, vomiting, skin rash and in severe cases vision loss due to retinal toxicity. Chloroquine that is a close analogue to hydroxychloroquine is however considered less safe but equally effective.

One significant benefit with using these drugs is that they have been on the market and used for a sufficiently long time. Hence a reasonable amount of information regarding contraindications, allergic responses, side effects, and efficacy is available that can kept in mind before using it to treat new diseases like COVID-19. Since they have been around for so long, generic versions are available, which may prove to be cost-effective for use in coronavirus treatment worldwide.

FUTURE PROSPECTIVES:

Hydroxychloroquine and Chloroquine are well established effective and relatively safe drugs used to treat wide range of disorders from malaria to autoimmunity. There is a greater requirement to gather more information on their mode of action of these drugs with respect to all the mentioned disorders. This can further be used to develop formulations and combinations with enhanced therapeutic activity.

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