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Review Article

HYDROXYCHOLOROQUINE: THE ONE-MAN ARMY PROTECTING HUMAN CIVILIZATION FROM THE DANGEROUS BITE OF MALARIA

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Abstract:

Abstract: *Hydroxychloroquine (HCQ), sold under the brand name Plaquenil among others, is a medication used to prevent and treat malaria in areas where malaria remains sensitive to chloroquine. Other uses include treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda. It is taken by mouth. It is also being studied as a treatment for coronavirus disease 2019 (COVID-19).*

Common side effects include vomiting, headache, changes in vision, and muscle weakness. Severe side effects may include allergic reactions, vision problems, and heart problems. Although all risk cannot be excluded, it remains a treatment for rheumatic disease during pregnancy. Hydroxychloroquine is in the antimalarial and 4-aminoquinoline families of medication. Hydroxychloroquine was approved for medical use in the United States in 1955. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system. In 2017, it was the 128th most commonly prescribed medication in the United States, with more than five million prescriptions. Hydroxychloroquine is used to treat systemic lupus erythematosus, rheumatic disorders like rheumatoid arthritis, porphyria cutanea tarda, and Q fever, and certain types of malaria. It is considered the first-line treatment for systemic lupus erythematosus. Certain types of malaria, resistant strains, and complicated cases require different or additional medication. It is widely used to treat primary Sjögren syndrome, but has not been shown to be effective. Hydroxychloroquine is widely used in the treatment of post-Lyme arthritis. It may have both an anti-spirochaete activity and an anti-inflammatory activity, similar to the treatment of rheumatoid arthritis. Recently, it is used to treat COVID-19 patients.

Keywords: Anti-Malarial Drug, DMARD, COVID-19, Malaria.

Introduction

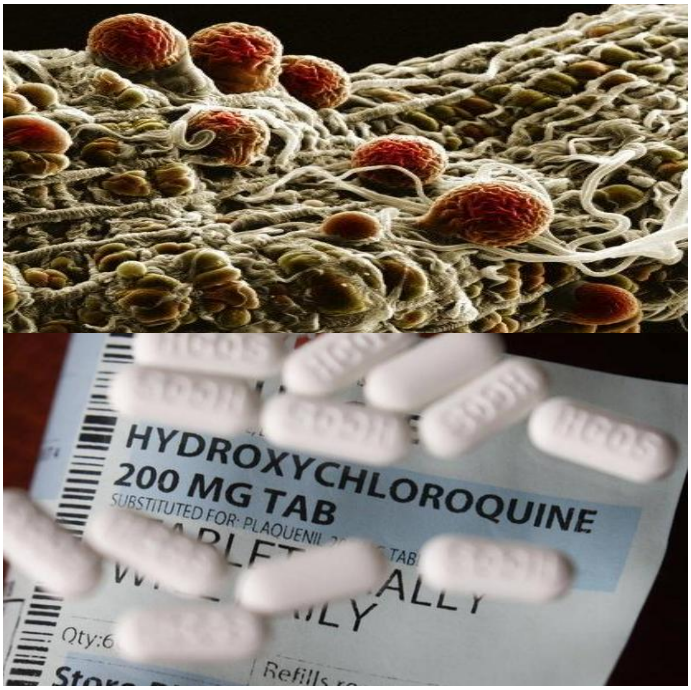


Figure 1: Scanning Electron Micrograph of malaria parasite and drug

Introduction: Hydroxychloroquine (Plaquenil) is considered a disease-modifying anti-rheumatic drug (DMARD). It can decrease the pain and swelling of arthritis. It may prevent joint damage and reduce the risk of long-term disability. Hydroxychloroquine is in a class of medications that was first used to prevent and treat malaria. Today, it is used to treat rheumatoid arthritis, some symptoms of lupus, childhood arthritis (or juvenile idiopathic arthritis) and other autoimmune diseases. It is not clear why hydroxychloroquine is effective at treating autoimmune diseases. It is believed that hydroxychloroquine interferes with the communication of cells in the immune system.[1]

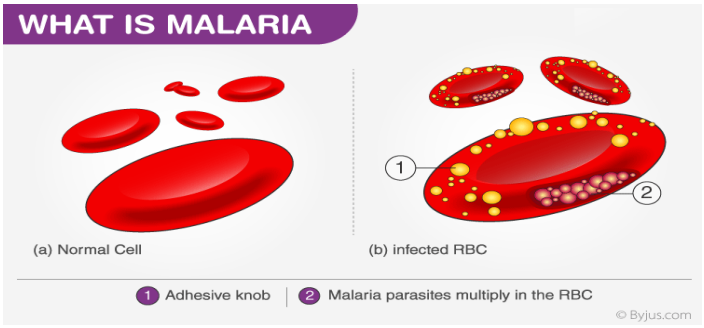
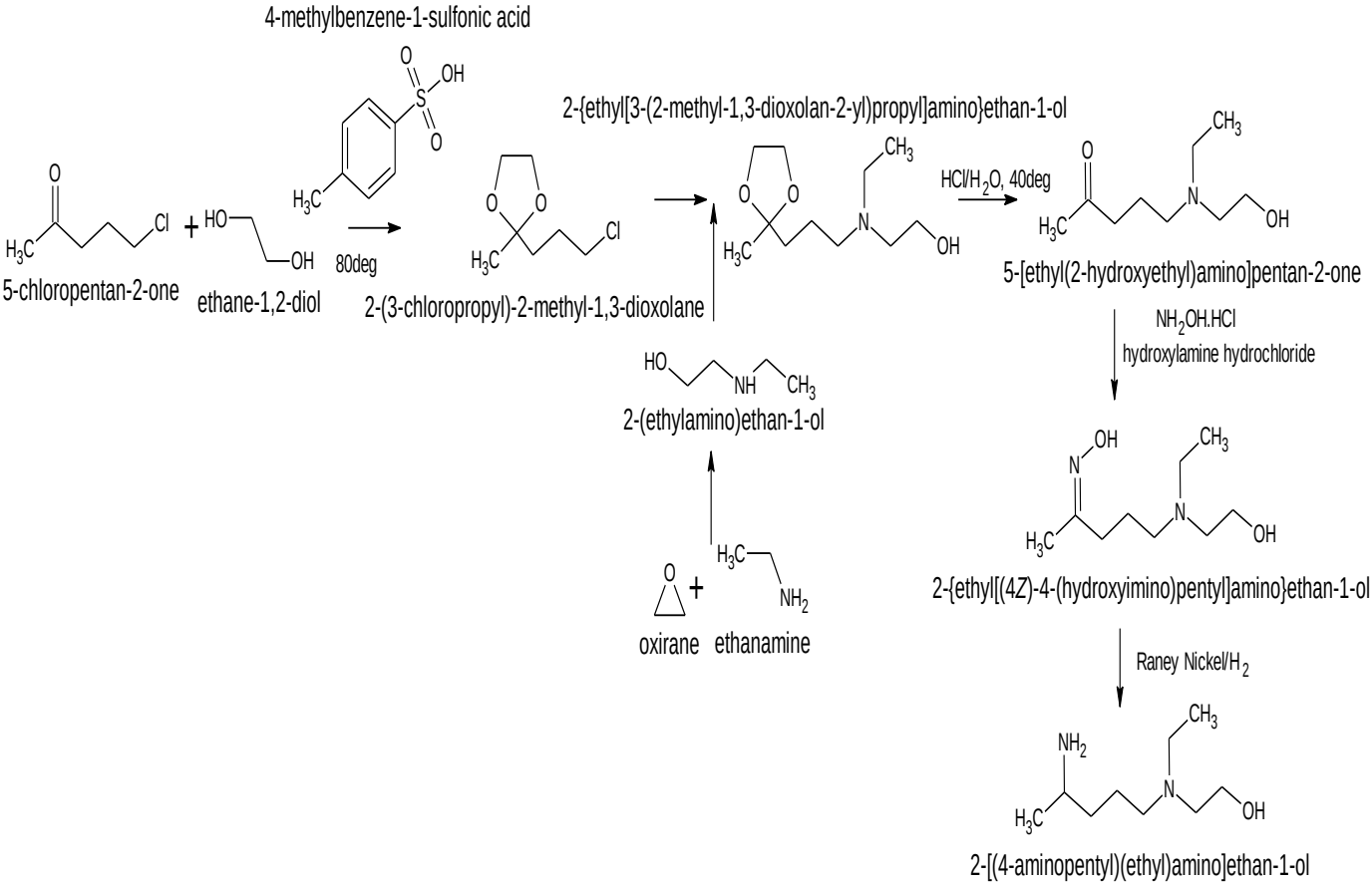


Figure 2: Malaria Parasite & Normal RBC & Malaria Infected RBC

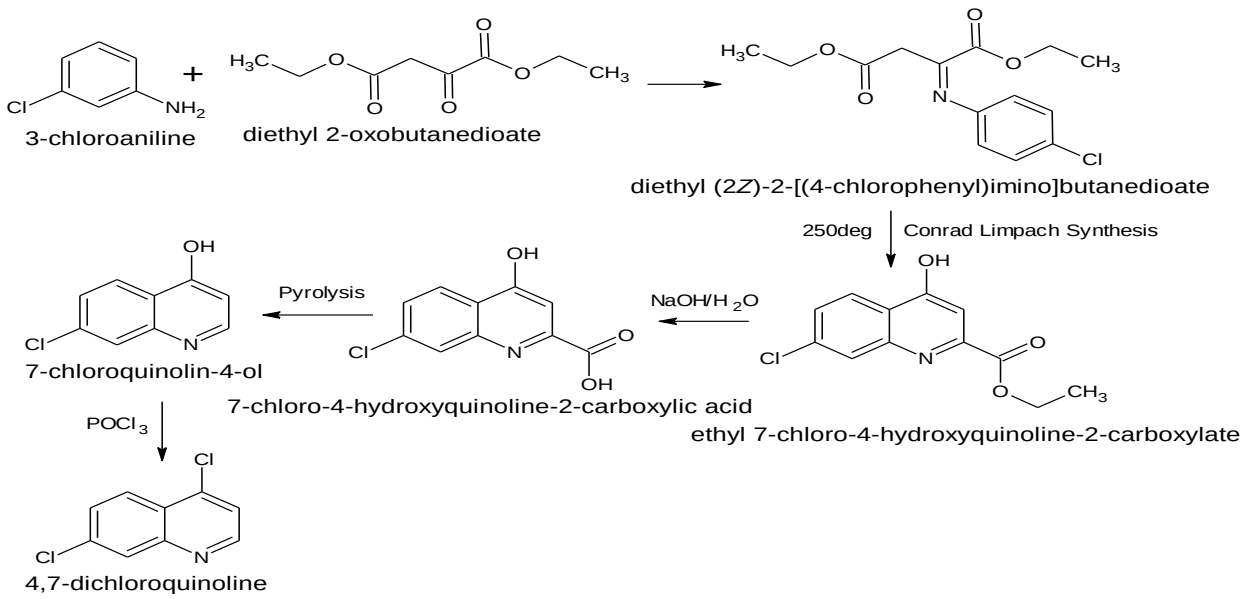
Synthesis: Hydroxychloroquine is synthesized in two halves. One is synthesis of 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one and reacting of this with hydroxylamine hydrochloride reacts with ketone to form oxime and this on reduction by Raney nickel/Hydrogen this oxime is reduced into amino functional group to produce **5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane** which is key intermediate of one half.

5-chloropentan-2-one is reacted with ethylene glycol in presence with tosic acid (p-toluene sulfonic acid) in cyclohexane at 80ºC. Here ketalization takes place in which ketone to produce 2-(3-chloropropyl)-2-methyl-1,3-dioxolane. This is then reacted with 2-(ethylamino) ethan-1-ol and this is synthesized by oxirane (ethylene oxide) with ethanamine (ethyl amine). 2-(3-chloropropyl)-2-methyl-1,3-dioxolane reacts with 2-(ethylamino)ethan-1-ol to produce 2-{ethyl[3-(2-methyl-1,3-dioxolan-2-yl)propyl]amino}ethan-1-ol. This reacts at 40ºC in HCl water mixture where dioxolane ring gets ruptured to form 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one [Scheme-1].



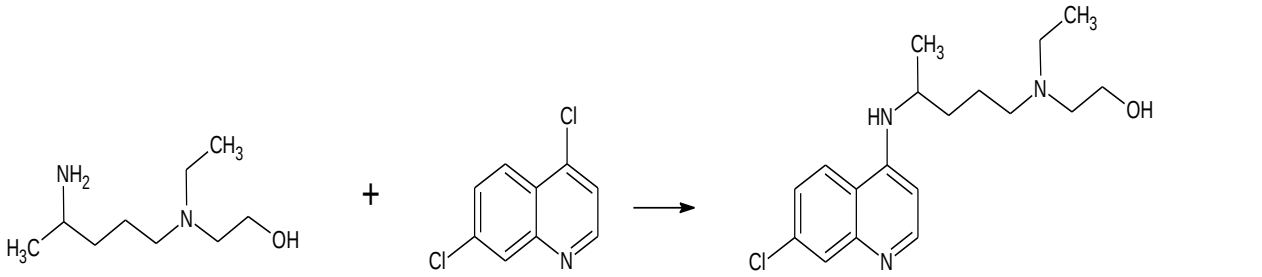
Scheme 1:

4,7-DCQ (4,7-dichloroquinoline) is the next half. It is synthesized by reacting 3-chloro aniline and reacted between ethyloxaloacetate (diethyl 2-oxobutanedioate) to form ethyl-(3-chloro phenyl)imino-succinate (diethyl (2Z)-2-[(4-chlorophenyl)imino]butanedioate) by Schiff's base. This by Conrad Limpach Synthesis at 250ºC cyclization takes place to form ethyl-7-chloro-4-hydroxy quinolone-2-carboxylate. This on alkaline hydrolysis in NaOH produces 7-chloro-4-hydroxy quinoline-2-carboxylic acid. This by pyrolysis decarboxylation takes place to form 7-chloro-4-hydroxy-quinoline. This by reaction by phosphorus oxychloride produces 4,7-dichloroquinoline [Scheme-2].



Scheme 2:

5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane **[**2-[(4-aminopentyl)(ethyl)amino]ethan-1-ol] is then reacted with 4,7-dichloroquinoline to produce **hydroxychloroquine** [2-[{4-[(7-chloroquinolin-4-yl)amino]pentyl}(ethyl)amino]ethan-1-ol] [Scheme-3].[2]



Scheme 3:

Pharmacokinetics: Hydroxychloroquine has similar pharmacokinetics to chloroquine, with rapid gastrointestinal absorption, large distribution volume, and elimination by the kidneys. Cytochrome P450 enzymes (CYP2D6, 2C8, 3A4 and 3A5) metabolize hydroxychloroquine to *N*-desethylhydroxychloroquine.[3]

Pharmacodynamics: Antimalarials are lipophilic weak bases and easily pass plasma membranes. The free base form accumulates in lysosomes (acidic cytoplasmic vesicles) and is then protonated, resulting in concentrations within lysosomes up to 1000 times higher than in culture media. This increases the pH of the lysosome from four to six. Alteration in pH causes inhibition of lysosomal acidic proteases causing a diminished proteolysis effect. Higher pH within lysosomes causes decreased intracellular processing, glycosylation and secretion of proteins with many immunologic and nonimmunologic consequences. These effects are believed to be the cause of a decreased immune cell functioning such as chemotaxis, phagocytosis and superoxide production by neutrophils. HCQ is a weak diprotic base that can pass through the lipid cell membrane and preferentially concentrate in acidic cytoplasmic vesicles. The higher pH of these vesicles in macrophages or other antigen-presenting cells limits the association of autoantigenic (any) peptides with class II MHC molecules in the compartment for peptide loading and/or the subsequent processing and transport of the peptide-MHC complex to the cell membrane.[4]

Mechanism of action: Hydroxychloroquine increases lysosomal pH in antigen-presenting cells. In inflammatory conditions, it blocks toll-like receptors on plasmacytoid dendritic cells (PDCs). Toll-like receptor 9 (TLR 9), which recognizes DNA-containing immune complexes, leads to the production of interferon and causes the dendritic cells to

mature and present antigen to T cells. Hydroxychloroquine, by decreasing TLR signaling, reduces the activation of dendritic cells and the inflammatory process.

In 2003, a novel mechanism was described wherein hydroxychloroquine inhibits stimulation of the toll-like receptor (TLR) 9 family receptors. TLRs are cellular receptors for microbial products that induce inflammatory responses through activation of the innate immune system.

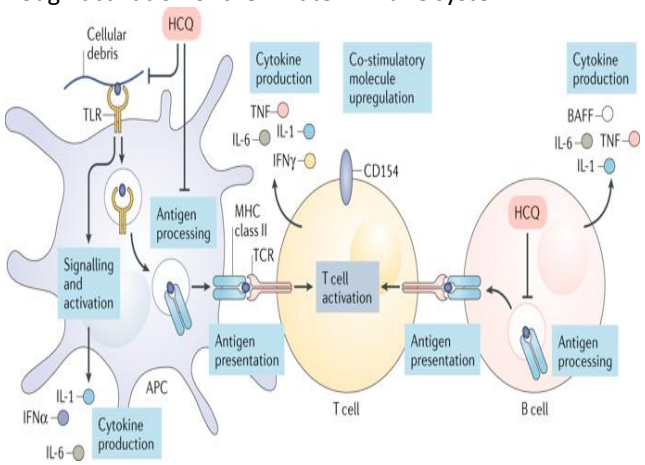


Figure 3: Mechanism of action of Hydroxychloroquine

As with other quinoline antimalarial drugs, the antimalarial mechanism of action of quinine has not been fully resolved. The most accepted model is based on hydrochloroquinine and involves the inhibition of hemozoin biocrystallization, which facilitates the aggregation of cytotoxic heme. Free cytotoxic heme accumulates in the parasites, causing death. The antimalarial agents chloroquine and hydroxychloroquine have been used widely for the treatment of rheumatoid arthritis and systemic lupus erythematosus. These compounds lead to improvement of clinical and laboratory parameters, but their slow onset of action distinguishes them from glucocorticoids and nonsteroidal antiinflammatory agents. Chloroquine and hydroxychloroquine increase pH within intracellular vacuoles and alter processes such as protein degradation by acidic hydrolases in the lysosome, assembly of macromolecules in the endosomes, and posttranslation modification of proteins in the Golgi apparatus. It is proposed that the antirheumatic properties of these compounds results from their interference with "antigen processing" in macrophages and other antigen-presenting cells. Acidic cytoplasmic compartments are required for the antigenic protein to be digested and for the peptides to assemble with the alpha and beta chains of MHC class II proteins. As a result, antimalarials diminish the formation of peptide-MHC protein complexes required to stimulate CD4+ T cells and result in down-regulation of the immune response against autoantigenic peptides. Because this mechanism differs from other antirheumatic drugs, antimalarials are well suited to complement these other compounds in combination drug therapy.[5]

Regulatory approval: On 17 March 2020, the AIFA Scientific Technical Commission of the Italian Medicines Agency expressed a favorable opinion on including the off-label use of chloroquine and hydroxychloroquine for the treatment of COVID-19. In the US, several state pharmacy boards reported that some doctors and dentists were writing prescriptions for hydroxychloroquine and a related drug, chloroquine, to themselves, family members, and staff. Sudden demand spikes caused by hospital use for severely ill COVID-19 patients and prescriptions for prophylaxis have resulted in shortages; doctors have expressed concern that patients who have long taken hydroxychloroquine for other approved indications, like lupus and rheumatoid arthritis, will be unable to procure needed medicine.[6]

On 28 March 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to allow hydroxychloroquine sulfate and chloroquine phosphate products donated to the Strategic National Stockpile (SNS) to be distributed and used for certain people who are hospitalized with COVID-19.

In anticipation of product shortages, the FDA issued product-specific guidance for chloroquine phosphate and for hydroxychloroquine sulfate for generic drug manufacturers.

Overdose: Serious symptoms of overdose generally occur within an hour of ingestion. These symptoms may include sleepiness, vision changes, seizures, stopping of breathing, and heart problems such as ventricular fibrillation and low blood pressure. Loss of vision may be permanent. Low blood potassium, to levels of 1 to 2 mmol/L, may also occur. Chloroquine has a risk of death in overdose in adults of about 20%, while hydroxychloroquine is estimated to be two or three-fold less toxic. While overdoses of hydroxychloroquine have historically been uncommon, one report documented three deaths out of eight cases. Treatment recommendations include early mechanical ventilation, cardiac monitoring, and activated charcoal. Intravenous fluids and vasopressors may be required with epinephrine being the vasopressor of choice. Gastric lavage may also be used. Seizures may be treated with benzodiazepines. Intravenous potassium chloride may be required however this may result in high blood potassium later in the course of the disease. Dialysis has not been found to be useful.[7]

Interactions: The drug transfers into breast milk and should be used with care by pregnant or nursing mothers. Care should be taken if combined with medication altering liver function as well as aurothioglucose (Solganal), cimetidine (Tagamet) or digoxin (Lanoxin). HCQ can increase plasma concentrations of penicillamine which may contribute to the

development of severe side effects. It enhances hypoglycemic effects of insulin and oral hypoglycemic agents. Dose altering is recommended to prevent profound hypoglycemia. Antacids may decrease the absorption of HCQ. Both neostigmine and pyridostigmine antagonize the action of hydroxychloroquine.

While there may be a link between hydroxychloroquine and hemolytic anemia in those with glucose-6-phosphate dehydrogenase deficiency, this risk may be low in those of African descent.[8]

Specifically, the US Food and Drug Administration's drug label for hydroxychloroquine lists the following drug interactions:

1. Digoxin (wherein it may result in increased serum digoxin levels)
2. Insulin or anti-diabetic medication (wherein it may enhance the effects of a hypoglycemic treatment)
3. Drugs that prolong QT interval and other arrhythmogenic drugs (as Hydroxychloroquine prolongs the QT interval and may increase the risk of inducing ventricular arrhythmias if used concurrently)
4. Mefloquine and other drugs known to lower the convulsive threshold (co-administration with other antimalarials known to lower the convulsion threshold may increase risk of convulsions)
5. Antiepileptics (concurrent use may impair the antiepileptic activity)
6. Methotrexate (combined use is unstudied and may increase the frequency of side effects)
7. Cyclosporin (wherein an increased plasma cyclosporin level was reported when used together).[9]

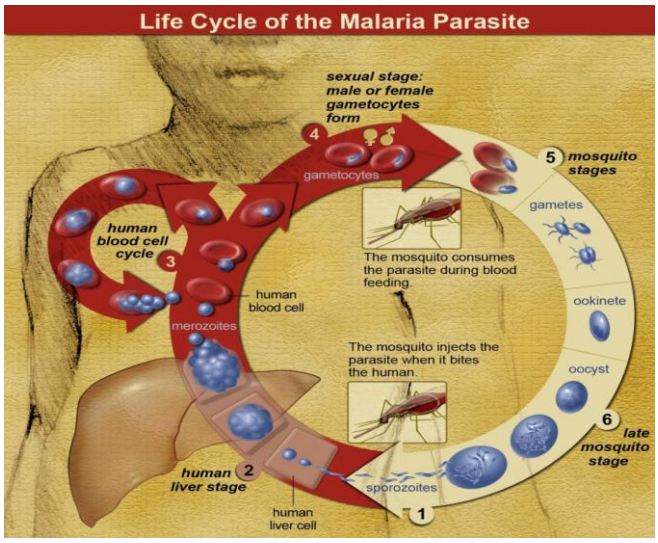


Figure 4: Malaria parasite life cycle

Adverse effects: The most common adverse effects are nausea, stomach cramps, and diarrhea. The most serious adverse effects affect the eye, with dose-related retinopathy as a concern even after hydroxychloroquine use is discontinued. For short-term treatment of acute malaria, adverse effects can include abdominal cramps, diarrhea, heart problems, reduced appetite, headache, nausea and vomiting. For prolonged treatment of lupus or rheumatoid arthritis, adverse effects include the acute symptoms, plus altered eye pigmentation, acne, anemia, bleaching of hair, blisters in mouth and eyes, blood disorders, convulsions, vision difficulties, diminished reflexes, emotional changes, excessive coloring of the skin, hearing loss, hives, itching, liver problems or liver failure, loss of hair, muscle paralysis, weakness or atrophy, nightmares, psoriasis, reading difficulties, tinnitus, skin inflammation and scaling, skin rash, vertigo, weight loss, and occasionally urinary incontinence. Hydroxychloroquine can worsen existing cases of both psoriasis and porphyria. Children may be especially vulnerable to developing adverse effects from hydroxychloroquine.[10]

Conclusion: Despite widespread clinical use of antimalarial drugs such as hydroxychloroquine and chloroquine in the treatment of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and other inflammatory rheumatic diseases, insights into the mechanism of action of these drugs are still emerging. Hydroxychloroquine and chloroquine are weak bases and have a characteristic ‘deep’ volume of distribution and a half-life of around 50 days. These drugs interfere with lysosomal activity and autophagy, interact with membrane stability and alter signalling pathways and transcriptional activity, which can result in inhibition of cytokine production and modulation of certain co-stimulatory molecules. These modes of action, together with the drug’s chemical properties, might explain the clinical efficacy and well-known adverse effects (such as retinopathy) of these drugs. The unknown dose–response relationships of these drugs and the lack of definitions of the minimum dose needed for clinical efficacy and what doses are toxic pose challenges to clinical practice. Further challenges include patient non-adherence and possible context-dependent variations in blood drug levels. Available mechanistic data give insights into the immunomodulatory potency of hydroxychloroquine and provide the rationale to search for more potent and/or selective inhibitors.

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