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Hydroxychloroquine – Beyond Malaria: Its Role in Rheumatology and COVID-19 – A Literature Review

Adam Jan Ząbek, Jakub Paweł Kuźniar , Emilia Gabriela Chrzanowska, Michalina Zagalska, Marta Turek, Tomasz Tamborski, Adam Grzebinoga, Julia Szlążek, Iwona Pudełko, Roguska Barbara

Adam Jan Ząbek
Katowice Oncology Center, ul. Raciborska 26, 40-074 Katowice
Email: adamzabek@vp.pl
ORCID: 0009-0003-6799-1814

Jakub Paweł Kuźniar
The Provincial Hospital in Bielsko-Biała Al. Armii Krajowej 101 43-316 Bielsko Biała
Email: kuba.kuzniar@gmail.com
ORCID: 0009-0002-6716-7502

Emilia Gabriela Chrzanowska
Medical University of Silesia, 18 Medyków Street 40-752 Katowice
Email: chrzanowska.e@gmail.com
ORCID: 0009-0001-6228-1878

Michalina Zagalska
Independent Public Clinical Hospital named Andrzej Mielęcki of the Silesian Medical University in Katowice, Francuska 20-24 Street, 40-027 Katowice
Email: michalina.zagalska24@gmail.com
ORCID: 0009-0002-7312-0065

Marta Turek
Independent Public Clinical Hospital named Andrzej Mielęcki of the Silesian Medical University in Katowice, Francuska 20-24 Street, 40-027 Katowice
Email: martaturek74@gmail.com
ORCID: 0009-0005-7713-6875

Tomasz Tamborski
County Hospital in Zawiercie, Miodowa street 14, 42-400 Zawiercie
Email: tomasztam97@gmail.com
ORCID: 0009-0003-6275-1010

Adam Grzebinoga
University Clinical Center of Prof. K. Gibiński of the Silesian Medical University in Katowice, Medyków 14 Street, 40-752 Katowice
Email: adam.grzebinoga99@wp.pl
ORCID: 0009-0001-5983-7564

Julia Szlążek
Medical University of Silesia, 18 Medyków Street 40-752 Katowice
Email: juliaszlazek@gmail.com
ORCID: 0009-0007-6977-8856

Iwona Pudełko
University Clinical Hospital in Wrocław, Borowska 213 street, 50-556 Wrocław
Email: i.pudelko.97@gmail.com
ORCID: 0009-0001-6403-4141

Barbara Roguska
Medical University of Silesia, 18 Medyków Street 40-752 Katowice
Email: b.m.c.roguska@gmail.com
ORCID: 0009-0006-6905-7517

Abstract

Introduction: Hydroxychloroquine (HCQ) is a well-established drug, initially used for malaria and later widely applied in autoimmune diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). As an immunomodulator, it helps manage chronic inflammation but requires monitoring due to potential adverse effects, including retinopathy and myopathy.[1]

Objective: This review examines HCQ's role in modern medicine and public health, particularly in autoimmune diseases. It also explores controversies surrounding its use during the COVID-19 pandemic and its implications for medical education and prevention.

Current Knowledge: HCQ modulates immune responses and lysosomal function, effectively controlling inflammation. While hypothesized to have antiviral properties against SARS-CoV-2, clinical trials disproved its efficacy, altering treatment recommendations.

Methods: A literature review of 32 articles from PubMed and Google Scholar was conducted, focusing on HCQ's history, mechanism, and medical applications.

Conclusion: HCQ remains essential for autoimmune disease treatment, though its long-term safety is under review. Ongoing research and medical education are crucial for optimizing its use, including potential applications in sports and rehabilitation, where chronic inflammation impacts recovery and performance.

Keywords: hydroxychloroquine, HCQ, autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus, malaria, COVID-19, mechanism of action, adverse effects, combination therapy

History of Hydroxychloroquine

The history of hydroxychloroquine dates back several centuries and originates from the discovery of the medicinal properties of quinine - a naturally occurring substance found in the bark of the cinchona tree. Over the centuries, this substance has played a key role in treating various diseases, and its derivatives, including hydroxychloroquine, have found applications in modern medicine. [1,2]

The first documented use of cinchona bark as an antipyretic occurred in the 1630s. Over the next two centuries, it was widely used as a universal remedy, particularly for treating malarial fever. In 1820, quinine was successfully extracted from cinchona bark, enabling more precise dosing and further research into its therapeutic properties. [2]

In the 1930s, mepacrine (atabrine), a synthetic antimalarial drug, was introduced. An interesting discovery was made by soldiers during World War II who were taking mepacrine and noticed its beneficial effects on symptoms of cutaneous lupus erythematosus and arthritis. This observation led to a publication in the prestigious journal "The Lancet", detailing mepacrine's effectiveness in treating systemic lupus erythematosus. [2,3]

In 1945, chloroquine, another quinine derivative, was synthesized and quickly became an effective antimalarial drug. [1,3] The early 1950s marked a significant breakthrough in chloroquine research, as its hydroxylation led to the development of hydroxychloroquine. This drug underwent extensive clinical testing, proving its effectiveness not only in treating malaria but also in managing systemic lupus erythematosus and rheumatoid arthritis. In 1955, the U.S.

Food and Drug Administration (FDA) officially approved hydroxychloroquine for medical use. [1]

In subsequent decades, research on the mechanism of action of chloroquine and its derivatives led to the discovery of their lysosomotropic properties, which had significant implications for the treatment of various autoimmune disorders. In the 1970s, this effect was identified as a key component of chloroquine's cellular mechanism of action. [3]

Modern interest in hydroxychloroquine surged in 2020 due to hypotheses regarding its potential use in the prevention and treatment of COVID-19. Despite initial enthusiasm, clinical studies did not confirm hydroxychloroquine's effectiveness in combating SARS-CoV-2 infection at any stage of the disease. [1,4]

Mechanisms of Action and Pharmacokinetics

Hydroxychloroquine (HCQ) and chloroquine (CQ) are drugs with similar chemical structures and mechanisms of action, affecting various cellular processes and the immune system. [5]

HCQ and CQ exhibit unique pharmacokinetic properties that determine their activity and metabolism in the body. Due to their planar aromatic structure and basic properties, these drugs accumulate intracellularly, particularly in acidic compartments such as lysosomes. [3,6] Their oral bioavailability is high, approaching nearly 100% when administered intravenously. Their distribution in the body follows a three-compartment model, including a central compartment containing plasma and rapidly perfused tissues, and two peripheral compartments where distribution occurs more slowly. They have a large volume of distribution, contributing to their long half-life and explaining the slow onset of action and prolonged therapeutic effect after discontinuation. HCQ and CQ metabolism primarily occurs in the liver and can be influenced by drug interactions and individual differences in cytochrome P450 isoform expression. For example, ketoconazole, a CYP3A4 inhibitor, can reduce desethylchloroquine formation by approximately 33%. The metabolites of these drugs, such as desethylchloroquine and bisdesethylchloroquine, reach 40-48% and 10-13% of the parent compound concentration, respectively. HCQ also exhibits melanin affinity, leading to its accumulation in specific cell types, such as retinal and skin cells. It is important to note that HCQ concentrations vary across biological matrices - lowest in plasma and highest in whole blood. [5,3]

HCQ's mechanism of action is multifaceted, making it an effective treatment for autoimmune diseases. One key effect is the modulation of lysosomal function and autophagy. HCQ accumulates in lysosomes, increasing their pH and inhibiting lysosomal enzyme activity, disrupting the degradation of endocytosed, phagocytosed, and intracellular material through autophagy. Blocking autophagosome-lysosome fusion impacts cellular homeostasis and may be relevant to various pathologies. HCQ significantly influences the immune response, reducing the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IFN-γ, thus limiting inflammation in autoimmune diseases. It also inhibits antigen presentation by major histocompatibility complex (MHC) class II molecules, weakening T-cell activation. Furthermore, HCQ modulates Toll-like receptor (TLR) activity by altering endosomal pH and directly interacting with TLR ligands. It also affects the balance between Th17 and Treg lymphocyte subpopulations, which is crucial in autoimmune disease pathogenesis. [6]

HCQ and CQ also influence cellular processes by inducing apoptosis in lymphocytes and synoviocytes, contributing to their therapeutic effect in rheumatoid arthritis. [7] Chloroquine can directly bind to DNA, potentially affecting gene expression regulation. [5]

Additionally, HCQ may modulate NADPH oxidase (NOX) activity, impacting oxidative reactions within cells, and influence calcium mobilization from the endoplasmic reticulum (ER), affecting signaling pathways. [6]

The efficacy of HCQ depends on its concentration in target cells. In vitro effective concentrations may not reflect in vivo levels due to complex intracellular sequestration and drug metabolism. Ongoing research continues to provide new insights into HCQ's mechanisms of action and potential therapeutic applications. [5]

Adverse Effects of Hydroxychloroquine

Hydroxychloroquine is a widely used antimalarial drug also employed in the treatment of chronic autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Despite its proven efficacy, hydroxychloroquine use is associated with the risk of adverse effects affecting various organ systems.

One significant area of adverse effects involves psychiatric disorders. Systematic reviews indicate that hydroxychloroquine may cause symptoms such as increased verbal activity, psychomotor agitation, irritability, auditory hallucinations, grandiose delusions, and, in extreme cases, even suicidal attempts. These symptoms may occur over a wide timeframe - from a few hours to as long as 11 weeks after initiating therapy though they usually resolve within a week of drug discontinuation. [8]

The most commonly reported adverse effects are gastrointestinal disturbances. About 10% of patients experience nausea, vomiting, loss of appetite, indigestion, taste disturbances, and abdominal cramps. Although rare, some cases involve severe complications such as fulminant liver failure, necessitating immediate medical intervention. [9,10]

Hydroxychloroquine can also affect body weight and gut microbiota. Long-term use, particularly in combination with doxycycline, may lead to abnormal weight gain, which could impact metabolism and overall health in patients on prolonged therapy. [10,9]

One of the most serious adverse effects of hydroxychloroquine is its impact on vision. Drug-induced retinopathy may cause irreversible visual field changes, especially in long-term therapy. Studies have shown that toxic retinal damage occurs in approximately 3.5% of patients using hydroxychloroquine for more than six years, emphasizing the need for regular ophthalmologic monitoring during treatment. [11]

Hydroxychloroquine can cause various skin reactions, including maculopapular and erythematous rashes, as well as skin discoloration. Some patients also develop psoriasiform dermatitis, photosensitivity, oral mucosal inflammation, nail pigmentation changes, and hair loss. More severe skin reactions, such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), or Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), require immediate drug discontinuation and intensive treatment. [9]

Long-term hydroxychloroquine use may also lead to myopathy, characterized by muscle weakness, elevated muscle enzyme levels, and histopathological muscle changes. These complications can significantly impair patients' mobility. [12,13]
Cardiotoxicity is another significant complication associated with hydroxychloroquine use. In some cases, the drug can lead to cardiomyopathy and atrioventricular block, increasing the risk of serious cardiovascular events. Due to this potential risk, patients receiving hydroxychloroquine should undergo strict cardiologic monitoring, especially when using high doses for extended periods. [9,14]
Studies indicate that adverse effects of hydroxychloroquine are more common in women over the age of 50. [9] The risk of occurrence depends on the dose and duration of therapy, highlighting the necessity of an individualized assessment of the benefits and risks associated with long-term drug use. [8]

Use of Hydroxychloroquine During Pregnancy
Hydroxychloroquine is a medication with proven efficacy in the treatment of autoimmune diseases, such as systemic lupus erythematosus (SLE). Its use during pregnancy is of interest to both patients and physicians due to the need to control disease activity while ensuring the safety of both the mother and the child. [15,16]

Indications for the Use of Hydroxychloroquine During Pregnancy
Hydroxychloroquine is recommended for pregnant women suffering from SLE, as it helps maintain disease control and reduces the risk of exacerbation. [17] In some cases, it is also used in patients with antiphospholipid syndrome, although its role in this group remains unclear. [18] The benefits of therapy include a reduced risk of pregnancy complications, such as gestational hypertension and preeclampsia. [17]

Dosage and Duration of Treatment
The recommended doses of hydroxychloroquine used in clinical studies range from 200 to 400 mg per day. One study analyzed the effects of a 200 mg dose taken twice daily in 26 pregnant women and a 200 mg dose taken once daily in 25 pregnant women. In some cases, treatment was initiated at least six months before conception and continued throughout pregnancy, suggesting that long-term therapy may be safe and effective. [18,17]

Safety of Hydroxychloroquine Use in the Mother
Hydroxychloroquine is generally considered a safe medication for pregnant women when used according to medical recommendations. [16] The benefits for the mother include a reduction in SLE activity, a lower risk of disease exacerbation, and a decreased likelihood of pregnancy complications. [17]

Safety of Hydroxychloroquine Use in the Child
Studies on the potential risk of congenital defects related to hydroxychloroquine exposure in the first trimester of pregnancy have shown a slight increase in the risk of congenital anomalies, including cleft lip and palate, as well as respiratory and urinary system defects.

However, in patients with autoimmune diseases, the benefits of treatment likely outweigh the potential risks.[15] There are also concerns regarding the toxic effects of hydroxychloroquine on the fetal retina. Some cases have reported retinal degeneration following in utero exposure to chloroquine, but large-scale studies have not demonstrated an increased risk of ocular abnormalities in children exposed to hydroxychloroquine prenatally. Additionally, there are reports suggesting a possible impact of hydroxychloroquine on fetal heart rhythm, necessitating further research. [16]

Hydroxychloroquine in SLE

Hydroxychloroquine (HCQ) and Its Role in Systemic Lupus Erythematosus (SLE)

Hydroxychloroquine (HCQ) plays a crucial role in the treatment of systemic lupus erythematosus (SLE), exhibiting multidirectional therapeutic effects [19]. HCQ helps reduce SLE activity by alleviating clinical symptoms and lowering inflammatory markers. This drug effectively limits disease activity indices, leading to better disease control [20]. Additionally, regular use of HCQ significantly reduces the risk of disease flares, as confirmed by numerous clinical studies [21,22]. Patients receiving HCQ experience fewer disease exacerbations compared to those not using the medication [19].

Organ Protection

The protective effects of HCQ on organs result from its impact on the immune system and inflammatory processes. Cohort studies indicate that patients using HCQ have a lower risk of cumulative organ damage, as assessed by the SLICC Damage Index [21].

Improvement in Metabolic Parameters and Antithrombotic Effects

Hydroxychloroquine has a beneficial effect on the lipid profile of SLE patients. Its use is associated with a reduction in LDL, VLDL, and triglyceride levels, along with an increase in HDL cholesterol levels. Furthermore, HCQ helps regulate blood glucose levels, reducing the risk of developing diabetes in lupus patients [20]. The drug also exerts antithrombotic effects by reducing platelet aggregation and lowering the risk of thrombotic events, both in patients with and without antiphospholipid antibodies [23].

Relationship Between HCQ Dosage, Blood Drug Levels, and Flare Risk

The recommended HCQ dosage is ≤5 mg/kg of body weight per day to minimize the risk of retinopathy. In the past, doses of 6.5 mg/kg of ideal body weight were used, but for safety reasons, lower doses are now preferred. Low HCQ blood levels have been linked to an increased risk of SLE flares, while maintaining levels above 500 ng/mL is associated with a lower likelihood of disease activation. Importantly, studies have shown no clear correlation between the prescribed HCQ dose and actual blood drug levels, highlighting the need for individualized assessment and monitoring of HCQ concentrations in patients. [22]

Consequences of HCQ Discontinuation

Discontinuing HCQ treatment can increase the risk of SLE flares. Patients who discontinue therapy are more likely to experience exacerbations, particularly in the form of arthritis and hematological abnormalities. Therefore, long-term HCQ use is recommended to maintain disease stability and prevent health deterioration in SLE patients. [19]

Effect of HCQ on Cardiovascular Risk and Atherosclerosis

Patients with SLE are at an increased risk of developing cardiovascular diseases, and HCQ may play a significant role in their prevention. The drug has a beneficial effect on lipid parameters by lowering harmful cholesterol fractions and reducing the risk of hyperglycemia [20,23]. Some studies suggest that HCQ may decrease atherosclerotic plaque burden and aortic stiffness, although not all analyses confirm a definitive impact of the drug on atherosclerosis presence. The mechanisms of HCQ action include modulation of Toll-like receptor (TLR) signaling, cytokine production, T lymphocyte and monocyte activation, reduction of oxidative stress, and improvement of endothelial function [23].

Hydroxychloroquine in Rheumatoid Arthritis (RA)

Hydroxychloroquine (HCQ) is an antimalarial drug that has been used for many years in the treatment of rheumatoid arthritis (RA) due to its immunomodulatory properties. In terms of therapeutic efficacy, HCQ can be used both as monotherapy and in combination with other disease-modifying antirheumatic drugs (DMARDs). As monotherapy, HCQ demonstrates clinical and structural effectiveness comparable to, though often lower than, methotrexate (MTX) and sulfasalazine (SSZ). However, combining HCQ with other DMARDs can enhance treatment efficacy, particularly when HCQ is used alongside MTX. Additionally, HCQ may increase the exposure to other DMARDs, which could further improve their effectiveness. Despite these benefits, HCQ monotherapy is not recommended as a first-line treatment strategy for most patients with early RA. Beyond its impact on joint inflammation, HCQ also provides benefits in managing RA-related complications. The drug may contribute to improved lipid profiles and a reduced risk of diabetes development. Furthermore, HCQ may help lower the risk of cardiovascular events and insulin resistance in RA patients. There is also evidence suggesting that HCQ can reduce hyperlipidemia and the incidence of cardiovascular diseases, including chronic kidney disease (CKD) [24,25].

The therapeutic effectiveness of HCQ may be linked to its blood concentration, although this relationship is not entirely clear. Studies indicate a weak but predictable correlation between the concentration of desethylhydroxychloroquine (DHCQ) in the blood and treatment efficacy. Higher HCQ concentrations, however, may increase the risk of gastrointestinal side effects. Moreover, DHCQ concentration was the only significant variable in regression models predicting treatment effectiveness. It is also noteworthy that there is a tendency for higher BDCQ blood concentrations in patients reporting ocular symptoms, which may suggest an association between HCQ and ophthalmologic changes [26].

One of the key aspects of long-term HCQ use is its effect on cardiovascular events in RA patients. Research has shown that HCQ is associated with a reduced risk of cardiovascular complications, making it a drug with a favorable cardiovascular profile. The mechanisms responsible for this effect may include improved lipid profiles and increased insulin sensitivity, which indirectly contribute to a lower risk of atherosclerosis and other cardiovascular diseases [27].

It is important to note that data regarding HCQ efficacy in RA are inconsistent, and studies often yield conflicting results. Nevertheless, HCQ remains a valuable drug in RA treatment, particularly when combined with other medications, due to its potential metabolic and cardiovascular benefits [25].

Hydroxychloroquine in COVID-19

Hydroxychloroquine (HCQ) as a COVID-19 Treatment

Hydroxychloroquine (HCQ) was one of the first drugs tested for the treatment of COVID-19. In the early phase of the pandemic, it was included in national treatment guidelines in some countries, such as India and the United States. However, despite initial enthusiasm regarding its potential efficacy, the actual effectiveness of HCQ in treating COVID-19 remains unclear and highly controversial [28].

Analysis of Studies on HCQ Efficacy

A meta-analysis of clinical trials did not show a significant impact of HCQ on reducing mortality in COVID-19 patients. Data indicate no meaningful difference in the risk of death between those treated with HCQ and those receiving standard medical care (RR 0.98; 95% CI 0.66–1.46).

Similarly, there were no clear benefits in reducing fever duration, with HCQ shortening fever by only 0.54 days compared to the control group (mean difference −0.54 days; 95% CI −1.19 to 0.11). Moreover, HCQ use did not reduce the risk of clinical deterioration, including the development of acute respiratory distress syndrome (ARDS) (RR 0.90; 95% CI 0.47–1.71) [28].

Safety Concerns of HCQ Use

One of the major concerns related to HCQ use in COVID-19 therapy was an increased risk of electrocardiogram (ECG) abnormalities and cardiac arrhythmias. Data analysis showed that patients receiving HCQ were more susceptible to arrhythmias and other cardiac complications compared to the control group (RR 1.46; 95% CI 1.04–2.06). Based on these findings, the quality of available scientific evidence regarding HCQ's efficacy was assessed as very low. As a result, current medical guidelines do not recommend its use as an effective COVID-19 treatment. Further well-designed clinical trials are necessary to definitively evaluate the drug's efficacy and safety [28].

Discontinued Trials and Regulatory Decisions

In one key study comparing HCQ efficacy with standard medical care in hospitalized COVID-19 patients, recruitment for the HCQ group was halted after an interim analysis. The results showed a lack of efficacy - 28-day mortality was slightly higher in the HCQ group (27.0%) compared to those receiving standard care (25.0%) (HR 1.09; 95% CI 0.97–1.23; P = 0.15). Additionally, analysis revealed that HCQ-treated patients were discharged from the hospital less frequently within 28 days compared to the control group (59.6% vs. 62.9%; HR 0.90; 95% CI 0.83–0.98). Among patients who did not initially require mechanical ventilation, those in the HCQ group were more likely to later require invasive respiratory support or die (30.7% vs. 26.9%; HR 1.14; 95% CI 1.03–1.27) [29].

Key Findings on HCQ Use in COVID-19 Treatment

- Lack of evidence for efficacy– A 2020 meta-analysis found that HCQ use did not reduce short-term mortality in hospitalized COVID-19 patients [30].
- Possible negative immunological effects – HCQ exhibits immunomodulatory properties that may weaken the innate immune response to SARS-CoV-2, disrupt adaptive immune reactions, and affect the repertoire of T and B lymphocytes responsible for fighting infection [31].
- Regulatory decisions – The U.S. Food and Drug Administration (FDA) initially issued an Emergency Use Authorization (EUA) for HCQ use in hospitalized COVID-19 patients [32,33]. However, due to a lack of evidence for efficacy, the EUA was later revoked, and both the World Health Organization (WHO) and the National Institutes of Health (NIH) discontinued further research on this drug for COVID-19 treatment [29].
- No significant benefits in observational studies – A study conducted in New York found that HCQ use had no significant impact on either reducing or increasing the risk of intubation and death in COVID-19 patients [32].

Conclusion

Hydroxychloroquine (HCQ) remains a crucial drug in the management of autoimmune diseases, providing significant immunomodulatory benefits. While its role in public health has evolved, especially during the COVID-19 pandemic, ongoing research is essential to refine its applications and assess its long-term safety. Additionally, HCQ's potential impact on metabolic health and cardiovascular risk reduction highlights its relevance beyond rheumatology. From an educational perspective, ensuring healthcare professionals and patients remain informed about its benefits and risks is key to optimizing treatment strategies. Understanding its mechanisms may also contribute to better therapeutic approaches in rehabilitation and sports medicine, where chronic inflammation plays a role in patient recovery and performance.

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Author's contribution
All authors contributed to the article.
Project administration: Ząbek A
Conceptualization: Ząbek A
Methodology: Kuźniar J, Chrzanowska E, Pudełko I
Software: Turek M, Zagalska M
Formal analysis: Tamborski T, Roguska B
Investigation: Ząbek A, Turek M, Kuźniar J
Resources: Chrzanowska E, Roguska B
Data curation: Grzebinoga A, Zagalska M, Pudełko I
Writing - rough preparation: Grzebinoga A, Ząbek A
Writing - review and editing: Tamborski T, Szlążek J
Visualization: Szlążek J , Turek M
Supervision: Roguska B, Tamborski T

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