REVIEW ARTICLE

Hydroxychloroquine as an important immunomodulator: a novel insight into an old drug

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KEY WORDS

antimalarials, hydroxychloroquine, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus

ABSTRACT

Hydroxychloroquine (HCQ) is an increasingly popular drug owing to its efficacy, long-term safety, and a wide range of therapeutic effects. Currently, due to the numerous benefits it provides, the use of the drug goes beyond the treatment of rheumatic and dermatologic diseases. As HCQ shows anti-inflammatory, immunomodulatory, antiproliferative, and photoprotective action, it has a great potential to be applied also in the treatment of oncologic diseases, multiple sclerosis, diabetes, cardiovascular diseases, or recurrent miscarriages. Nevertheless, antimalarial drugs are still most widely used in the long-term treatment of systemic rheumatic disorders, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and primary Sjögren syndrome, as they continue to offer satisfactory outcomes. They reduce the need for glucocorticoids and immunosuppressants and increase their effectiveness. In addition, they reduce the risk of possible side effects and complications. This paper presents the latest data on HCQ, its mechanisms of action, its therapeutic potential in current clinical practice as well as future perspectives. It also discusses the correct dosing regimen and long-term monitoring, with consideration of possible rare complications. Finally, it focuses on the enormous benefits for patients with rheumatic diseases in terms of reducing the disease activity and organ damage, preventing flares and pregnancy-related complications, and, most importantly, lowering mortality rates in SLE patients.

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Received: November 29, 2023.
Revision accepted: December 22, 2023.
Published online: January 2, 2024.
Pol Arch Intern Med. 2024; 134 (1): 16656
doi:10.20452/pamw.16656

Introduction Antimalarial drugs are currently being rediscovered and increasingly appreciated for their properties. Historically, they have been known for about 400 years, and the first antimalarial drug was quinine, an alkaloid produced from the bark of the Cinchona tree in South America. Quinine was originally used as a drug that inhibited proper cell functioning by forming a complex with DNA of the malaria-causing parasite *Plasmodium falciparum*. It also had additional antipyretic and analgesic effects, which was particularly important in medicine at that time. The use of quinine for an indication other than malaria was first described by Payne in 1894, when he reported successful treatment of cutaneous lupus manifestations. As an antiprotozoal drug, quinine carried the risk of complications, especially neurotoxic ones, such as vision and hearing disorders. Therefore, investigators continued to search for equally effective treatments without adverse effects.[1,2]

Chloroquine was the first artificially synthesized quinine analogue used as an antimalarial drug. However, it also showed an adverse safety profile. Toxic effects included cutaneous and intestinal complications, cardiac damage, retinopathy, and myelopathy. More advanced forms of antimalarial drugs, mepacrine and hydroxychloroquine (HCQ), were not used until the 20th century.[3] During World War II, millions of soldiers took chloroquine and HCQ as part of a program testing the synthetic derivatives of 4-aminoquinolines for the prevention of inflammatory cutaneous lesions and arthritis. This led to research confirming the effectiveness of antimalarial drugs in the treatment of systemic lupus erythematosus (SLE).

In 1955, HCQ was approved for use in the United States. This synthetic form of quinine lacked

1 hydroxyl group, thus providing a better safety profile. The primary role of HCQ is the inhibition of proinflammatory cells. HCQ also affects numerous immune processes, for example, by inhibiting antigen presentation (mainly of antigens with lower affinity to antibodies). This explains the immunomodulatory rather than the immunosuppressive effect of HCQ. However, the exact mechanisms underlying the drug's action at the molecular and cellular levels remain to be fully elucidated.[4] Moreover, new mechanisms of action continue to be discovered for antimalarial drugs, which may contribute to expanding the therapeutic indications for HCQ. So far, antimalarials have been used mainly in rheumatic diseases including SLE,[5] rheumatoid arthritis (RA),[4] antiphospholipid syndrome (APS),[6] and primary Sjögren syndrome (SS).[7] However, HCQ is also investigated for its potential benefits in oncologic diseases, multiple sclerosis, diabetes, cardiovascular disease, and recurrent miscarriages. Antimalarials increase the potency of glucocorticoids and immunosuppressants and reduce their potential adverse effects.[8] Thus, lower doses of these drugs can be administered when using antimalarials. HCQ demonstrates a high potential as an anticoagulant,[9] hypolipidemic,[10] and hypoglycemic agent,[11] which translates into its antiatherosclerotic effect[12] and indirectly contributes to lower cardiovascular risk.[13,14] Finally, HCQ protects against serious bacterial, viral, and fungal infections and their complications, providing additional benefits for modern immunosuppressive treatment of rheumatic diseases.[15]

In SLE, it is particularly important that HCQ treatment is administered over a long period. When used as primary treatment, HCQ reduces the disease activity and the risk of flares, and, most importantly, prevents progression of organ damage. Moreover, HCQ improves long-term outcomes, which translates into reduced mortality.[8,16,17] Currently, HCQ is recommended as primary treatment for all SLE patients in the absence of contraindications, such as retinopathy and cardiomyopathy. However, these conditions are relatively rare, and the risk applies only to high HCQ doses.[18] Finally, HCQ can also be administered to reduce the frequency of SLE flares in pregnant women.[3,19]

It is important to note that the beneficial effects of HCQ can occur only if its therapeutic levels are maintained for a sufficiently long period of time. This may be challenging due to poor adherence among patients in terms of the dosing regimen and regular use of HCQ.[20]

Pharmacokinetics and pharmacodynamics of hydroxychloroquine The pharmacokinetics of HCQ is important in terms of long-term outcomes. The choice of an adequate dose and the assessment of treatment efficacy are difficult owing to considerable variations in serum HCQ levels between individuals. This may be caused by different sequestration of the drug in lysosomes, differences in the drug's ability to accumulate in tissues, and the effect of other factors, such as chronic inflammatory processes, on the drug distribution.[21] The drug is almost completely (75%–100%) absorbed from the gastrointestinal tract when administered orally, and its bioavailability increases when taken with food, especially if the meal is rich in fat and protein. On average, 50% of HCQ binds to plasma proteins; therefore, its distribution volume is relatively large.[21] Stable serum HCQ levels are reached after 3 to 6 hours from intake, but the therapeutic concentrations are not achieved until after about 3 to 6 months of treatment. In the rapid-release phase, the drug has a half-life of up to 3 days. On the other hand, in the slow-release phase, it has a half-life of up to 40 to 50 days due to its accumulation in tissues and organs.[3,22]

HCQ is metabolized in the liver via cytochrome P450. Apart from the liver, it is accumulated in the adrenal glands, pineal gland, spleen, and leukocytes. However, the highest HCQ levels were noted in epidermal cells (100- to 200-fold higher than in blood serum and higher than in the dermis). This is due to a strong binding of HCQ to melanin, resulting in the accumulation of HCQ in tissues containing large amounts of melanin, such as the skin and the eye.[23] HCQ is excreted mainly through the kidneys (40%–50%; with urinary acidifying agents increasing its excretion), the gastrointestinal tract (24%–25%), and the skin (5%).[21] Therefore, renal clearance rates and increased bioavailability remain challenging in the treatment of patients with renal impairment, although there are no recommendations to reduce the HCQ dose in this population. The use of HCQ in patients with end-stage renal disease was also reported.[24] Interestingly, as HCQ has a long half-life, it can be detected in urine even up to several years after the end of treatment.[25] Thus, considering the pharmacokinetic profile of HCQ, it is important to remember that the drug has a slow onset of action (weeks or even months) and remains present in the body long after the treatment has been completed.

In terms of pregnancy and childbirth, it should be mentioned that while HCQ crosses the placenta, it does not cause adverse effects, such as congenital malformations.[26] Penetration of the drug into breast milk is minimal and does not threaten the life or health of the child. Hence, the drug is safe to use during breastfeeding.[27]

Anti-inflammatory and immunomodulatory effects of hydroxychloroquine The main mechanism of action of HCQ is its anti-inflammatory effect. However, by acting on the innate and acquired immune response, HCQ exerts also immunomodulatory effects.[4] At the molecular and cellular level, the following 4 mechanisms underly the anti-inflammatory action of HCQ: 1) inhibition of lysosomal activity and autophagy, 2) inhibition of the proinflammatory cytokine signaling pathway, 3) inhibition of nicotinamide

adenine dinucleotide phosphate (NADPH) oxidase, and 4) inhibition of the secondary calcium signaling pathway.

Inhibition of lysosomal activity and autophagy Recent research showed that lysosomes are not only responsible for degradation of cellular waste but also serve as dynamic organelles activating lysosome-dependent signaling pathways that control the adaptation of cell metabolism to various environmental factors.[28] The presence of the lipophilic ring makes it possible for HCQ to easily penetrate the cell membrane and accumulate inside the lysosomes and endosomes. As a result, pH of the lysosomal matrix increases from 4 to 6, leading to inactivation of various enzymes, including lysosomal hydrolases. Alkalization is one of the main factors responsible for disrupting several immune response processes, including antigen presentation on the surface of macrophages and dendritic cells, activation of these cells, and chemotaxis and stimulation of inflammatory mediators. Functional disruption of cellular organelles associated with pH alkalinization may also account for restoring the normal activity of transforming growth factor β, which controls the proliferation and differentiation of most cell types as well as regulates cell apoptosis.[29] The ability of HCQ to act via such mechanisms also affects autophagy and its inhibition. Unlike apoptosis and necrosis, autophagy is not synonymous with cell death. On the contrary, it is a strategy for cell survival and a defense mechanism aimed at restoring homeostasis by degrading unnecessary intracellular components, proteins, cellular organelles, and infectious agents via the lysosomal pathway. Recent findings showed that impaired autophagy is involved not only in tumorigenesis and neurodegeneration but also in inflammatory processes and immune disorders, including immune overresponse underlying development of autoimmune diseases.[4,30]

Inhibition of proinflammatory cytokine signaling pathway Proinflammatory cytokines are produced and secreted following the activation of Toll-like receptors (TLRs) belonging to the family of pattern recognition receptors. These receptors participate in maintaining the balance between the host organism and factors that disrupt its homeostasis, such as microorganisms. TLRs are crucial in the early innate defense mechanisms of the immune system, but their overstimulation underlies the development of numerous autoimmune rheumatic diseases. Therefore, the strong therapeutic potential of HCQ lies in its ability to inhibit TLRs (mainly TLR3, TLR7, and TLR9).[31,32]

The primary mechanism that inhibits TLR activation is alkalinization of the endosome environment, as TLRs require acidic environment for activation. TLRs can detect fragments of genetic material also contained in immune complexes. All these direct and indirect mechanisms inhibit the secretion of numerous proinflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukins (IL)-1, IL-2, and IL-6, as well as interferons α and γ.[4,33] This, in turn, has clinical implications for the reduction of disease activity and symptoms.[34]

Nicotinamide adenine dinucleotide phosphate oxidase inhibition NADPH oxidase is a protein complex found in the cell membrane. Its activation in endosomes leads to the formation of reactive oxygen species (ROS). The resulting oxidative stress enhances oxidation and reduces bioavailability of nitric oxide in several physiological processes. An example of a degenerative effect of ROS accumulation is atherogenesis in active SLE. HCQ inhibits NADPH oxidase-dependent activation of the inflammatory cascade by impeding translocation of the NADPH oxidase subunit from the cytosol to the endosomal membrane, regardless of the acidity of endosomes. HCQ also prevents redistribution of TLR8 from the endoplasmic reticulum to the endosome, which is essential for the activation of the inflammatory response.[35]

Inhibition of secondary calcium signaling pathway Calcium is mainly stored in the endoplasmic reticulum and is mobilized into the cytoplasm in the secondary signaling pathway to activate signal transduction and transcription of factors regulating the expression and secretion of cytokines and other immune mediators. Calcium release from the endoplasmic reticulum can be affected by HCQ in a dose-dependent manner. HCQ interferes with calcium signaling dependent on T- and B-cell receptors, a mechanism that accounts for its immunomodulatory properties.[36]

Effects of antimalarial drugs on the immune system Immune system overstimulation underlies development of rheumatic diseases. HCQ exerts its therapeutic effects by inhibiting the innate and acquired immune response, leading to reduced inflammation and disease activity. The release of circulating proinflammatory cytokines is reduced by inhibition of several processes, including antigen presentation, T and B lymphocyte activation, regulatory processes between T-regulatory and T-helper-17 cells, as well as NADPH oxidase-dependent processes (FIGURE 1).[4,22,35] Other immunomodulatory mechanisms of HCQ include DNA binding and stabilization as well as inhibition of response to ultraviolet radiation, phospholipase A2, prostaglandin synthesis, and metalloproteinases.[3]

Multidirectional effect of hydroxychloroquine **Antimicrobial effect** In addition to its antiprotozoal effect, HCQ shows antimicrobial, antiviral, and antifungal properties. Owing to its ability to change pH of the cellular endosomes, the drug inhibits the entry of viral or bacterial material into the cell.[37] Thus, it can reduce replication of tropical viruses, such as the dengue virus and chikungunya virus, but also of such common viruses as

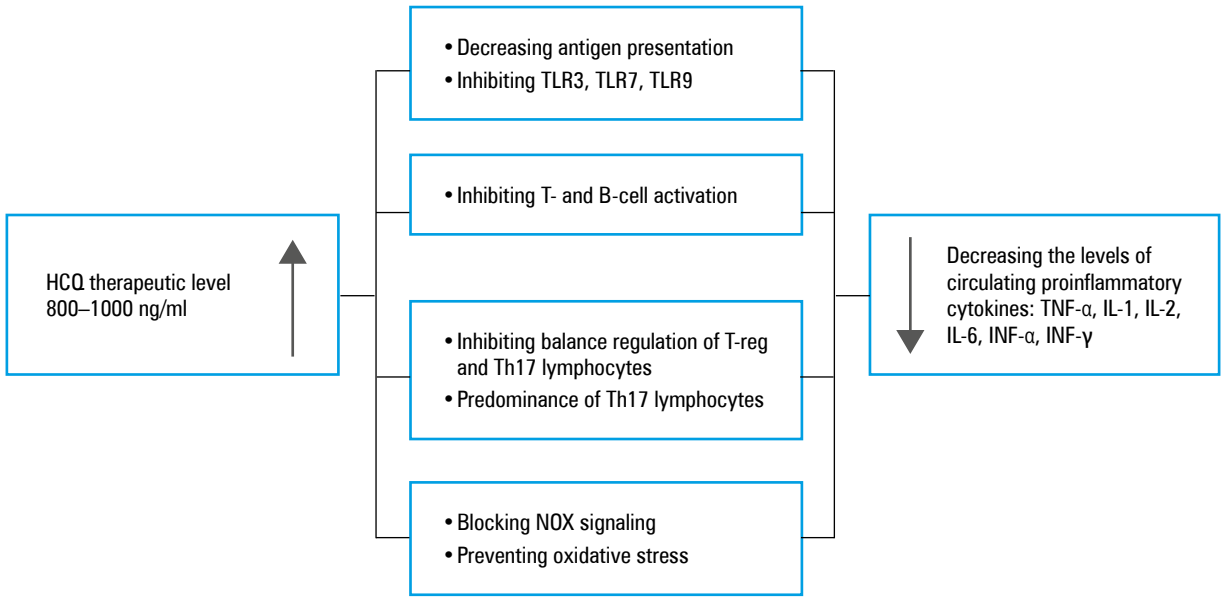

FIGURE 1 Effect of hydroxychloroquine (HCQ) on the immune system
Abbreviations: IL, interleukin; INF, interferon; NOX, nicotinamide adenine dinucleotide phosphate oxidase; TH17, T-helper-17 cells; TLR, Toll-like receptor; TNF, tumor necrosis factor

hepatitis A, hepatitis C, influenza A, or SARS--CoV-2. HCQ also inhibits the post-translational modification of proteins necessary for microorganisms to mature and survive. In terms of antimicrobial activity, HCQ is best known for its beneficial effects in patients with endocarditis associated with chronic Q fever caused by *Coxiella burnetii*.

Most of the above effects of antimalarial drugs were observed in vitro and were not confirmed by in vivo studies. Antimalarials have no potential for the treatment of infections.[37] HCQ effects at the molecular level do not translate into prevention of infectious diseases, but the drug may have a supportive role. It was reported to significantly reduce the risk of infection in patients with SLE.[38,39]

Metabolic and cardiovascular effects Clinical and experimental studies showed significant benefits of antimalarial drugs in terms of reducing atherogenesis, which is the main cause of increased cardiovascular risk in patients with rheumatic disorders. Higher cardiovascular risk is also associated with chronic inflammation and autoimmune processes. Thus, primary cardiovascular prevention is important in these patients.[40] As an anti-inflammatory and immunomodulatory drug, HCQ acts via the mechanisms that underlie the acceleration of atherosclerosis. A meta--analysis of 19 observational studies[13] found that antimalarial drugs reduce cardiovascular risk by almost 30% in patients with rheumatic diseases thanks to hypoglycemic, hypolipemic, and vasodilatory effects. By reducing platelet aggregation, they also reduce thromboembolic risk.

Hypoglycemic effect HCQ exerts its hypoglycemic action by reducing insulin breakdown and clearance, while increasing C-peptide secretion. It also inhibits gluconeogenesis, prolongs the half--life of the endosomal insulin receptor, and increases glucose uptake by peripheral tissues. As a result, an insulin dose can be reduced by 30% and glycated hemoglobin levels drop significantly in patients both with insulin-dependent and insulin-independent diabetes mellitus.[41] This has important implications for the treatment of patients with diabetes, but also, by inducing the hypoglycemic effect, it provides benefits for patients on long-term glucocorticoid treatment and those with diseases associated with iatrogenic hyperglycemia. Hence, HCQ not only improves glycemic control[11] but also reduces the risk of diabetes in RA, psoriatic arthritis, and SLE.[42-44]

Hypolipidemic effect Two randomized controlled trials (RCTs)[45,46] and numerous observational studies[47-49] demonstrated that HCQ improves the lipid profile in patients with SLE. The hypolipidemic effect is exerted through a decrease in the levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein cholesterol, and triglycerides, and through an increase in the levels of high-density lipoprotein cholesterol. HCQ affects the removal of LDL cholesterol from blood by increasing the number of receptors for LDL cholesterol, thus neutralizing the proatherogenic lipid profile.[50] Antimalarials also act in a way similar to statins by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which is responsible for cholesterol synthesis.[3] HCQ reduces the hepatic synthesis of LDL cholesterol in patients on long-term steroid treatment. As a result, associations between HCQ use and lower serum levels of the various atherogenic fractions of cholesterol were confirmed not only in SLE but also in other rheumatic diseases.[10,50] The hypolipidemic effect of HCQ

is observed regardless of whether patients are on long-term steroid treatment.[51] Moreover, it is important to note that hypolipidemic action can be expected after at least 12 months of treatment.

Anticoagulant effect The regulation of the endothelial microenvironment is becoming a target in the prevention and treatment of cardiovascular incidents also in patients with autoimmune diseases.[14] By inhibiting NADPH oxidase and ROS formation in the mechanism of oxidative stress, antimalarial drugs counteract the factors that cause endothelial damage through vasoconstriction.[52] The use of HCQ in patients with rheumatic diseases reduces the risk of venous and arterial thrombosis[53,54] by inhibiting platelet aggregation, arachidonic acid secretion,[12] and antiphospholipid (aPL) antibody binding.[6] Higher serum HCQ levels are also associated with a lower risk of thrombosis in patients with other cardiovascular risk factors, such as hyperglycemia and diabetes, as well as in patients with lupus nephritis.[9,44,55] A considerable thrombotic risk reduction was reported in SLE patients with primary and secondary APS. In this setting, HCQ prevents platelet activation; however, the exact mechanism of its anticoagulant effect is not fully understood.[53,56]

Antitumor effect HCQ inhibits autophagy, which is one of the basic mechanisms that ensure cell survival. Autophagy also plays an important role in uncontrolled proliferation of cancer cells.[4] The mechanism whereby HCQ inhibits tumor cell growth in vitro was first described in 1970.[57] In 1998, Murakami reported an inhibitory effect of HCQ on autophagy.[58] In subsequent years, the antitumor effect of antimalarial drugs was found first in glioblastoma and then in numerous other types of malignancies, non-Hodgkin lymphomas, or solid tumors. A link between HCQ treatment and the risk of tumorigenesis was also reported for patients with SLE.[59] Moreover, available research shows that HCQ treatment in combination with chemotherapy or radiation therapy offers greater benefits in terms of cancer treatment outcomes. However, the HCQ doses used to inhibit autophagy in cancer were higher than those used in standard treatment: 400–1200 mg/d vs 200–400 mg/d.[60,61]

Dosing regimen in hydroxychloroquine treatment

The measurement of therapeutic serum HCQ levels provides important information about the clinical outcomes, especially regarding SLE treatment. It is known that excessively low serum HCQ levels predict disease flares, and nonadherence with HCQ dosing recommendations is a major cause of relapse in SLE patients.[62,63] The benefits of HCQ treatment, such as reduced risk of flares, mortality, and organ damage, can be achieved only if the drug is used long-term and at appropriate doses.[64] Therefore, it is important that patients with rheumatic diseases adhere to the dosing regimen. The optimal therapeutic dose of HCQ that does not cause toxicity or does not increase the risk of complications is 5 mg/kg/d body weight (bw) or 200 to 400 mg/d. Such dosing should ensure a target serum drug levels of 800 to 1000 ng/ml.[63,65] However, the target level is often difficult to achieve. In clinical practice, 7% to 29% of patients treated with HCQ achieved drug levels of less than 200 ng/ml.[5,62] In addition to the problem of nonadherence, there are also individual variations in serum drug levels between patients, which most likely result from the mechanism of drug binding in tissues, drug metabolism, as well as distribution and sequestration of the drug in lysosomes.[21]

The relationship between the HCQ dose and the therapeutic effect remains unclear. Therefore, the dose of up to 5 mg/kg/d bw is controversial, because some investigators and clinicians believe it may be too low to achieve the therapeutic effect. The dose of 5 mg/kg/d bw was established mainly on the basis of a study reporting potential ocular toxicity due to long-term treatment. However, this refers to the time period of 10 to 25 years.[18] Higher HCQ doses are recommended especially in SLE patients with flares. Moreover, most studies that confirmed the efficacy of HCQ used higher doses (ie, 6.5 mg/kg/d bw) than those recommended by the European Alliance of Associations for Rheumatology (EULAR) and ophthalmologic societies. The highest doses of HCQ were used in patients with cancer (up to 1200 mg/d). No adverse effects other than cytopenia were reported.[18,66] However, it is important to note that the duration of treatment in oncologic diseases is shorter than that in chronic rheumatic diseases. While monitoring serum HCQ levels might allow for a more personalized treatment with individual adjustment of the drug dosage, it is not routinely used in clinical practice.

Hydroxychloroquine treatment in rheumatic diseases

In modern rheumatology, HCQ is the primary drug used in the long-term treatment of SLE, primarily due to its ability to reduce mortality and prevent organ damage. However, SLE is not the only indication for this type of treatment, because HCQ is used for most systemic diseases with a slow onset, especially at the early diagnostic stage. The second major indication for HCQ treatment is primary SS. In RA, HCQ is one of the inflammation-modifying drugs, and in combination therapy, it may constitute an option at some stage of treatment. Owing to its ability to inhibit aPL binding, HCQ plays a major role in the treatment of primary and secondary APS.[3]

The role of hydroxychloroquine in systemic lupus erythematosus The beneficial effects of HCQ were first observed in Canadian RCTs assessing the effect of antimalarial treatment withdrawal that resulted in a 2.5-fold increase in the rate of SLE exacerbations.[67,68] In subsequent studies, an improvement of clinical symptoms in the joints (arthralgia, arthritis) and skin was observed, along

with a reduction of SLE activity. This correlated with lower levels of proinflammatory cytokines, improvement of metabolic parameters, reduced risk of flares, and sustained long-term remission.[69] While RCTs provide comprehensive data on the benefits of HCQ in SLE, not all HCQ effects were confirmed by RCTs. The greatest clinical value of HCQ was proven by numerous observational studies of SLE populations (Hopkins Lupus Cohort, GLADEL Cohort, Toronto Lupus Cohort).[15-17]

In current clinical practice, HCQ is the primary drug used in most patients with SLE,[70] and it is recommended regardless of the clinical manifestation and disease activity.[18,71] The HCQ treatment often lasts many years and is continued even during pregnancy and breastfeeding. It was shown that antimalarials given consistently during the first 5 years of the disease improve treatment outcomes.[72] The importance of HCQ in SLE treatment lies in the fact that the persistent inflammatory process over the course of the disease causes irreversible organ damage. This, in turn, increases morbidity and mortality rates in SLE patients. Therefore, HCQ has the potential to reduce mortality in this population,[5,17,55,73] as it reduces the disease activity,[8,34,74] lowers the risk of flares,[16,63,64,75] helps maintain remission,[8,76] and prevents organ damage.[8,77,78] Another significant benefit of HCQ in SLE is the possibility of using lower glucocorticoid doses.[8,79] This helps avoid complications of glucocorticoid treatment, mainly by improving the lipid profile,[10,45-48,51] preventing diabetes,[80] and reducing the risk of thrombosis.[9,14,53,81]

As mentioned above, adherence to medical recommendations is one of the most important issues in the management of patients with SLE, because long-term use of HCQ at optimal doses and in line with a goal-oriented treatment strategy is crucial for the disease control and prevention of complications. In addition, higher annual doses of HCQ were shown to be associated with lower SLE activity based on objective assessment (using dedicated scales), and thus with reduced rates of cardiovascular incidents, such as myocardial infarction or stroke.[5,65,82] On the other hand, nonadherence to treatment is associated with higher morbidity, more frequent SLE flares,[62,63,67] and increased need for acute care.[83]

Hydroxychloroquine in Sjögren syndrome Despite the lack of convincing evidence from RCTs on the efficacy of HCQ in SS, the drug may help alleviate musculoskeletal pain.[7,20] Therefore, EULAR recommends the use of HCQ for recurrent symptoms of active disease, similarly to other immunomodulatory or immunosuppressive drugs, after considering the risks and benefits of treatment.[7]

Hydroxychloroquine in rheumatoid arthritis HCQ is a standard disease-modifying antirheumatic drug used in the treatment of RA, most often in combination with methotrexate.[4,66] HCQ not only improves clinical outcomes but also has a beneficial metabolic effect and beneficial structural efficacy.[84] Additionally, antimalarials reduce cardiovascular risk, which in patients with RA is elevated by chronic inflammation and its consequences.[13,40]

Hydroxychloroquine in pregnancy and breastfeeding

An imbalance between proinflammatory and anti-inflammatory cytokines driven by rheumatic diseases underlies development of numerous complications in pregnant women. Fetal growth is associated with elevated levels of TNF-α, one of the main proinflammatory cytokines in rheumatic diseases. Excessive proinflammatory stimulation leads to endothelial dysfunction, which may result in pre-eclampsia. HCQ was shown to potentially alleviate TNF-α–induced endothelial dysfunction in pre-eclampsia. The drug reduces aPL binding to syncytiotrophoblasts and reverses the aPL-dependent impairment of the anticoagulant effect of annexin A5.[85]

There is also clinical evidence of HCQ safety[86] and efficacy[87,88] in pregnant women with SLE. The drug was shown to reduce the disease activity and the risk of flares in this population.[87,88] Other benefits of HCQ treatment included prevention of pregnancy-related complications, such as intrauterine fetal growth restriction[89] and placental abruption.[90] However, as these data come from observational studies, RCTs in a larger group of pregnant women are necessary to provide more precise data on the prevention of complications. Nevertheless, it should be noted that while HCQ offers control of the disease activity, it cannot replace immunosuppressive therapy or the need for intensified treatment with biologic drugs.

There are also data regarding the management of pregnant women who have developed specific antibodies. The effect of HCQ was shown to be beneficial in pregnant women with anti-SSA/SSB antibodies due to over a 50% reduction in the risk of recurrent fetal congenital heart block. This indicates that HCQ in these women may be beneficial as secondary prevention of intracardiac conduction defects in the fetus and neonate.[91] The presence of aPLs is a serious threat in pregnancy. This refers particularly to aPLs against β2glycoprotein-I, which are most pathogenic in obstetric APS. In the healthy population, the prevalence of aPLs does not exceed 5%. However, among women with recurrent miscarriages, it reaches up to 20%. Women that are seropositive for aPLs develop pregnancy complications, and half of them experience recurrent miscarriages.[92] Antiphospholipid antibodies negatively affect trophoblast cells and were shown to influence the vascular remodeling of the placenta, both in vitro and in vivo, leading to its abnormal development and secondary placental failure.[93] HCQ exerts protective effects by inhibiting aPL binding to trophoblast cells and facilitating placental development. Hence, the drug might prevent pregnancy complications.[94] However, there

are insufficient data from RCTs to support this hypothesis. Currently, empiric HCQ use is recommended in patients with obstetric APS when standard treatment with heparin and low-dose acetylsalicylic acid fails.[93]

Adverse effects and complications Antimalarial drugs are generally well tolerated and rarely cause adverse effects. Cutaneous or gastrointestinal reactions occur most often, while cardiomyopathy or cytopenia is much less common. Retinopathy, although rare, constitutes one of the most serious complications of long-term treatment with antimalarial drugs. It is a dose- and time-dependent complication caused more often by chloroquine than by HCQ. The risk of retinopathy was estimated at 1% after 5 years of treatment, 2% after 10 years, and up to 20% after 20 years, but the analysis did not consider serum drug concentrations[95]. Due to the risk of retinopathy, the recommended HCQ doses for long-term treatment were lowered from 6.5 to 5 mg/kg/d bw.[95-97] However, when considering not only the HCQ dose but also the obtained serum drug levels, the estimated risk of retinopathy was 1% in the first 5 years of treatment, 1.8% after 6 to 10 years, 3.3% after 11 to 15 years, and 8% after more than 21 years. In addition, age, body mass index, and the time of HCQ treatment were assumed as risk factors of retinal toxicity.[96] However, with adequate knowledge of the risk groups and access to specialist ophthalmic examination, the prevalence of retinopathy can be reduced.

Considering the unquestionable benefits of HCQ treatment, most experts share the opinion that long-term HCQ use in patients with SLE requires caution when reducing the drug dose. Moreover, an individualized approach is needed to estimate the risk of complications. Monitoring serum drug levels could become a useful tool to increase the effectiveness of therapy and to reduce the risk of adverse effects.[96] Unfortunately, serum HCQ levels are not routinely assessed in clinical practice. If the approach to HCQ use is not careful enough and too conservative, it may increase the risk, number, and severity of flares,[67,75] increase the risk of pregnancy complications for the mother and child,[90,98] and contribute to higher mortality in patients with SLE.[5,13]

Summary Considering recent data, the benefits of long-term HCQ treatment in autoimmune rheumatic diseases outweigh the risks, and the risks are lower than previously thought. A new approach to this long-used drug should consider the underestimated anti-inflammatory and immunomodulatory effects, along with a very good safety profile. It should be noted that HCQ was synthesized as a drug with a better safety profile, better tolerance, and a lower rate of adverse effects than its predecessor, chloroquine. The use of HCQ at recommended doses in individuals without risk factors offers long-term clinical benefits, including a lower risk of adverse effects. Long-term observational studies and RCTs demonstrate that antimalarial drugs positively affect metabolism and atherogenic processes caused by chronic inflammation and its treatment.

HCQ plays the most important role not only in SLE but also in SS, RA, and APS. While a reduction of mortality rates in patients with SLE may seem a distant goal, HCQ significantly lowers the risk and severity of disease flares, thereby preventing multiorgan damage and decreasing the risk of related complications. The long-term use of HCQ at doses that ensure optimal serum drug levels provides the most desirable effect in terms of reduced cardiovascular mortality in SLE patients. Hence, HCQ is a primary drug at any stage of the disease regardless of its activity and also during pregnancy and breastfeeding. In conclusion, considering the numerous benefits of long-term HCQ use, any decision that might result in treatment discontinuation should be made with caution, especially in patients with SLE.

ARTICLE INFORMATION

ACKNOWLEDGMENTS Professional editing of the text and language assistance were provided Proper Medical Writing, Warsaw, Poland, and sponsored by Medac GmbH.

FUNDING None.

CONFLICT OF INTEREST None declared.

HOW TO CITE Pawlak-Buś K, Leszczyński P. Hydroxychloroquine as an important immunomodulator: a novel insight into an old drug. Pol Arch Intern Med. 2024; 134: 16656. doi:10.20452/pamw.16656

REFERENCES

1 Schmidt W, Pawlak-Buś K, Leszczyński P. A history of diagnostics and management of systemic lupus erythematosus [in Polish]. Forum Reumatol. 2021; 7: 71-77.

2 Achan J, Talisuna AO, Erhart A, et al. Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. Malar J. 2011; 10: 144.

3 Haładyj E, Sikora M, Felis-Giemza A, et al. Antimalarials - are they effective and safe in rheumatic diseases? Reumatologia. 2018; 56: 164-173.

4 Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020; 16: 155-166.

5 Alarcón GS, McGwin G, Bertoli AM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). Ann Rheum Dis. 2007; 66: 1168-1172.

6 Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. Curr Rheumatol Rep. 2011; 13: 77-80.

7 Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al. EULAR Recommendations for the management of Sjögren's syndrome with topical and systemic therapies. Ann Rheum Dis. 2020; 79: 3-18.

8 Pons-Estel GJ, Alarcón GS, McGwin G, Jr., et al. Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. Arthritis Rheum. 2009; 61: 830-839.

9 Petri M, Konig MF, Li J, et al. Association of higher hydroxychloroquine blood levels with reduced thrombosis risk in systemic lupus erythematosus. Arthritis Rheumatol. 2021; 73: 997-1004.

10 Durcan L, Winegar DA, Connelly MA, et al. Longitudinal evaluation of lipoprotein variables in systemic lupus erythematosus reveals adverse changes with disease activity and prednisone and more favorable profiles with hydroxychloroquine therapy. J Rheumatol. 2016; 43: 745-750.

11 Rekedal LR, Massarotti E, Garg R, et al. Changes in glycosylated hemoglobin after initiation of hydroxychloroquine or methotrexate treatment in diabetes patients with rheumatic diseases. Arthritis Rheum. 2010; 62: 3569-3573.

12 Nosál R, Jancinová V, Petríková M. Chloroquine inhibits stimulated platelets at the arachidonic acid pathway. Thromb Res. 1995; 77: 531-542.

13 Liu D, Li X, Zhang Y, et al. Chloroquine and hydroxychloroquine are associated with reduced cardiovascular risk: a systematic review and meta-analysis. Drug Des Devel Ther. 2018; 12: 1685-1695.

14 Fasano S, Pierro L, Pantano I, et al. Longterm hydroxychloroquine therapy and low-dose aspirin may have an additive effectiveness in the primary prevention of cardiovascular events in patients with systemic lupus erythematosus. J Rheumatol. 2017; 44: 1032-1038.

15 Pimentel-Quiroz VR, Ugarte-Gil MF, Harvey GB, et al. Factors predictive of serious infections over time in systemic lupus erythematosus patients: data from a multi-ethnic, multi-national, Latin American lupus cohort. Lupus. 2019; 28: 1101-1110.

16 Babaoğlu H, Li J, Goldman D, et al. Time to lupus low disease activity state in the Hopkins lupus cohort: role of African American ethnicity. Arthritis Care Res (Hoboken). 2020; 72: 225-232.

17 Urowitz MB, Gladman DD, Tom BD, et al. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol. 2008; 35: 2152-2158.

18 Fanouriakis A, Tziolos N, Bertsias G, et al. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis. 2021; 80: 14-25.

19 Kaplan YC, Ozsarfati J, Nickel C, et al. Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: a systematic review and meta-analysis. Br J Clin Pharmacol. 2016; 81: 835-848.

20 Gottenberg JE, Ravaud P, Puéchal X, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. JAMA. 2014; 312: 249-258.

21 Furst DE. Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. Lupus. 1996; 5: S11-S15.

22 Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. Semin Arthritis Rheum. 1993; 23: 82-91.

23 Sardana K, Sinha S, Sachdeva S. Hydroxychloroquine in dermatology and beyond: recent update. Indian Dermatol Online J. 2020; 11: 453-464.

24 Bethel M, Yang FM, Li S, et al. Hydroxychloroquine in patients with systemic lupus erythematosus with end-stage renal disease. J Investig Med. 2016; 64: 908-910.

25 McLachlan AJ, Tett SE, Cutler DJ, et al. Bioavailability of hydroxychloroquine tablets in patients with rheumatoid arthritis. Br J Rheumatol. 1994; 33: 235-239.

26 Costedoat-Chalumeau N, Amoura Z, Huong DL, et al. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases. Review of the literature. Autoimmun Rev. 2005; 4: 111-115.

27 Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Rheumatol. 2020; 72: 529-556.

28 Ballabio A, Bonifacino JS. Lysosomes as dynamic regulators of cell and organismal homeostasis. Nat Rev Mol Cell Biol. 2020; 21: 101-118.

29 Perkett EA, Ornatowski W, Poschet JF, et al. Chloroquine normalizes aberrant transforming growth factor beta activity in cystic fibrosis bronchial epithelial cells. Pediatr Pulmonol. 2006; 41: 771-778.

30 Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. Nature. 2011; 469: 323-335.

31 Lafyatis R, York M, Marshak-Rothstein A. Antimalarial agents: closing the gate on Toll-like receptors? Arthritis Rheum. 2006; 54: 3068-3070.

32 Kyburz D, Brentano F, Gay S. Mode of action of hydroxychloroquine in RA-evidence of an inhibitory effect on toll-like receptor signaling. Nat Clin Pract Rheumatol. 2006; 2: 458-459.

33 Sperber K, Quraishi H, Kalb TH, et al. Selective regulation of cytokine secretion by hydroxychloroquine: inhibition of interleukin 1 alpha (IL-1-alpha) and IL-6 in human monocytes and T cells. J Rheumatol. 1993; 20: 803-808.

34 Willis R, Seif AM, McGwin G, Jr., et al. Effect of hydroxychloroquine treatment on pro-inflammatory cytokines and disease activity in SLE patients: data from LUMINA (LXXV), a multiethnic US cohort. Lupus. 2012; 21: 830-835.

35 Müller-Calleja N, Manukyan D, Canisius A, et al. Hydroxychloroquine inhibits proinflammatory signalling pathways by targeting endosomal NADPH oxidase. Ann Rheum Dis. 2017; 76: 891-897.

36 Goldman FD, Gilman AL, Hollenback C, et al. Hydroxychloroquine inhibits calcium signals in T cells: a new mechanism to explain its immunomodulatory properties. Blood. 2000; 95: 3460-3466.

37 Ohkuma S, Poole B. Fluorescence probe measurement of the intralysosomal pH in living cells and the perturbation of pH by various agents. Proc Natl Acad Sci U S A. 1978; 75: 3327-3331.

38 Ruiz-Irastorza G, Olivares N, Ruiz-Arruza I, et al. Predictors of major infections in systemic lupus erythematosus. Arthritis Res Ther. 2009; 11: R109.

39 Herrinton LJ, Liu L, Goldfien R, et al. Risk of serious infection for patients with systemic lupus erythematosus starting glucocorticoids with or without antimalarials. J Rheumatol. 2016; 43: 1503-1509.

40 Symmons DP, Gabriel SE. Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nat Rev Rheumatol. 2011; 7: 399-408.

41 Powrie JK, Smith GD, Shojaee-Moradie F, et al. Mode of action of chloroquine in patients with non-insulin-dependent diabetes mellitus. Am J Physiol. 1991; 260: E897-E904.

42 Bili A, Sartorius JA, Kirchner HL, et al. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. J Clin Rheumatol. 2011; 17: 115-120.

43 Solomon DH, Massarotti E, Garg R, et al. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. JAMA. 2011; 305: 2525-2531.

44 Chen YM, Lin CH, Lan TH, et al. Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study. Rheumatology (Oxford). 2015; 54: 1244-1249.

45 Meng J, Lu Y, Dong X, et al. Long-term effects of hydroxychloroquine on metabolism of serum lipids and left ventricular structure and function in patients of systemic lupus erythematosus. Zhonghua Yi Xue Za Zhi. 2014; 94: 965-968.

46 Kavanaugh A, Adams-Huet B, Jain R, et al. Hydroxychloroquine Effects on Lipoprotein Profiles (the HELP trial): a double-blind, randomized, placebo-controlled, pilot study in patients with systemic lupus erythematosus. J Clin Rheumatol. 1997; 3: 3-8.

47 Nikpour M, Gladman DD, Ibanez D, et al. Variability over time and correlates of cholesterol and blood pressure in systemic lupus erythematosus: a longitudinal cohort study. Arthritis Res Ther. 2010; 12: R125.

48 Cairoli E, Rebella M, Danese N, et al. Hydroxychloroquine reduces low-density lipoprotein cholesterol levels in systemic lupus erythematosus: a longitudinal evaluation of the lipid-lowering effect. Lupus. 2012; 21: 1178-1182.

49 Rahman P, Gladman DD, Urowitz MB, et al. The cholesterol lowering effect of antimalarial drugs is enhanced in patients with lupus taking corticosteroid drugs. J Rheumatol. 1999; 26: 325-330.

50 Morris SJ, Wasko MC, Antohe JL, et al. Hydroxychloroquine use associated with improvement in lipid profiles in rheumatoid arthritis patients. Arthritis Care Res (Hoboken). 2011; 63: 530-534.

51 Borba EF, Bonfá E. Longterm beneficial effect of chloroquine diphosphate on lipoprotein profile in lupus patients with and without steroid therapy. J Rheumatol. 2001; 28: 780-785.

52 Virdis A, Tani C, Duranti E, et al. Early treatment with hydroxychloroquine prevents the development of endothelial dysfunction in a murine model of systemic lupus erythematosus. Arthritis Res Ther. 2015; 17: 277.

53 Law G, Magder L, Fang H, et al. SAT0222 hydroxychloroquine reduces thrombosis (both arterial and venous) in systemic lupus erythematosus, particularly in antiphospholipid positive patients. Ann Rheum Dis. 2013; 71: 547-547.

54 Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. Ann Rheum Dis. 2009; 68: 238-241.

55 Sisó A, Ramos-Casals M, Bové A, et al. Previous antimalarial therapy in patients diagnosed with lupus nephritis: influence on outcomes and survival. Lupus. 2008; 17: 281-288.

56 Tektonidou MG, Laskari K, Panagiotakos DB, et al. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. Arthritis Rheum. 2009; 61: 29-36.

57 Levy JMM, Towers CG, Thorburn A. Targeting autophagy in cancer. Nat Rev Cancer. 2017; 17: 528-542.

58 Murakami N, Oyama F, Gu Y, et al. Accumulation of tau in autophagic vacuoles in chloroquine myopathy. J Neuropathol Exp Neurol. 1998; 57: 664-673.

59 Ruiz-Irastorza G, Ugarte A, Egurbide MV, et al. Antimalarials may influence the risk of malignancy in systemic lupus erythematosus. Ann Rheum Dis. 2007; 66: 815-817.

60 Rosenfeld MR, Ye X, Supko JG, et al. A phase I/II trial of hydroxychloroquine in conjunction with radiation therapy and concurrent and adjuvant temozolomide in patients with newly diagnosed glioblastoma multiforme. Autophagy. 2014; 10: 1359-1368.

61 Wolpin BM, Rubinson DA, Wang X, et al. Phase II and pharmacodynamic study of autophagy inhibition using hydroxychloroquine in patients with metastatic pancreatic adenocarcinoma. Oncologist. 2014; 19: 637-638.

62 Costedoat-Chalumeau N, Houssiau F, Izmirly P, et al. A prospective international study on adherence to treatment in 305 patients with flaring SLE: assessment by drug levels and self-administered questionnaires. Clin Pharmacol Ther. 2019; 106: 374-382.

63 Costedoat-Chalumeau N, Amoura Z, Hulot JS, et al. Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus. Arthritis Rheum. 2006; 54: 3284-3290.

64 Costedoat-Chalumeau N, Galicier L, Aumaître O, et al. Hydroxychloroquine in systemic lupus erythematosus: results of a French multicentre controlled trial (PLUS Study). Ann Rheum Dis. 2013; 72: 1786-1792.

65 Alarcón GS, Ugarte-Gil MF, Pons-Estel G, et al. Remission and low disease activity state (LDAS) are protective of intermediate and long-term outcomes in SLE patients. Results from LUMINA (LXXVIII), a multiethnic, multicenter US cohort. Lupus. 2019; 28: 423-426.

66 Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR Recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023; 82: 3-18.

67 Tsakonas E, Joseph L, Esdaile JM, et al. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. Lupus. 1998; 7: 80-85.

68 Group CHS. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. N Engl J Med. 1991; 324: 150-154.

69 Pawlak-Buś K, Schmidt W, Leszczyński P. Remission and low disease activity in Polish patients with systemic lupus erythematosus - real-life, five-year follow-up outcomes. Eur Rev Med Pharmacol Sci. 2023; 27: 949-959.

70 Pawlak-Buś K, Schmidt W, Leszczyński P. Neuropsychiatric manifestations and their attribution to systemic lupus erythematosus: a retrospective single-center study in a Polish population. Pol Arch Intern Med. 2022; 132: 16319.

71 Pawlak-Buś K, Schmidt W, Dudziec E, et al. Current treatment of systemic lupus erythematosus: a clinician's perspective. Rheumatol Int. 2023; 43: 1395-1407.

72 Pakchotanon R, Gladman DD, Su J, et al. More consistent antimalarial intake in first 5 years of disease is associated with better prognosis in patients with systemic lupus erythematosus. J Rheumatol. 2018; 45: 90-94.

73 Mok CC, Tse SM, Chan KL, et al. Effect of immunosuppressive therapies on survival of systemic lupus erythematosus: a propensity score analysis of a longitudinal cohort. Lupus. 2018; 27: 722-727.

74 Giannakou I, Chatzidionysiou K, Magder LS, et al. Predictors of persistent disease activity and long quiescence in systemic lupus erythematosus: results from the Hopkins Lupus Cohort. Lupus Sci Med. 2018; 5: e000287.

75 Zen M, Saccon F, Gatto M, et al. Prevalence and predictors of flare after immunosuppressant discontinuation in patients with systemic lupus erythematosus in remission. Rheumatology (Oxford). 2020; 59: 1591-1598.

76 Kasitanon N, Fine DM, Haas M, et al. Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. Lupus. 2006; 15: 366-370.

77 Akhavan PS, Su J, Lou W, et al. The early protective effect of hydroxychloroquine on the risk of cumulative damage in patients with systemic lupus erythematosus. J Rheumatol. 2013; 40: 831-841.

78 Molad Y, Gorshtein A, Wysenbeek AJ, et al. Protective effect of hydroxychloroquine in systemic lupus erythematosus. Prospective long-term study of an Israeli cohort. Lupus. 2002; 11: 356-361.

79 Dima A, Jurcut C, Arnaud L. Hydroxychloroquine in systemic and autoimmune diseases: where are we now? Joint Bone Spine. 2021; 88: 105143.

80 Penn SK, Kao AH, Schott LL, et al. Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol. 2010; 37: 1136-1142.

81 Jung H, Bobba R, Su J, et al. The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus. Arthritis Rheum. 2010; 62: 863-868.

82 Durcan L, Clarke WA, Magder LS, et al. Hydroxychloroquine blood levels in systemic lupus erythematosus: clarifying dosing controversies and improving adherence. J Rheumatol. 2015; 42: 2092-2097.

83 Rosa GPD, Ortega MF, Teixeira A, et al. Causes and factors related to hospitalizations in patients with systemic lupus erythematosus: analysis of a 20-year period (1995-2015) from a single referral centre in Catalonia. Lupus. 2019; 28: 1158-1166.

84 Rempenault C, Combe B, Barnetche T, et al. Clinical and structural efficacy of hydroxychloroquine in rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken). 2020; 72: 36-40.

85 de Moreuil C, Alavi Z, Pasquier E. Hydroxychloroquine may be beneficial in preeclampsia and recurrent miscarriage. Br J Clin Pharmacol. 2020; 86: 39-49.

86 Levy RA, Vilela VS, Cataldo MJ, et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus. 2001; 10: 401-404.

87 Cortés-Hernández J, Ordi-Ros J, Paredes F, et al. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. Rheumatology (Oxford). 2002; 41: 643-650.

88 Koh JH, Ko HS, Kwok SK, et al. Hydroxychloroquine and pregnancy on lupus flares in Korean patients with systemic lupus erythematosus. Lupus. 2015; 24: 210-217.

89 Balevic SJ, Cohen-Wolkowiez M, Eudy AM, et al. Hydroxychloroquine levels throughout pregnancies complicated by rheumatic disease: implications for maternal and neonatal outcomes. J Rheumatol. 2019; 46: 57-63.

90 Saavedra M, Miranda-Hernández D, Lara-Mejía A, et al. Use of antimalarial drugs is associated with a lower risk of preeclampsia in lupus pregnancy: a prospective cohort study. Int J Rheum Dis. 2020; 23: 633-640.

91 Izmirly P, Kim M, Friedman DM, et al. Hydroxychloroquine to prevent recurrent congenital heart block in fetuses of anti-SSA/Ro-positive mothers. J Am Coll Cardiol. 2020; 76: 292-302.

92 Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, et al. Comparative study of obstetric antiphospholipid syndrome (OAPS) and non-criteria obstetric APS (NC-OAPS): report of 1640 cases from the EUROAPS registry. Rheumatology (Oxford). 2020; 59: 1306-1314.

93 De Carolis S, Rizzo F, Tabacco S. Hydroxychloroquine as additional treatment in pregnant patients with refractory APS. Am J Obstet Gynecol. 2017; 217: 711-712.

94 Sciascia S, Hunt BJ, Talavera-Garcia E, et al. The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies. Am J Obstet Gynecol. 2016; 214: 273.e1-273.e8.

95 Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol. 2014; 132: 1453-1460.

96 Petri M, Elkhalifa M, Li J, et al. Hydroxychloroquine blood levels predict hydroxychloroquine retinopathy. Arthritis Rheumatol. 2020; 72: 448-453.

97 Marmor MF, Kellner U, Lai TY, et al. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology. 2011; 118: 415-422.

98 Hu Z, Gao R, Huang W, et al. Effect of hydroxychloroquine on lupus activity, preeclampsia and intrauterine growth restriction in pregnant women with systemic lupus erythematosus and/or antiphospholipid syndrome: a systematic review and meta-analysis. J Clin Med. 2023; 12: 485.