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# Hydroxychloroquine: An old drug with new relevance

## ABSTRACT

Hydroxychloroquine is an immunomodulatory drug that has been used for 60 years to treat malaria and autoimmune diseases such as systemic lupus erythematosus and inflammatory arthritis, and potential new uses and benefits continue to emerge. Toxicity concerns have been addressed with updated prescribing recommendations.

## KEY POINTS

Hydroxychloroquine acts by suppressing Toll-like receptors to trigger important immunomodulatory effects.

Hydroxychloroquine is a well-established and effective therapy for systemic and cutaneous lupus and other autoimmune diseases.

Patients with systemic lupus erythematosus treated with hydroxychloroquine have lower mortality rates and a lower risk of lupus nephritis.

Retinal toxicity is the most serious potential complication of hydroxychloroquine therapy. Adherence to current ophthalmologic screening recommendations and proper dosing protocols lowers this risk.

A 29-YEAR-OLD AFRICAN AMERICAN woman presents with a photosensitive malar rash, fatigue, morning stiffness, and swelling in her hands. She is found to have elevated anti-nuclear antibody at a titer of 1:320. A complete blood cell count demonstrates leukopenia and thrombocytopenia. Results of renal function testing and urinalysis are within normal limits. She has no other medical problems and no history of blood clots or pregnancy loss.

Her arthritis and rash suggest systemic lupus erythematosus. She is counseled to avoid sun exposure, and treatment with hydroxychloroquine is considered.

## ■ WHAT IS HYDROXYCHLOROQUINE?

Hydroxychloroquine was developed to treat malaria but was later found to have immunomodulatory properties. It is now approved by the US Food and Drug Administration for treatment of discoid lupus, systemic lupus erythematosus, and rheumatoid arthritis. It is also approved to treat malaria; however, of the several malarial parasites, only *Plasmodium falciparum* can still be cured by hydroxychloroquine, and growing resistance limits the geographic locations where this drug can be used effectively.<sup>1,2</sup>

## ■ HISTORICAL BACKGROUND

Antimalarial drugs were discovered shortly before World War II. Their production was industrialized during the war because malaria was a leading cause of disease among soldiers, especially those deployed to the South Pacific.<sup>3</sup>

Atabrine (quinacrine), the first antimalarial widely used, had numerous side effects including yellowing of the skin. Aggressive research efforts to develop an alternative led to

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field testing of one of its derivative compounds, chloroquine, by the US Army in 1943. Continued chemical modification would create hydroxychloroquine, introduced in 1955.

A serendipitous consequence of the mass use of antimalarials during World War II was the discovery that they could be used to treat inflammatory arthritis and lupus. Eight years after the war ended, Shee<sup>4</sup> reported that chloroquine had a beneficial effect on lupus and rheumatoid arthritis in US soldiers. Hydroxychloroquine is now the most commonly prescribed antimalarial for treatment of autoimmune disease.

### ■ HOW HYDROXYCHLOROQUINE WORKS

The primary mechanism by which hydroxychloroquine modulates systemic lupus erythematosus is by suppressing activation of Toll-like receptors, which exist on the surface of endosomes and play a significant role in the innate immune response and in autoimmune disease. Their activation is necessary for the expression of interferon-regulated genes and production of tumor necrosis factor alpha, which are key in the cell-mediated inflammatory response.

Antimalarial drugs such as hydroxychloroquine prevent Toll-like receptor activation by binding directly to nucleic acids in the activation pathway.<sup>5</sup> In vitro studies show that blocking this pathway blunts the body's primary cell-mediated inflammatory response; in vivo studies show that use of hydroxychloroquine is strongly correlated with a reduction in interferon alpha levels.<sup>6</sup> The powerful effect of hydroxychloroquine on the cell-mediated pattern of inflammation found in lupus is consistent with this theory.

It was previously hypothesized that the immune-modulating effects of hydroxychloroquine were associated with a more general dysregulation of cellular lysosomes through inhibition of proteolysis or changes in cellular pH.<sup>7</sup> This theory has since been displaced by the more specific and elegant mechanism described above.<sup>5</sup>

### ■ HOW WELL DOES IT WORK?

#### **Benefit in systemic lupus erythematosus**

Hydroxychloroquine has consistently demonstrated significant and multifaceted benefit in patients with systemic lupus erythematosus.

A systematic review of 95 articles<sup>8</sup> concluded that this drug decreases lupus flares and decreases mortality rates in lupus patients by at least 50%, with a high level of evidence. Beneficial effects that had a moderate level of evidence were an increase in bone mineral density, fewer thrombotic events, and fewer cases of irreversible organ damage.

The preventive effect of hydroxychloroquine on thrombosis in lupus patients has been consistently demonstrated and is one of the key reasons the drug is considered a cornerstone of therapy in this disease.<sup>9</sup> A nested case-control study of patients with lupus and thromboembolism demonstrated an odds ratio of 0.31 and relative risk reduction of 68% for those using antimalarials.<sup>10</sup>

#### **Benefit in antiphospholipid antibody syndrome**

Hydroxychloroquine prevents thrombosis in other diseases as well. For example, it has been shown to reduce the incidence of thrombotic events in patients with primary antiphospholipid syndrome.

In a retrospective cohort study in 114 patients with this disease, hydroxychloroquine significantly reduced the incidence of arterial thrombotic events over 10 years of follow-up (recurrence incidence 0 in those treated with hydroxychloroquine vs 1.14% in those not treated).<sup>11</sup> The study also tracked levels of antiphospholipid antibodies and reported that hydroxychloroquine significantly reduced the levels of antibodies to cardiolipin and beta-2 glycoprotein 1, both implicated in the pathology of thrombosis.<sup>11</sup>

In vitro studies have also demonstrated that hydroxychloroquine can modulate a dysregulated inflammatory system to reduce thrombosis. For example, it has been shown that hydroxychloroquine can reverse platelet activation by antiphospholipid antibodies, prevent linking of antibody complexes to cell membranes, and promote proper membrane protein expression, thereby reducing the thrombotic qualities of antiphospholipid antibodies and even improving clearance times of antiphospholipid-related thrombi.<sup>12</sup>

#### **Benefit in rheumatoid arthritis**

Though there is less evidence, hydroxychloroquine has also shown benefit in rheumatoid

**Toll-like receptors play a role in innate immunity and autoimmune diseases**

arthritis, where it can be used by itself in mild disease or as part of combination therapy with active arthritis. Compared with biologic therapy in patients with early aggressive rheumatoid arthritis, triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine was nearly as effective in terms of quality of life, and it cost only one-third as much, saving \$20,000 per year of therapy per patient.<sup>13</sup>

Hydroxychloroquine has also been compared directly with chloroquine, its closest relation, in a large study incorporating patients with rheumatoid arthritis and patients with systemic lupus erythematosus. Patients using chloroquine experienced significantly more side effects, though it did prove marginally more effective.<sup>14</sup>

### No benefit shown in Sjögren syndrome

Unfortunately, despite widespread use, hydroxychloroquine has not demonstrated positive clinical effects when used to treat primary Sjögren syndrome. Most notably, a 2014 randomized controlled trial of hydroxychloroquine vs placebo in 120 Sjögren patients found no significant improvement in primary symptoms of dryness, pain, or fatigue after 6 months of therapy.<sup>15</sup>

### Metabolic benefits

Unexpectedly, hydroxychloroquine is associated with multiple metabolic benefits including improved lipid profiles and lower blood glucose levels. These findings, in addition to a reduced incidence of thrombosis, were initially reported in the Baltimore Lupus Cohort in 1996.<sup>16</sup> Specifically, longitudinal evaluation of a cohort of lupus patients showed that hydroxychloroquine use was associated with a 7.6% reduction in total cholesterol and a 13.7% reduction in low-density lipoprotein cholesterol (LDL-C) over 3 months of therapy.<sup>17</sup>

Similar findings, including a reduction in LDL-C and an increase in high-density lipoprotein cholesterol, were strongly associated with the addition of hydroxychloroquine to methotrexate or to methotrexate and etanercept in a large cohort of rheumatoid arthritis patients followed over 2 years of therapy.<sup>18</sup>

In nondiabetic women with systemic lupus erythematosus or rheumatoid arthritis, average blood glucose was significantly lower in those taking hydroxychloroquine than in

nonusers. The incidence of insulin resistance was also lower, but the difference was not statistically significant.<sup>19</sup>

Some have suggested that hydroxychloroquine may prevent diabetes mellitus. In a retrospective case series, compared with rheumatoid arthritis patients not taking the drug, patients treated with hydroxychloroquine for more than 4 years had a 25% lower risk of developing diabetes mellitus.<sup>20</sup>

In view of these metabolic benefits, especially regarding lipid regulation, and the above described antithrombotic properties of hydroxychloroquine, some researchers have recently hypothesized that hydroxychloroquine may be of benefit in patients with coronary artery disease.<sup>21</sup> They suggested that the inflammatory contribution to the mechanism of coronary artery disease could be lessened by hydroxychloroquine even in patients without lupus erythematosus or rheumatoid arthritis.

## ■ PHARMACOLOGIC PROPERTIES

Understanding the pharmacologic properties of hydroxychloroquine is key to using it appropriately in clinical practice.

The half-life of elimination of hydroxychloroquine is 40 to 50 days, with half of the drug excreted renally in a concentration-dependent fashion.<sup>22,23</sup> The drug reaches 95% of its steady-state concentration by about 6 months of therapy. Shorter durations of therapy do not provide adequate time for the drug to achieve steady-state concentration and may not allow patients and providers time to see its full clinical results. Therefore, its manufacturers recommend a 6-month trial of therapy to adequately determine if the drug improves symptoms.<sup>1</sup>

The oral bioavailability of hydroxychloroquine is about 75%, but pharmacokinetics vary among individuals.<sup>22,23</sup> It has been suggested that this variability affects the efficacy of hydroxychloroquine. In a study of 300 patients with cutaneous lupus erythematosus, those whose treatment failed had significantly lower blood concentrations of hydroxychloroquine, while those who achieved complete remission had significantly higher concentrations.<sup>24</sup>

**Unexpectedly, this drug has positive effects on lipids and blood glucose**

**TABLE 1**

**Recommended screening for retinopathy in patients on hydroxychloroquine**

	<b>Low-risk patients</b>	<b>Patients with risk factors<sup>a</sup></b>
<b>Initial screening</b>	Within first year of therapy	Within first year of therapy
<b>Repeat screening</b>	After 5 years of therapy, then annually	Annually

<sup>a</sup>Higher medical dose, decreased renal function, tamoxifen use, or macular disease.

Based on information in references 27 and 28.

Another study found that titrating doses to target therapeutic blood concentrations can reduce disease activity in cutaneous lupus erythematosus.<sup>25</sup> Measuring the blood concentration of hydroxychloroquine is not common in clinical practice but may have a role in select patients in whom initial therapy using a standard dosing regimen does not produce the desired results.

**■ HOW SAFE IS HYDROXYCHLOROQUINE?**

Hydroxychloroquine has numerous adverse effects, necessitating vigilance on the part of the prescriber. Most commonly reported are retinopathy, hyperpigmentation, myopathy, and skin reactions.<sup>1</sup>

**Retinopathy**

Retinopathy's irreversibility—the threat of permanent vision loss—and its substantial prevalence in patients with a large drug exposure history, have marked retinopathy as the most concerning potential toxicity. The risk of ocular toxicity increases with the cumulative hydroxychloroquine dose. The prevalence of retinopathy in those using the drug less than 10 years is less than 2%; in contrast, the prevalence in patients with more than 20 years of exposure is reported to be as high as 20%.<sup>26</sup>

The American Academy of Ophthalmology has long stated that retinopathy is a significant risk of hydroxychloroquine therapy and that patients taking hydroxychloroquine should therefore undergo routine retinal and visual field screening by an ophthalmologist.

Currently, initial screening followed by yearly screening beginning 5 years thereafter is recommended for patients at low risk

of toxicity (**Table 1**).<sup>27</sup> Patients determined by an ophthalmologist to be at higher risk of retinopathy should be screened yearly. As identified by the American Academy of Ophthalmology, major risk factors for retinopathy include duration of use, concomitant tamoxifen exposure, significant renal disease, and preexisting retinal and macular disease.<sup>26,28</sup>

Recommendations for hydroxychloroquine dosing and screening were recently revised, for 2 reasons. Initially, its manufacturers recommended that hydroxychloroquine dosage be no higher than 6.5 mg/kg of ideal body weight to prevent retinopathy.<sup>1,29,30</sup> However, it has recently been demonstrated that real body weight is a better predictor of risk of retinopathy than ideal body weight when dosing hydroxychloroquine, perhaps because of the increasing variance of real body weight in our patient population.<sup>26</sup>

Further, an atypical pattern of retinopathy called pericentral retinopathy is more common in Asians. A study of about 200 patients with a history of hydroxychloroquine retinopathy, including 36 Asian patients, found that the pericentral pattern occurred in half the Asian patients but only 2% of the white patients.<sup>31</sup> The mechanism for this finding is unclear, but because pericentral retinopathy spares the macula, it can be missed using standard screening methods. Therefore, the American Academy of Ophthalmology now recommends that the dose limit be reduced from 6.5 mg/kg of ideal body weight to no more than 5.0 mg/kg of real body weight (**Table 2**).<sup>28</sup>

It is also recommended that screening methods such as automated visual fields and optical coherence tomography extend their

**Hydroxychloroquine has a long elimination half-life of 40–50 days**



TABLE 2

**Antimalarial dosing**

<b>Hydroxychloroquine</b>	≤ 5.0 mg/kg/day real body weight, but no more than 400 mg total daily dose
<b>Chloroquine</b>	≤ 2.3 mg/kg/day real body weight

Based on information in reference 28.

fields beyond the macula in Asian patients to ensure that pericentral retinopathy is not missed.<sup>28</sup>

Optical coherence tomography is a particularly useful tool in the ocular evaluation of patients taking hydroxychloroquine. It can detect subtle changes such as thinning of the foveal photoreceptor outer segment, thickening of the retinal pigment epithelium, and loss of the macular ganglion cell–inner plexiform layer before there are visible signs of retinopathy and before symptoms arise.<sup>32</sup>

Currently, these guidelines are underutilized in clinical practice. Physician adherence to ophthalmologic guidelines is reported at about 50%.<sup>33</sup> This statistic is jarring, given the potential for permanent loss of vision in those with hydroxychloroquine-mediated retinopathy, and demonstrates the importance of reinforcing proper understanding of the use of hydroxychloroquine in clinical practice.

**Other adverse effects**

**Cutaneous hyperpigmentation** can occur with hydroxychloroquine use (**Figure 1**). The hyperpigmentation appears to be due to local bruising following deposition of iron in the soft tissue.

A case-control study<sup>34</sup> in 24 patients with systemic lupus erythematosus and hydroxychloroquine-associated skin pigmentation found that 23 (96%) of those with pigmentation had conditions that predisposed to bruising; 22 (92%) also experienced local bruising before the appearance of pigmentation. An association between pigmentation and the use of oral anticoagulants and antiplatelet drugs was found. The mechanism by which hydroxychloroquine either encourages bruising or prevents proper healing and resorption of



**Figure 1.** Chronic facial skin hyperpigmentation in a patient with a lifetime hydroxychloroquine dose of 2,000 g. Hyperpigmentation and retinopathy may occur independently of each other, but a high cumulative medication dose is a risk factor for both conditions.

pigment is unclear.

While the pigmentation may persist permanently and cause an undesirable cosmetic effect, it has not been associated with other adverse outcomes.

**Myopathy** is a rare adverse effect. In one case series, 3 of 214 patients treated with hydroxychloroquine developed hydroxychloroquine-induced myopathy.<sup>35</sup> Over the duration of their therapy, this was equivalent to an incidence of 1 case of myopathy in 100 patient-years of therapy. Myopathy improves with discontinuation of therapy, though it can persist for weeks, likely because of hydroxychloroquine's prolonged elimination half-life.

**Cardiomyopathy**, specifically neurocardiomyopathy, is also an extremely rare adverse effect of hydroxychloroquine use. The mechanism is believed to be associated with the effect of hydroxychloroquine on lysosomal action, leading to an acquired lysosomal storage disorder with the typical cardiac hypertrophy and conduction abnormalities associated with this family of diseases.<sup>36</sup>

**TABLE 3**

**Considerations before hydroxychloroquine use**

- Measure glucose-6 phosphate dehydrogenase if indicated
- Take ocular history and order baseline ophthalmologic evaluation
- Screen for digoxin use
- Screen for history of cardiomyopathy or severe heart failure
- Counsel patient on risks of use, including permanent loss of vision and recommended frequency of screening retinal examination
- Counsel on risks of skin rashes, gastrointestinal upset, increased hair and skin pigmentation
- Obtain baseline laboratory testing

**Hydroxychloroquine has numerous adverse effects, necessitating vigilance by the prescriber**

**Acute generalized exanthematous pustulosis** is another rare complication of hydroxychloroquine therapy. The appearance of the reaction is similar to that of pustular psoriasis, with pustules overlying flaking and scaling skin. It usually resolves within 2 weeks after cessation of hydroxychloroquine therapy. In a select few cases, the reaction persists or waxes and wanes over a period of weeks to months, and longer durations of recovery are thought to be due to hydroxychloroquine’s long half-life, as in hydroxychloroquine-induced myopathy.<sup>37</sup>

In view of this rare reaction, manufacturers of hydroxychloroquine recommend caution when using the drug in patients with psoriasis.<sup>1</sup>

**Hematologic abnormalities.** In very rare cases, hydroxychloroquine is associated with hematologic abnormalities including agranulocytosis, anemia, aplastic anemia, leukopenia, and thrombocytopenia.<sup>1</sup>

While no specific guidelines exist, caution is warranted when using hydroxychloroquine in patients with porphyria. Additionally, hydroxychloroquine and other antimalarials including primaquine have been associated with hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The risk of hemolysis is generally considered low except at high hydroxychloroquine doses in patients with severe G6PD deficiency.<sup>38</sup>

For the above reasons, manufacturers recommended baseline and routine blood counts, and some providers screen patients for G6PD deficiency when prescribing hydroxychloroquine (Table 3).

**■ PREGNANCY**

Hydroxychloroquine is in pregnancy category C. Information is limited, and in view of the risks, the manufacturer says that it should be avoided in pregnancy.<sup>1</sup> Nevertheless, it is generally considered safe during pregnancy, and its benefits may make it acceptable to continue in a patient who becomes pregnant, in spite of the possible risks.

We favor continuing hydroxychloroquine. This drug has been associated with improved maternal and fetal outcomes in lupus patients. Its use during pregnancy has not been associated with congenital malformations. The adverse visual effects of long-term hydroxychloroquine use, namely retinopathy, have never been reported in children as a consequence of exposure in utero.

In addition, hydroxychloroquine is transmitted only in minute quantities in breast milk.<sup>39</sup> In pregnant women with systemic lupus erythematosus, hydroxychloroquine was associated with a lower risk of adverse outcomes, including preterm delivery and intrauterine growth restriction.<sup>40</sup> However, hydroxychloroquine is far more toxic when ingested directly by infants than in adults.<sup>1</sup>

Maternal outcomes are also improved with the use of hydroxychloroquine. Stopping hydroxychloroquine during pregnancy in women with systemic lupus erythematosus is associated with significantly higher disease activity—fully twice as high as in those who continue hydroxychloroquine.<sup>41</sup> These study results were corroborated in a small randomized trial in which pregnant women with lupus on placebo had significantly higher lupus disease activity scores than those pregnant women who were given hydroxychloroquine.<sup>42</sup> The women taking hydroxychloroquine experienced no severe lupus flares for the duration of their pregnancies.

These findings suggest not only that hydroxychloroquine is safe in pregnancy, but also that it should be continued in lupus patients during pregnancy to prevent disease flares and adverse fetal outcomes.

**■ AREAS OF UNCERTAINTY**

**Benefit in preclinical lupus?**

Hydroxychloroquine has a consistently profound effect on outcomes in systemic lupus

erythematosus. These findings, in addition to the more widespread use of antibody screening, have led to suggestions that hydroxychloroquine could be of benefit even before systemic lupus erythematosus is diagnosed.

A study in US military personnel found that patients taking hydroxychloroquine experienced a significantly longer lag time between first reported clinical symptoms of lupus and official diagnosis compared with matched controls who also went on to develop the disease, averaging 1.08 vs 0.29 years to disease classification.<sup>43</sup> Those who used hydroxychloroquine also had lower rates of autoantibody accumulation. Therefore, hydroxychloroquine could be of benefit in carefully selected candidates at high risk of developing systemic lupus erythematosus.

The beneficial effects of hydroxychloroquine on patients with lupus and rheumatoid arthritis, in terms of primary measures of disease activity and secondary outcomes, were discovered fortuitously and were not the original intended targets of the drug. Because of its versatility, there are numerous other disease states in which hydroxychloroquine has shown a degree of benefit or has shown a potential for benefit.

#### Antiviral activity?

It has been suggested that antimalarial drugs could serve as adjunctive therapies against filoviruses such as Marburg and Ebola. There is a small body of in vitro and in vivo evidence that hydroxychloroquine could temper severe systemic inflammatory responses to filoviruses both through dysregulation of lysosomes and lysosomal pH (filoviruses have a pH-dependent mechanism of action) and through decreased production of tumor necrosis factor alpha and interferons. Heavy burdens of interferons and tumor necrosis factor alpha are associated with increased mortality rates in those infected with filoviruses.<sup>44</sup>

#### Antineoplastic activity?

Hydroxychloroquine has undergone in vitro testing as an adjunct to cancer therapies. There are several mechanisms by which it is theorized that hydroxychloroquine could target malignant cells, including inhibition of multidrug resistance pumps or autophagy, im-

provement of chemotherapy cell penetration, potentiation of presentation of major histocompatibility complexes, or even intercalation directly into DNA.<sup>45,46</sup> However, it can also impair natural anticancer immunity and may allow cancer cells better nutrient supply through vascular effects.

In vitro studies have shown tumoricidal effects in lymphoma and melanoma, and inhibition of growth in lung, colon, breast, cervix, larynx, liver, and prostate cancers. In vivo studies have shown that hydroxychloroquine in high doses can prolong survival in glioblastoma.<sup>45</sup>

Unfortunately, all of these theorized or observed effects are dose-dependent and likely require doses that exceed currently recommended maximums.

#### Negative chronotropic effect?

Hydroxychloroquine has been found to decrease the resting heart rate in a cumulative dose-dependent fashion.<sup>47</sup> Further, hydroxychloroquine has been known to increase digoxin levels, and the medications should not be used in combination.<sup>1</sup>

Whether the decrease in resting heart rate is associated with harm or benefit and whether the effect is significant enough to be considered when implementing therapy remain unanswered and deserve further investigation, as does the primary use of hydroxychloroquine for beneficial lipid and glucose reduction in patients who are otherwise healthy.

#### ■ CASE CONCLUSION

The patient described at the beginning of this article was provided with information on the risks and benefits of hydroxychloroquine for treatment of her arthritis and rash suggestive of mild systemic lupus, and she opted to begin therapy. Her baseline eye screening was within normal limits. Based on her weight of 62 kg, she was started on 300 mg of hydroxychloroquine daily.

She had no significant adverse effects from the medication and reported slow improvement in her rash and joint complaints over the next 2 months. She remained on hydroxychloroquine over the next year without adverse effects or new evidence of autoimmune disease. ■

**Old maximum dose was  $\leq 6.5$  mg/kg ideal body weight; new maximum dose is  $\leq 5.0$  mg/kg real body weight**



## REFERENCES

1. **Sanofi-Aventis.** Product monograph: Plaquenil. <http://products.sanofi.ca/en/plaquenil.pdf>. Accessed May 2, 2018.
2. **Centers for Disease Control and Prevention (CDC).** Malaria information and prophylaxis, by country. [www.cdc.gov/malaria/travelers/country\\_table/a.html](http://www.cdc.gov/malaria/travelers/country_table/a.html). Accessed May 2, 2018.
3. **Wallace DJ.** The history of antimalarials. *Lupus* 1996; 5(suppl 1):S2–S3. PMID:8803902
4. **Shee JC.** Lupus erythematosus treated with chloroquine. *Lancet* 1953; 265(6778):201–202. PMID:13070595
5. **Kuznik A, Bencina M, Svajger U, Jeras M, Rozman B, Jerala R.** Mechanism of endosomal TLR inhibition by antimalarial drugs and imidazoquinolines. *J Immunol* 2011; 186:4794–4804. doi:10.4049/jimmunol.1000702
6. **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, a multiethnic US cohort. *Lupus* 2012; 21(8):830–835. doi:10.1177/0961203312437270
7. **Fox R.** Anti-malarial drugs: possible mechanisms of action in autoimmune disease and prospects for drug development. *Lupus* 1996; 5(suppl 1):S4–S10. PMID:8803903
8. **Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA.** Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2010; 69(1):20–28. doi:10.1136/ard.2008.101766
9. **Lam NC, Ghetu MV, Bieniek ML.** Systemic lupus erythematosus: primary care approach to diagnosis and management. *Am Fam Physician* 2016; 94(4):284–294. PMID:27548593
10. **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(3):863–868. doi:10.1002/art.27289
11. **Nuri E, Taraborelli M, Andreoli L, et al.** Long-term use of hydroxychloroquine reduces antiphospholipid antibodies levels in patients with primary antiphospholipid syndrome. *Immunol Res* 2017; 65(1):17–24. doi:10.1007/s12026-016-8812-z
12. **Erkan D, Aguiar CL, Andrade D, et al.** 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. *Autoimmun Rev* 2014; 13(6):685–696. doi:10.1016/j.autrev.2014.01.053
13. **Jalal H, O'Dell JR, Bridges SL Jr, et al.** Cost-effectiveness of triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2016; 68(12):1751–1757. doi:10.1002/acr.22895
14. **Avina-Zubieta JA, Galindo-Rodriguez G, Newman S, Suarez-Almazor ME, Russell AS.** Long-term effectiveness of antimalarial drugs in rheumatic diseases. *Ann Rheum Dis* 1998; 57(10):582–587. PMID:9893568
15. **Gottenberg JE, Ravaut P, Puechal X, et al.** Effects of hydroxychloroquine on symptomatic improvement in primary Sjogren syndrome. *JAMA* 2014; 312(3):249–258. doi:10.1001/jama.2014.7682
16. **Petri M.** Hydroxychloroquine use in the Baltimore Lupus Cohort: effects on lipids, glucose and thrombosis. *Lupus* 1996; 5(suppl 1):S16–S22. PMID:8803905
17. **Cairolì E, Rebella M, Danese N, Garra V, Borba EF.** Hydroxychloroquine reduces low-density lipoprotein cholesterol levels in systemic lupus erythematosus: a longitudinal evaluation of the lipid-lowering effect. *Lupus* 2012; 21(11):1178–1182. doi:10.1177/0961203312450084
18. **Charles-Schoeman C, Wang X, Lee YY, et al.** Association of triple therapy with improvement in cholesterol profiles over two-year followup in the treatment of early aggressive rheumatoid arthritis trial. *Arthritis Rheumatol* 2016; 68(3):577–586. doi:10.1002/art.39502
19. **Penn SK, Kao AH, Schott LL, et al.** Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. *J Rheumatol* 2010; 37(6):1136–1142. doi:10.3899/jrheum.090994
20. **Wasko MC, Hubert HB, Lingala VB, et al.** Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. *JAMA* 2007; 298(2):187–193. doi:10.1001/jama.298.2.187
21. **Sun L, Liu M, Li R, et al.** Hydroxychloroquine, a promising choice for coronary artery disease? *Med Hypotheses* 2016; 93:5–7. doi:10.1016/j.mehy.2016.04.045
22. **Tett SE, Cutler DJ, Day RO, Brown KF.** Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol* 1989; 27(6):771–779. PMID:2757893
23. **Furst DE.** Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. *Lupus* 1996; 5(suppl 1):S11–S15. PMID:8803904
24. **Frances C, Cosnes A, Duhaut P, et al.** Low blood concentration of hydroxychloroquine in patients with refractory cutaneous lupus erythematosus. *Arch Dermatol* 2012; 148(4):479–484. doi:10.1001/archdermatol.2011.2558
25. **Chasset F, Arnaud L, Costedoat-Chalumeau N, Zahr N, Bessis D, Francès C.** The effect of increasing the dose of hydroxychloroquine in patients with refractory cutaneous lupus erythematosus: an open-label prospective pilot study. *J Am Acad Dermatol* 2016; 74(4):693–699.e3. doi:10.1016/j.jaad.2015.09.064
26. **Melles RB, Marmor MF.** The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol* 2014; 132(12):1453–1460. doi:10.1001/jamaophthol.2014.3459
27. **Committee on Rheumatologic Care.** American College of Rheumatology position statement. Screening for hydroxychloroquine retinopathy. [www.rheumatology.org/Portals/0/Files/Screening-for-Hydroxychloroquine-Retinopathy-Position-Statement.pdf](http://www.rheumatology.org/Portals/0/Files/Screening-for-Hydroxychloroquine-Retinopathy-Position-Statement.pdf). Accessed April 2, 2018.
28. **Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF; American Academy of Ophthalmology.** Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology* 2016; 123(6):1386–1394. doi:10.1016/j.ophtha.2016.01.058
29. **Mackenzie AH.** Antimalarial drugs for rheumatoid arthritis. *Am J Med* 1983; 75(6A):48–58. PMID:6362406
30. **Mackenzie AH.** Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983; 75(1A):40–45. PMID:6869410
31. **Melles RB, Marmor MF.** Pericentral retinopathy and racial differences in hydroxychloroquine toxicity. *Ophthalmology* 2015; 122(1):110–116. doi:10.1016/j.ophtha.2014.07.018
32. **Uslu H, Gurler B, Yildirim A, et al.** Effect of hydroxychloroquine on the retinal layers: a quantitative evaluation with spectral-domain optical coherence tomography. *J Ophthalmol* 2016; 2016:8643174. doi:10.1155/2016/8643174
33. **Au A, Parikh V, Modi YS, Ehlers JP, Schachat AP, Singh RP.** Hydroxychloroquine screening practice patterns within a large multispecialty ophthalmic practice. *Am J Ophthalmol* 2015; 160(3):561–568.e2. doi:10.1016/j.ajo.2015.06.009
34. **Jallouli M, Frances C, Plette JC, et al; Plaquenil Lupus Systemic Study Group.** Hydroxychloroquine-induced pigmentation in patients with systemic lupus erythematosus. *JAMA Dermatol* 2013; 149(8):935–940. doi:10.1001/jamadermatol.2013.709
35. **Avina-Zubieta JA, Johnson ES, Suarez-Almazor ME, Russell AS.** Incidence of myopathy in patients treated with antimalarials: a report of three cases and review of the literature. *Br J Rheumatol* 1995; 34(2):166–170. PMID:7704464
36. **Yogasundaram H, Putko BN, Tien J, et al.** Hydroxychloroquine-induced cardiomyopathy: case report, pathophysiology, diagnosis, and treatment. *Can J Cardiol* 2014; 30:1706–1715. doi:10.1016/j.cjca.2014.08.016
37. **Pearson KC, Morrell DS, Runge SR, Jolly P.** Prolonged pustular eruption from hydroxychloroquine: an unusual case of acute generalized exanthematous pustulosis. *Cutis* 2016; 97(3):212–216. PMID:27023083
38. **Youngster I, Arcavi L, Schechmaster R, et al.** Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Saf* 2010; 33(9):713–726. doi:10.2165/11536520-000000000-00000
39. **Ostensen M, Khamashta M, Lockshin M, et al.** Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther* 2006; 8(3):209. doi:10.1186/ar1957



40. **Leroux M, Desveaux C, Parveaux M, et al.** Impact of hydroxychloroquine on preterm delivery and intrauterine growth restriction in pregnant women with systemic lupus erythematosus: a descriptive cohort study. *Lupus* 2015; 24(13):1384–1391. doi:10.1177/0961203315591027
41. **Clowse MEB, Magder L, Witter F, Petri M.** Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum* 2006; 54(11):3640–3647. doi:10.1002/art.22159
42. **Levy RA, Vilela VS, Cataldo MJ, et al.** Hydroxychloroquine in lupus pregnancy: double-blind and placebo-controlled study. *Lupus* 2001; 10(6):401–404. doi:10.1191/096120301678646137
43. **James JA, Kim-Howard XR, Bruner BF, et al.** Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus. *Lupus* 2007; 16(6):401–409. doi:10.1177/0961203307078579
44. **Akpovwa H.** Chloroquine could be used for the treatment of filoviral infections and other viral infections that emerge or emerged from viruses requiring an acidic pH for infectivity. *Cell Biochem Funct* 2016; 34(4):191–196. doi:10.1002/cbf.3182
45. **Pascolo S.** Time to use a dose of chloroquine as an adjuvant to anti-cancer chemotherapies. *Eur J Pharmacol* 2016; 771:139–144. doi:10.1016/j.ejphar.2015.12.017
46. **Furlong HC, Wessels JM, Guerra MT, Stämpfli MR, Foster WG.** Hydroxychloroquine attenuates cigarette smoke induced autophagic signaling in the mouse ovary. *Reprod Toxicol* 2016; 61:105–113. doi:10.1016/j.reprotox.2016.03.044
47. **Cairolì E, Danese N, Teliz M, et al.** Cumulative dose of hydroxychloroquine is associated with a decrease of resting heart rate in patients with systemic lupus erythematosus: a pilot study. *Lupus* 2015; 24(11):1204–1209. doi:10.1177/0961203315580870

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