


Hydroxychloroquine Alternatives for Chronic Disease: Response to a Growing Shortage Amid the Global COVID-19 Pandemic

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Abstract

With the emergence of a novel severe acute respiratory syndrome coronavirus, investigators worldwide are scrambling to identify appropriate treatment modalities, develop accurate testing, and produce a vaccine. To date, effective treatment remains elusive. Chloroquine phosphate and hydroxychloroquine sulfate (HCQ), well-known antimalarial drugs effective in the treatment of systemic lupus erythematosus, rheumatoid arthritis, porphyria cutanea tarda, and chronic Q fever, are currently under investigation. The United States Food and Drug Administration recently issued an Emergency Use Authorization for CQ and HCQ use in the treatment of coronavirus disease 2019 (COVID-19). With spikes in HCQ use and demand, ethical considerations encompassing appropriate use, patient autonomy, nonmaleficence, and distributive justice abound. As drug experts, pharmacists are uniquely positioned to advocate for patients with chronic conditions necessitating HCQ use, assist in the appropriate prescribing of HCQ for COVID-19, and ensure patients and health care professionals are continually educated during this public health crisis. This review highlights the worldwide pandemic, describes appropriate HCQ use for chronic conditions, highlights available alternatives, and deliberates evolving ethical questions. With assistance from colleagues, state boards of pharmacy, and national organizations, pharmacists ensure the just distribution of valuable pharmaceuticals to patients having COVID-19 while supporting the needs of patients requiring HCQ for chronic conditions.

Keywords

coronavirus disease 2019, distributive justice, hydroxychloroquine, nonmaleficence

Introduction

Hydroxychloroquine Emergency Approval for COVID-19

In December 2019, a novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) emerged in Wuhan, China. The virus quickly spread worldwide with the United States confirming the first case of coronavirus disease 2019 (COVID-19) on January 20, 2020.¹ To date, the US Food and Drug Administration (FDA) has not approved any drug for the treatment of COVID-19.

On March 28, 2020, the FDA issued an Emergency Use Authorization (EUA) for use of 2 antimalarial drugs for COVID-19 treatment: chloroquine phosphate (CQ) and hydroxychloroquine sulfate (HCQ).² An EUA ensures both drugs are added to the Strategic National Stockpile (SNS). The SNS houses life-saving supplies and medicines during a public health crisis in which immediate shortages threaten state and local inventories.³

Although limited research supports CQ and HCQ use in reducing SARS-CoV-2 replication in vitro, a recent retrospective study involving 368 patients in the United States concluded HCQ with and without azithromycin is ineffective in treatment of COVID-19 and does not reduce the risk of

mechanical ventilation.⁴ Additionally, HCQ alone was associated with an increase in overall mortality.⁴ Recent focus on HCQ used as post-exposure prophylaxis did not demonstrate a significant benefit in the prevention of SARS-CoV-2 infection.⁵ Until strong evidence is available and/or a viable alternative achieves FDA approval, HCQ remains a hotly debated therapeutic option for COVID-19. For now, the FDA recommends both HCQ and CQ be used for the treatment of hospitalized patients with COVID-19 enrolled in clinical trials.²

Distribution/Prescribing Practices

In 2017, over 1.1 million prescriptions for HCQ were filled in US outpatient settings for use in the long-term management of

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Table 1. First-Line Uses of Hydroxychloroquine.

Disease state	Hydroxychloroquine dosing: Adults ¹⁰
Malaria (<i>Plasmodium vivax</i> , <i>P. ovale</i> , <i>P. malariae</i> , <i>P. knowlesi</i>) in chloroquine susceptible countries	Treatment: 800 mg × 1 dose, followed by 400 mg at 6, 24, and 48 hours after initial dose [total dose = 2 g] Chemoprophylaxis: 400 mg once weekly beginning 1-2 weeks before travel and continuing for 4 weeks after leaving area
Systemic lupus erythematosus	200-400 mg/d in 1-2 divided doses
Rheumatoid arthritis	200-400 mg/d in 1-2 divided doses
Porphyria cutanea tarda	100 mg twice weekly
Chronic Q fever	600 mg/d in 1-3 divided doses in combination with doxycycline

chronic conditions.⁶ On March 31, 2020, 3 days after EUA issuance, both CQ and HCQ were confirmed to be in short supply.⁷ Although CQ shortages were resolved in May, drug manufactures continue to report limited HCQ supply subject to allocation.⁸

HCQ is FDA-approved for the treatment of chloroquine-sensitive malaria (*Plasmodium vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA).⁹ Off-label uses include the treatment of porphyria cutanea tarda (PCT) and chronic Q fever.¹⁰ HCQ dosing regimens vary widely (Table 1).

Ongoing drug shortages in the midst of a public health emergency raise significant concerns for those who use HCQ for first-line, FDA-approved or off-label uses. Limited supply negatively affects those who have relied on HCQ for years, and sudden drug withdrawal could trigger disease exacerbation in these patients.¹¹ Pharmacists are faced with significant ethical dilemmas in COVID-19 treatment, involving but not limited to, patient autonomy, distributive justice, and nonmaleficence. This review describes appropriate HCQ use for chronic conditions, highlights available alternatives, deliberates evolving ethical questions, and seeks to prepare pharmacists to ensure both the urgent needs of patients having COVID-19 and the long-term needs of patients requiring HCQ for chronic conditions are met.

First-Line Uses of HCQ

Malaria

HCQ is a well-known antimalarial drug. Although not well understood, the drug is thought to inhibit polymerization of heme by creating a weak base environment in acidic vesicles.⁹ *Plasmodium* species require heme as a cofactor during mosquito growth.⁹ Although CQ and HCQ are used widely in geographic areas containing chloroquine-sensitive *Plasmodium* species, additional antimalarials are available including artemisinin derivatives such as artemether-lumefantrine (CoartemTM) and antifolates such as atovaquone-proguanil (MalaroneTM).¹² Negatives to these alternatives include drug cost, dose regimens, adverse drug reactions, and resistance. Coartem 20 mg/120 mg × 24 U is required for the treatment of malaria compared to 4 U of HCQ (Table 1).¹² Malarone causes strange/vivid dreams or nightmares in many patients;

there have been cases of hepatitis, seizures, and anaphylaxis, though rarely. Ototoxicity and QT prolongation have been reported after Coartem administration.¹³ Despite HCQ's affordability, providers may prescribe these alternative agents if HCQ demand remains high, and current shortages continue to affect supply and distribution of HCQ.

Systemic Lupus Erythematosus

An estimated 1.5 million people in the United States have SLE, RA, and other connective tissue disorders.¹⁴ As an FDA-approved first-line indication, many of these patients receive HCQ for effective treatment.¹⁴ Not only has HCQ been shown to prevent lupus flares, it also increases long-term survival of patients with SLE.¹⁵ It exhibits protective effects against lupus-associated organ damage, thrombosis, and loss of bone density.¹⁵ In addition, HCQ is considered safe to use during pregnancy and breastfeeding.¹⁶ From 2001 to 2015, there was a rise in the proportion of women starting HCQ during pregnancy suggesting a population in need.¹⁷ Patients with renal impairment may experience HCQ toxicity. Therefore, patients with lupus nephritis require careful HCQ dose consideration, and use of antihypertensives, lipid-lowering therapy, and immunosuppression is preferred.¹⁸ According to the Lupus Foundation of America, no other drug provides similar broad benefits as HCQ.¹⁹

Rheumatoid Arthritis

HCQ is FDA-approved for the treatment of RA. The drug interferes with RA's underlying pathophysiology through inhibition of antigen presentation in dendritic cells, cytokine production in macrophages, and calcium and Toll-like receptor signaling in B, T, and other immune cells.²⁰ HCQ is a conventional disease-modifying antirheumatic drug (DMARD). Treatment regimens for patients with RA are highly patient-specific, ranging from monotherapy to many different combination therapy regimens. Studies have shown combination therapies with conventional DMARDs, such as methotrexate (MTX) and sulfasalazine, and biological DMARDs, such as anti-tumor necrosis factor (TNF) agents, to be superior to monotherapy.²¹ Although numerous drug combinations are available for patients with RA, it is important to note that HCQ has the best safety profile of all conventional DMARDs, in addition to its affordability, prior accessibility, and relative safety during

pregnancy.²¹ Adverse cardiac effects are rare, although studies have reported HCQ-associated cardiomyopathies and HCQ-induced rhythm disorders in patients with rheumatic disease.²² When coadministered, HCQ reduces gastrointestinal absorption of MTX and may lessen the chance for MTX-associated liver toxicity.²² DMARD monotherapy with MTX is preferred for symptomatic early RA or moderate to high disease activity in established RA.²³ If disease activity remains moderate to high despite DMARD monotherapy, combination DMARDs, a TNF inhibitor, or a non-TNF biologic may be used with or without MTX in no order of preference.²³ A patient with a new RA diagnosis during the global pandemic may be prescribed an alternative monotherapy or combination regimen to avoid HCQ supply limitations. Women of childbearing age, particularly if actively planning for pregnancy or currently pregnant, and patients already receiving HCQ as part of a combination DMARD regimen should be prioritized. Inter-professional coordination between pharmacy, physician, and specialist (ie, rheumatology) is imperative for patients with emergent loss to HCQ access.

Porphyria Cutanea Tarda

PCT is a disease of uroporphyrinogen decarboxylase inhibition, an enzyme involved in heme synthesis.²⁴ Decreased enzymatic activity leads to accumulation of carboxylated porphyrinogens in the blood and later in the skin and liver.²⁴ When exposed to light, carboxylated porphyrinogens produce reactive oxygen species that damage the surrounding tissue, causing the skin to blister.²⁴ Treatment for PCT involves repeated phlebotomy every 2 weeks or treatment with HCQ or CQ.²⁴ Phlebotomy removes large quantities of blood which removes iron, a substrate involved in heme synthesis. HCQ is hypothesized to bind porphyrins within hepatocytes leading to their urinary excretion.²⁵ HCQ is an effective treatment strategy for PCT and may be superior to phlebotomy.^{24,26} Low, oral doses of HCQ 100 mg by mouth twice weekly reduces potential adverse effects while maintaining comparable safety and efficacy to phlebotomy.²⁴ Considering patient compliance, cost, and convenience, HCQ is a reasonable option for patients with PCT. HCQ should be avoided in patients with severe liver damage, renal insufficiency, glucose-6-phosphate dehydrogenase deficiency, and preexistent retinopathy.²⁵ Phlebotomy remains an effective primary treatment modality and invaluable alternative while a global pandemic strains HCQ supply.

Chronic Q Fever

Coxiella burnetii, a gram-negative coccobacillus, causes Q fever. Acute disease presents as febrile illness often accompanied by self-limiting headache and myalgias. Chronic disease manifests with endocarditis, developing in approximately 1% to 5% of patients infected with *C burnetii*.²⁷ First-line treatment for chronic Q fever endocarditis is combination doxycycline and HCQ for at least 18 months with native valves and 24 months with prosthetic valves.²⁷ HCQs alkalinizing effect on

phagolysosomes in combination with doxycycline has been shown to have in vitro bactericidal activity against *C burnetii*.²⁸ Other drugs have been used in place of HCQ (eg, ofloxacin) but HCQ is preferred for its shorter treatment durations and lower risk of disease relapse. Combination HCQ-doxycycline reduced median duration of treatment by 2 years compared to doxycycline-ofloxacin and showed no relapse in disease after 18 months of therapy.²⁸ Whenever possible, HCQ should be included or continued in the combination regimen for chronic Q fever. Although alternatives appear safe and effective, addition of HCQ offers shorter overall duration of treatment and less risk of relapse.

Hydroxychloroquine Sulfate Alternatives

Effective HCQ alternatives exist for the management of malaria, RA, and PCT (Table 2). Alternative combination regimens for chronic Q fever require shared decision-making between health care provider and patient given the significant benefits HCQ affords. Although additional supportive measures have been proposed for SLE, HCQ should not be substituted. In all instances, when evaluating HCQ for chronic, emergent, and investigational uses, health care professionals must carefully weigh adverse effects against potential benefits.²⁰ CQ derivatives may cause severe adverse effects, most notably cardiac arrhythmias (QT prolongation) and retinal toxicity.

COVID-19 Treatment

According to the National Institutes of Health (NIH), numerous active and recruiting clinical trials worldwide are studying the role of HCQ in the treatment of COVID-19.³² To date, the literature published has not demonstrated HCQ to be efficacious in the treatment of COVID-19. Evidence is released at an unprecedented rate, requiring pharmacists to evaluate current prescribing practices daily. NIH COVID-19 Treatment Guidelines recommend against the use of HCQ or CQ treatment, except in a clinical trial (Table 3).³³ Most recently, the FDA found sufficient evidence to support investigational remdesivir for use in adults and children with confirmed or suspected COVID-19, issuing an EUA on May 1, 2020.³⁴ This provides a potential alternative to HCQ, but one not easily substituted as the drug is not yet commercially available.³⁵ Remdesivir is recommended for hospitalized patients with severe disease; however, available data are insufficient to recommend for or against remdesivir use for mild to moderate COVID-19.³³ Scientists and health care professionals are evaluating immune-based therapies including convalescent plasma, interleukin-1 inhibitors (ie, anakinra), interleukin-6 inhibitors (ie, sarilumab, siltuximab, tocilizumab), and others, but there are insufficient clinical trial data to recommend for or against these treatment strategies at this time.³³ Unfortunately, no agent (whether given as pre- or post-exposure prophylaxis) is effective in the prevention of SARS-CoV-2 infection to date.³³

Table 2. Hydroxychloroquine Alternatives for First-Line Uses.

Disease state	Alternative suggested	Alternative intervention(s)	Guidelines
Malaria (<i>Plasmodium vivax</i> , <i>P. ovale</i> , <i>P. malariae</i> , <i>P. knowlesi</i>) in chloroquine susceptible countries	Yes, treat similar to uncomplicated <i>P. falciparum</i> with artemisinin-based combinations ²⁹	Artemisinin-based combinations ²⁹ : <ul style="list-style-type: none"> • Artemether + lumefantrine • Artesunate + amodiaquine • Artesunate + mefloquine • Dihydroartemisinin + piperazine • Artesunate + sulfadoxine-pyrimethamine 	World Health Organization. Guidelines for the treatment of malaria, 3rd ed, WHO, Geneva 2015.
Systemic lupus erythematosus	No, HCQ recommended for all patients with SLE ³⁰	Add-on therapies include glucocorticoids, immunosuppressive drugs (methotrexate, azathioprine), biologics (belimumab) ³⁰	Fanouriakis et al (2019) Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus, <i>Ann Rheum Dis</i> 2019;78:736-745.
Rheumatoid arthritis	Yes	Disease-modifying antirheumatic drugs (leflunomide, methotrexate, sulfasalazine) as monotherapy or in combination; tumor-necrosis factor inhibitor (TNFi); non-TNF biologic ²³	Singh et al (2015) American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. <i>Arthritis Care Res.</i> 2016; 68:1.
Porphyria cutanea tarda	Yes	Phlebotomy ²⁴	Anderson et al. Recommendations for the Diagnosis and Treatment of the Acute Porphyrias. <i>Ann Intern Med</i> 2005;142(6):439-450.
Chronic Q fever	Yes; however, HCQ-doxycycline offers shorter treatment duration and less risk of relapse ³¹	Tetracycline plus a quinolone ³¹	van Roeden et al. Treatment of Chronic Q Fever: Clinical Efficacy and Toxicity of Antibiotic Regimens. <i>Clin Infect Dis</i> 2018;66(5):719-26.

Abbreviation: HCQ, hydroxychloroquine sulfate.

Table 3. Antivirals Under Investigation for COVID-19.³³

Drug; Route of administration	Dosing: Adults	Recommendation
Hydroxychloroquine; oral	Day 1: 800 mg once on day 1; Days 2-7: 400 mg/d for a total treatment duration of 4 to 7 days	Not recommended for treatment, except in a clinical trial
Remdesivir; intravenous	Day 1: 200 mg × 1 dose; Days 2-10: 100 mg once daily	Recommended for hospitalized patients with SpO ₂ ≤94% on ambient air (at sea level) or those who require supplemental oxygen Recommended for patients who are on mechanical ventilation or extracorporeal membrane oxygenation Insufficient data to recommend for or against use as treatment of mild or moderate COVID-19

Abbreviation: COVID-19, coronavirus disease 2019.

HCQ, CQ, and protease inhibitors for human immunodeficiency virus are currently under evaluation.³³

Ethics—Nonmaleficence and Distributive Justice

As SARS-CoV-2 treatment strategies evolve, HCQ demand outweighs supply, creating repercussions for patients. Ethical dilemmas abound regarding the distribution of drug between those who are being efficaciously treated with HCQ versus those infected with SARS-CoV-2, whose treatment with HCQ is found to be both inconclusive and harmful. Patients may request HCQ prophylaxis, requiring pharmacists to forego

individual patient autonomy in favor of distributive justice and nonmaleficence.

HCQ scarcity prompted large coordinated responses from national organizations. The American College of Rheumatologists acknowledges the potential utility of HCQ during this global pandemic but also recognizes local conditions may change HCQ demand and decisions of allocation should be made by health care providers using cautionary prescribing practices. The Lupus Foundation of America expresses similar concern about HCQ supply limitations affecting the treatment of existing patients. Patients have been unable to refill their prescriptions due to widespread HCQ shortages, pharmacies requiring third-party

approval to prove patient eligibility, and health care systems stockpiling.³⁶ Both organizations recognize the severity of the global health care crisis but plead that their patients not be forgotten as original candidates for HCQ treatment.

The American Medical Association, American Pharmacists Association, and American Society of Health-System Pharmacists released a joint statement emphasizing the desperate need for pharmacists, health care providers, and health systems to remain stewards of valuable resources.³⁷ These societies strongly discourage prescribing for friends and family, stockpiling, and filling prescriptions for unproven, illegitimate medical purposes.³⁷ Pharmacists are empowered to make reasonable inquiries regarding prescribing practices.³⁷ In addition, state boards of pharmacy have individually released new rules and guidance to support pharmacists in practice.³⁸ State recommendations vary significantly, ranging from limiting days' supply, to altering prescribing, documentation, and refill requirements.³⁸ In some states, new prescriptions of HCQ have been limited to a 14-day supply with a 30-day allowance for patients with an established indication.³⁸ If prescribing HCQ for COVID-19, states have required diagnosis code inclusion, documentation of positive test results, and no refills.³⁸ At the most restrictive, states have issued emergency rules prohibiting HCQ dispensing for the treatment or prevention of COVID-19.³⁸ Support from colleagues, state boards, and national organizations build a firm foundation from which a pharmacist can ensure valuable drugs are preserved for those with legitimate medical needs.

HCQ shortages are detrimental to the individuals with chronic conditions filling millions of prescriptions each year. This strain further taxes the health care system. Distributive justice and non-maleficence must come before patient autonomy. HCQ should be reserved for first-line indications, ensuring those patients are not forgotten in this pandemic. Although the counterargument may be made that emergent use for a life-threatening disease takes precedence, we must not prevent patients who are already receiving effective HCQ treatment from accessing necessary pharmaceuticals and risking relapse as well as increased morbidity/mortality. While refusal to fill HCQ prescriptions in outpatient settings for COVID-19 may diminish patient autonomy, it reflects the promise to do no harm, given the significant risk of adverse events. All health care providers swear to uphold this principle, especially when benefits do not outweigh risks.

Conclusion

The global COVID-19 pandemic requires the pharmaceutical industry to search diligently for treatment that can ease the burden of this novel virus. Today, HCQ lacks the proper scientific evidence to be approved as a first-line therapy for COVID-19. Meanwhile, strong evidence supports HCQ use as first-line treatment for malaria, SLE, RA, PCT, and chronic Q fever endocarditis. In these uncertain times, pharmacists must advocate for patients with SLE, recommending they are prioritized for HCQ distribution. Pharmacists may participate in shared decision-making and design of effective chronic Q fever regimens given HCQ's significant benefits in treatment.

Finally, pharmacists are uniquely poised to educate and suggest alternative therapies for malaria, RA, and PCT. Through appropriate monitoring of HCQ distribution, pharmacists guarantee the urgent needs of patients are met while aiding hospitals in their fight against this worldwide pandemic.

Authors' Note

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