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LETTER TO THE EDITOR

Ophthalmologic implications to consider when using hydroxychloroquine to treat COVID-19 and induced arthritis

Marco Zeppieri

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Abstract

As the world continues to grapple with the novel coronavirus [coronavirus disease 2019 (COVID-19)], many treatments have been proposed to help alleviate the symptoms and reduce the mortality rate. Hydroxychloroquine (HCQ) is an antimalarial drug that is typically used for several autoimmune, rheumatic, and dermatological conditions. It has also been considered to treat and prevent COVID-19 and subsequent arthritis associated with the infection. This drug is known to cause retinal toxicity, which can lead to vision impairment or loss. While the exact mechanism is not yet fully understood, it is thought to be due to the accumulation of the drug in the retinal pigment epithelium. The risk of toxicity increases with long-term use or with high doses of the drug and is more likely to occur in patients with pre-existing retinal diseases or those who are predisposed to retinal diseases. In this context, several steps can be taken to monitor and minimize the risk of ophthalmological adverse events when using HCQ to treat patients with COVID-19.

Key Words: COVID-19; Hydroxychloroquine; SARS-CoV-2; Retinopathy; Maculopathy; Post-COVID-19 arthritis

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Core Tip: Hydroxychloroquine (HCQ) is typically considered when treating rheumatic and autoimmune diseases. It has been currently considered to help treat symptoms of coronavirus disease 2019 and to help alleviate several clinical manifestations after infection. In this letter, several ophthalmological implications that should be taken into consideration when using this drug are discussed. While the drug may be beneficial in treating symptoms, ophthalmological manifestations can be of clinical importance. Proper diagnoses, periodic testing, and correct management of patients in chronic treatment with HCQ can ensure that any potential ophthalmological side effects are minimized.

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TO THE EDITOR

The paper by Bajpai *et al*[1] reports an interesting thorough review of the use of hydroxychloroquine (HCQ) and azithromycin therapy to treat and prevent coronavirus disease 2019 (COVID-19). HCQ is a synthetic derivative of quinine. The drug works by inhibiting the growth of the virus, thus reducing the severity of clinical manifestations of the disease. HCQ binds to the viral protein responsible for replica-ting the virus and preventing the virus from replicating[2]. It has been found to be effective in treating the symptoms of COVID-19, including fever, cough, and difficulty breathing [3]. In addition, HCQ also has anti-inflammatory properties, which can help reduce inflammation caused by the virus. A recent commentary by Swarnakar *et al*[4] based on the review by Bajpai *et al*[1] presented the possible interesting use of HCQ to treat arthritis induced after viral infection. Numerous studies in the literature have shown the benefits offered by HCQ in alleviating debilitating symptoms. The aim of this letter article is to summarize the important ophthalmologic considerations when HCQ is considered in the treatment of COVID-19. The issues regarding whether or not HCQ is effective in treating COVID-19, which was reported in the papers recently published in this journal[1,4], will not be considered in this article. Here, the important potential risk factors and ophthalmological side effects are briefly mentioned, with the aim of reminding clinicians about the ophthalmological considerations and best practices to monitor, diagnose, and manage patients using HCQ. This is imperative to ensure that any potential ophthalmological side effects and toxic damage are minimized.

HCQ is a drug traditionally used to treat and prevent a variety of different conditions. In brief, it is an antimalarial and anti-inflammatory medication that works by inhibiting the growth and spread of certain parasites, bacteria, and viruses. At the molecular level, HCQ works by inhibiting the activity of certain enzymes known as heme polymerases[5]. These enzymes are responsible for the synthesis of heme, a molecule that is essential for the development of some parasites, bacteria, and viruses. By blocking the activity of heme polymerases, HCQ prevents the growth and spread of certain parasites, bacteria, and viruses. HCQ is used to treat a variety of conditions, including malaria, lupus, and rheu-matoid arthritis[6]. In malaria, it is used to prevent and treat the disease, while in lupus and rheumatoid arthritis, it is used to reduce inflammation and relieve symptoms. In addition, HCQ is also used to treat and prevent certain types of malaria.

HCQ is generally considered to be safe and well tolerated, but some people may experience systemic side effects such as nausea, dizziness, and headache. Studies have shown that HCQ can sometimes cause glucose abnormalities, cardiotoxicity (conduction abnormalities, cardiovascular collapse, cardio-myopathy, *etc.*), gastrointestinal effects, neuromyotoxicity, neuropsychiatric events, and dermatologic reactions[7].

There are several important ophthalmologic effects of HCQ[8]. This drug has been shown to influence cellular autophagy and lysosomal activity. HCQ can also interact with membrane stability and alter transcriptional activity and signaling pathways[9]. The ocular side effects include corneal deposits, retinal pigmentary changes, maculopathy, and optic neuritis. These complications need to be closely monitored and managed in patients using high doses and long-term therapy with HCQ. Differential diagnosis, alternative therapies for underlying disorders, proper periodic testing for functional and anatomical toxicity, and treatment options are imperative to limit drug toxicity in patients under chronic HCQ medication.

Corneal deposits are usually seen in patients taking HCQ for more than 5 years and are generally considered benign. Corneal deposits and damage induced by HCQ can vary depending on the dosage and duration of treatment. Damage to the cornea can manifest in the form of corneal opacity and corneal deposits. These deposits are typically referred to as corneal verticillata and are comprised of amor-phous, yellow-white deposits scattered throughout the cornea[10]. Corneal verticillata can cause significant visual impairment if they are dense enough to obscure vision. The mechanism of action by which HCQ induces corneal deposits is not fully understood. It is believed that HCQ accumulates in the corneal epithelium and forms a complex with proteins and lipids, resulting in the formation of deposits[11]. This could also possibly be due to reduced tear turnover and accumulation of the drug in the tear film. Additionally, it is thought that HCQ can interfere with the normal metabolism of the cornea, resulting in the accumulation of lipids and other deposits. The effects of HCQ on the cornea can be severe and can lead to permanent vision loss. Therefore, it is important to monitor patients taking HCQ for the development of corneal deposits and damage. If corneal deposits are found, HCQ should be discontinued and other treatments can be considered.

Retinal pigmentary changes are characterized by granular deposits at the level of the retinal pigment epithelium (RPE) and can lead to decreased visual acuity and progressive visual field loss[12]. Maculo-pathy is a form of retinopathy that is characterized by a bull's eye maculopathy, which is a specific pattern of retinal damage that specifically affects the circular area of damage to the macula. This small area is the central part of the retina responsible for sharp, central vision [13]. The mechanism of bull's eye maculopathy due to HCQ toxicity is not completely understood, but it is thought to involve the drug's effects on the RPE cells due to the accumulation of the drug in the RPE, leading to the formation of pigmentary changes. These RPE cells play a key role in supporting the function of the photoreceptor cells in the retina, and HCQ may disrupt this support system, leading to damage to the photoreceptor cells and the characteristic bull's eye pattern of damage. This can lead to decreased visual acuity and pro-gressive visual field loss.

Diagnosis of bull's eye maculopathy due to HCQ toxicity can be challenging, as it can be difficult to distinguish from other retinal disorders. Differential diagnosis includes other forms of macular degeneration, such as age-related macular degeneration and Stargardt disease, as well as other retinal disorders such as cone dystrophy and macular dystrophy[14]. Testing for HCQ toxicity includes complete ophthalmologic examination with vision testing and dilated fundus assessment, visual field testing, spectral domain optical coherence tomography, fundus autofluorescence imaging, and multi-focal electroretinography[15].

Optic neuritis is an inflammatory disorder of the optic nerve, which can lead to reduced visual acuity, decreased color vision, and decreased peripheral vision. This complication due to HCQ is very rare. Differential diagnosis can be made by magnetic resonance imaging, angiography, blood tests, visual field testing, and visual evoked responses[16]. The mechanism of action is thought to be due to an autoimmune response to the drug, leading to inflammation of the optic nerve[17].

The incidence of HCQ toxicity is dose-dependent, with higher doses and longer duration of treatment increasing the risk of toxicity[18]. The recommended daily dose of HCQ that is generally considered safe is up to 6.5 mg/kg/d, but at higher doses, the risk of toxicity increases. Risk factors include a cumula-tive dose of > 1000 g of HCQ, treatment duration of more than 5 years, preexisting liver or renal dysfunction, being very elderly, and preexisting retinopathy[19].

It is yet unclear how HCQ can cause retinal damage. According to studies, the medication impacts the metabolism of retinal cells and binds to melanin in the RPE, which may help to explain why some people continue to experience side effects even after stopping the prescription. With regards to dysfunction related to toxicity, it is thought that HCQ binds to melanin in the RPE, blocking its function, which can lead to irreversible photoreceptor loss and resulting visual field defects over the afflicted sector of the retina. In some cases, bull's eye configuration can be seen as a ring scotoma on a visual field test when RPE malfunction leading to atrophy occurs across the perifoveal ring when the central fovea is spared. The half-life of HCQ is about 1 mo, with a washout period of about 6 mo. Early diagnosis of HCQ retinal toxicity is crucial to prevent maculopathy from progressing after HCQ use is stopped[20]. Besides retinopathy, the other ocular side effects, which tend to be benign or infrequent with low doses of HCQ, include keratopathy, corneal deposits, punctate/linear corneal opacities, infiltrates, ciliary body deposits, ocular muscular imbalance, lens opacities, papilledema, *etc*[21].

Treatment for HCQ toxicity involves cessation of the drug and monitoring for further progression of retinal damage. The prognosis for patients with bull's eye maculopathy due to HCQ toxicity is variable, with some patients experiencing improvement in visual function after cessation of the drug, while others may experience permanent vision loss[20-22]. In some cases, the damage caused by the drug may be delayed and irreversible, resulting in permanent vision loss. There are currently no Food and Drug Administration-approved treatments for bull's eye maculopathy due to HCQ toxicity [22].

In closing, it is important to remember that HCQ can cause several systemic and ophthalmological side effects, most of which are minor and reversible. The prognosis for patients receiving treatment with HCQ for COVID-19 and associated arthritis is generally good. Further research is needed to evaluate the potential long-term ophthalmological side effects associated with the use of the drug to treat and prevent COVID-19 and associated arthritis. Ophthalmological consider-ations should be evaluated prior to initiating the therapy, including baseline visual acuity, fundus examination, and visual field testing to exclude the presence of underlying preexisting ophthalmic retinal disorders. HCQ should be avoided in patients with ophthalmopathies, including any form of retinopathy. Patients receiving HCQ should be period-ically monitored for potential ophthalmological side effects, including retinopathy, corneal deposits, and papilledema. Immediate termination of HCQ and alternative treatment regimens need to be considered in patients that develop HCQ toxicity.

FOOTNOTES

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