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Prevalence of ocular toxicity induced by antimalarial drugs in patients with rheumatic diseases

Mohsen G. Soroush[1*], Mehdi Dadpour[2]

[1]*Rheumatic Diseases Research Center, AJA University of Medical Sciences, Tehran, Iran.*

Several studies have reported the possibility of ocular toxicity with the use of antimalarial drugs by patients with rheumatic diseases. Thus, the present study intended to investigate the prevalence of such toxicity in these patients and the feasibility of the regression of changes after medication discontinuation. The present retrospective study included the medical records of 598 patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and mixed connective tissue disorders (MCTDs) who took chloroquine (CQ) or hydroxychloroquine (HCQ) and underwent routine ophthalmologic examinations. Moreover, if a patient had any ocular abnormality reported by the examining ophthalmologist, he/she was referred to another ophthalmologist to confirm the primary findings. Also, the patients with abnormal ocular findings who discontinued the drugs were re-examined 12 months after the drug discontinuation to evaluate the rate of regression of the ocular changes. According to our findings, 81 out of 598 patients (13.6%) had ocular toxicity in routine ophthalmologic examinations. However, ocular changes were ruled out in 49 (8.2%) patients using a second examination by another ophthalmologist. Therefore, retinopathy was confirmed in 32 out of 598 (5.4%) cases. Moreover, the patients with eye complications were significantly older than those without ocular toxicity (P = 0.03), while no significant relationship was found between ocular toxicity and other variables. Finally, of 32 patients with ocular toxicity, 12 patients were re-examined 12 months after the drug discontinuation, revealing normal findings in 7 (58%) patients, while 5 (42%) had irreversible ocular abnormalities. According to our findings, the prevalence of HCQ- and CQ-induced retinopathy was quite considerable in patients receiving these drugs. Therefore, despite the current controversies, we recommend that all patients receiving antimalarial drugs undergo screening for ocular toxicity.

Keywords: ocular toxicity; antimalarial drugs; screening; rheumatoid arthritis.

Introduction

Since their introduction in the early 50s, prescribing antimalarial agents, chloroquine (CQ) and hydroxychloroquine (HCQ), has become increasingly prevalent for several collagen vascular diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and mixed connective tissue diseases (MCTD). However, the application of these medications may result in several complications, the most common of which include gastrointestinal side effects, skin rash, and headache. Moreover, these drugs may cause some dangerous ocular complications, including keratopathy, ciliary body involvement,

*Corresponding author: Mohsen G. Soroush, Associate Professor of Rheumatology, AJA University of Medical Sciences, Tehran, Iran; Tel: 0098-9122156137; Email: mohsensoroosh@gmail.com

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lens opacity, and retinopathy. Of these two agents, HCQ has a better safety profile compared to CQ and is more widely prescribed by clinicians [1].

CQ-induced retinopathy may manifest itself with the loss of central vision, color vision deficits, and central scotoma. Among all the ocular complications of these drugs, retinopathy must be taken seriously due to the possibility of permanent visual loss [1]. Moreover, maculopathy may present in a wide range of severities, from subtle retinal pigment epithelium disturbances to bull's-eye maculopathy [2]. According to different studies, the prevalence of HCQ-induced retinopathy has been estimated to be 0-4%, considering different characteristics of the affected patients and varying definitions of retinopathy [3- 8]. Also, it is worth noting that genetic predisposition can affect the chance of HCQ-induced retinopathy, so these reports may vary in different countries. Other risk factors for HCQ-induced retinopathy include daily dose, treatment duration, cumulative dose, underlying renal or hepatic dysfunction, age, obesity, and concomitant retinal disease.

All patients with HCQ-induced retinopathy have fundus or visual field abnormalities. However, a few may remain asymptomatic while most of them experience reading problems, visual impairment, central vision deficits, glares, blurry vision, light flashes, or metamorphopsia [2]. Considering the rare occurrence of HCQ-induced ocular toxicity, no gold standard method of ocular examination has been established for predicting its impending development [9]. However, several methods have been suggested: ophthalmologic examination, visual field test [10], color vision test, fluorescein angiography, electrophysiological investigation [11], and spectral-domain optical coherence tomography [12]. It is believed that early detection and regular follow-up may help in minimizing or halting the process of retinal damage as soon as possible. However, there are still controversies regarding the frequency of visits for preventive ocular examinations in patients receiving antimalarial agents.

Materials and Methods

The present retrospective study evaluated the medical records of 598 patients with RA, SLE, and MCTD who received antimalarial drugs and attended regular follow-up visits for at least a year. All patients had already been informed about the side effects and benefits of these drugs. Moreover, 13 patients who discontinued the medication due to hyperpigmentation were excluded from the study. Also, the present study was approved by the Ethics Committee of the AJA University of Medical Sciences (ethics code: IR.AJAUMS. REC.1396.95). We did not use an informed written consent form due to the retrospective nature of the study.

Data extraction included the demographic characteristics, disease duration, treatment duration, daily dose of the antimalarial drugs, cumulative dose of the drugs, and presence of co-morbidities, such as renal or hepatic insufficiency dysfunction. According to our center's protocol, if a patient had any ocular abnormality reported by the examining ophthalmologist, he/she was referred to another ophthalmologist to confirm the primary findings. Cumulative doses of HCQ and CQ were calculated using the patients' self-reports of the related daily dose and treatment duration. Also, the ocular examination included corrected visual acuity for distant and near vision, red Amsler grid screening, under lamp examination, and fundoscopy. Finally, data analysis was performed using the SPSS software version 21 and descriptive and analytical statistical indices.

Results

The present study included a total of 598 patients, 124 men (20.7%) and 474 women (79.3%), who received HCQ or CQ for RA (n = 465), SLE (n = 61), or MCTD (n = 11) and were under regular follow-up and ophthalmologic examinations for at least a year. Of all the patients, 31 patients had renal insufficiency, while 8 had hepatic insuff-iciency based on their laboratory test results. Moreover, the patients' mean age was 50.6 ± 14.6 years. The mean treatment duration was 22.8 ± 22 and 15.4 ± 15.8 months for HCQ with a daily dose of 200 and 400 mg, respectively, while the mean treatment duration was 15.4 ± 15.8 months for CQ with a daily dose of 150 mg. Thus, the mean treatment duration was 45.7 ± 29.8 months for both

drugs. Also, the mean cumulative dose of HCQ was 414.6 ± 287.1 g.

On the other hand, 81 patients (13.6%) had abnormal ocular findings in their routine ophthalmologic examinations, while 517 patients (86.5%) had no ocular abnormalities. The patients with abnormal findings were referred to another ophthalmologist for re-examinations, which ruled out ocular toxicity in 49 patients and confirmed the previous findings in only 32 patients (5.4%), who were all asymptomatic.

According to our findings, old age was a significant risk factor for HCQ- or CQ-induced ocular toxicity. In the present study, the patients with ocular toxicity were significantly older than those without ocular toxicity (P = 0.03). Moreover, underlying collagen vascular disease had no significant impact on the risk of HCQ- or CQ-induced ocular toxicity, since there was no significant difference in the chance of ocular toxicity between the patients with RA, SLE, and MCTD (P = 0.1). Also, underlying renal or hepatic disease did not change the chance of developing ocular toxicity (P = 0.7). On the other hand, the duration of the underlying disease (P > 0.05), the history of treatment with multi-drug regimens (P > 0.05), and the cumulative dose of HCQ (P = 0.80) did not have a significant effect on the chance of ocular toxicity. Moreover, the chance of ocular toxicity was not significantly different between the patients using HCQ and CQ (P = 0.41). Also, 12 out of 32 patients with ocular toxicity underwent ophthalmologic examinations after discontinuing the antimalarial drugs. After the completion of the study, 12 out of 32 patients with ocular toxicity in the examination were followed and underwent another ophthalmologic examination, which revealed normal findings in 7 patients (58%), while other 5 patients (42%) had permanent ocular toxicity.

Discussion

The retinal toxicity of antimalarial drugs initiates with the development of a paracentral scotoma, which can be diagnosed using the visual field test before any fundus changes in ophthalmoscopy. If the paracentral scotoma is detected timely and the antimalarial medication is discontinued, other irreversible ocular complications can be avoided.

The real problem is the extremely low prevalence of retinopathy in patients receiving CQ and HCQ, which has drawn controversy on the necessity andfrequency of serial visual examinations. Several ophthalmologists even believe that the actual prevalence of this phenomenon is lower than what is being reported in the studies, which can be explained by their lack of expertise or the use of assessment tools with low sensitivity for diagnosing such subtle changes.

In the present study, all the patients who were primarily diagnosed with drug-induced ocular abnormalities were referred to a second expert ophthalmologist to confirm the diagnosis and minimize the number of false-positive cases. Finally, 32 out of 598 patients were diagnosed with definite ocular toxicity, revealing a prevalence of 5.4%, which is much higher than what was reported in the previous studies. Moreover, a recent study by Mellas et al. [13] reported a prevalence of 7.5% for HCQ-induced retinal toxicity after the exclusion of misdiagnosed cases with a second ophthalmologic examination, revealing a quite high prevalence.

Several risk factors have been suggested for HCQ- and CQ-induced ocular toxicity. However, the significance of these risk factors has not been approved in all related studies. Considering the lack of consensus on these relationships, no specific criteria have ever been approved for screening HCQ- and CQ-induced ocular toxicity. The present study evaluated some of these potential risk factors, including age, cumulative and daily doses of HCQ and CQ, disease duration, treatment duration, and underlying renal and hepatic dysfunction. However, we only found a significant effect for age (P = 0.03), showing a higher chance of ocular toxicity in older patients. Considering these findings, we recommend all patients receiving antimalarial drugs undergo regular ophthalmologic examinations by an expert ophthalmologist from the initiation of treatment regardless of the daily and cumulative doses of the drugs, underlying rheumatologic disease, and the presence of comorbidities. The development of irreversible ocular complications and bull’s eye retinopathy can be prevented by early detection of subtle ocular abnormalities. Moreover, it is worth

noting that recent studies have shown the possibility of ocular toxicity progression even after the drug discontinuation, which shows the necessity of regular follow-ups even after the drug discontinuation [14]. Also, we expect that the symptoms of some patients get worse with the progression of the disease.

The present study had some limitations as well. For example, we did not use Optical Coherence Tomography (OCT) routinely in the present study. However, this approach was accepted by the majority of our ophthalmologists.

Conclusion

According to our findings, the prevalence of HCQ- and CQ-induced retinopathy was quite considerable, showing the necessity of regular follow-up and eye examinations by expert ophthalmologists in the patients receiving these drugs. Moreover, we recommend performing a baseline eye examination before the initiation of these drugs to rule out any pre-existing ocular problems that may later mimic the drug-induced ocular toxicity. Also, it is necessary to establish a reliable protocol for screening the patients receiving antimalarial drugs in terms of ocular toxicity because we believe that the prevalence of drug discontinuation for HCQ- and CQ-induced retinopathy is higher than the real prevalence of such toxicity. Furthermore, we observed that some of the retinal changes in the patients with HCQ- or CQ-induced retinopathy were transient.

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Conflict of Interests

The authors declare no conflict of interest.

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