Hydroxychloroquine retinal toxicity in two patients with dermatology conditions

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Abstract

A 58 year-old female developed hydroxychloroquine retinal toxicity with bull's-eye maculopathy after treatment for lichen sclerosus (3.7 - 7.3 mg/kg, treatment duration 6 years). A 69 year-old female developed hydroxychloroquine retinal toxicity with an essentially normal fundus, diagnosed on ancillary testing, after treatment for lichen planopilaris (11.4 mg/kg, treatment duration 29 months). Recently revised guidelines lowered the recommended maximum daily dose to 5 mg/kg total body weight. There is no treatment for hydroxychloroquine retinal toxicity, so appropriate monitoring is imperative. All members of a patient's multidisciplinary team should be self-informed about the ocular risks of hydroxychloroquine and the role of appropriate monitoring in reducing the risk of visual loss.

Keywords

Hydroxychloroquine

Toxicity

Retina

Lichen sclerosus

Lichen planopilaris

Learning Points

1. Patients developing hydroxychloroquine retinopathy are frequently asymptomatic and may have minimal retinal changes on fundoscopy. Patients receiving hydroxychloroquine are recommended to have ophthalmic examination at baseline, and annually after 5 years of continuous dosing, or earlier if symptoms develop or risk factors (dose >5 mg/kg actual body weight, renal disease, tamoxifen use, pre-existing macular disease) are present.
2. Recent international ophthalmology recommendations have lowered the maximum recommended hydroxychloroquine dose from 6.5 mg/kg lean body weight to 5.0 mg/kg actual body weight.

Introduction

Hydroxychloroquine (HCQ) is an anti-malarial medication used in treating dermatological[1] and rheumatological inflammatory conditions. The mechanism of action is not clear, but is known to be multifactorial and includes immunomodulatory, anti-inflammatory and antiproliferative effects. Treatment is generally well tolerated but can be complicated by adverse events in up to 25% of patients.[2] Dermatologic, gastro-intestinal, and neurologic side effects are the most common.[2] We report two patients who developed retinal toxicity while being treated for dermatologic conditions and discuss recent changes to screening guidelines.

Patient 1

An asymptomatic 58-year-old Caucasian woman presented for ophthalmic assessment in 2007. She had taken HCQ between 1996 and 2002 for lichen sclerosus (dose 400mg/day, 7.3mg/kg actual body weight). HCQ was ceased in 2002 on ophthalmic advice when bull's eye maculopathy developed, but restarted by another practitioner in 2004 and continued until presentation (dose 200 mg/day, 3.7mg/kg actual body weight). Her cumulative dose was >1160g). She had left optic neuritis in 1995, with chronic reduced vision. She had asthma, hypertension and hypercholesterolaemia, but no renal failure and did not smoke

cigarettes. Her medications were methotrexate, fluticasone/salmeterol, tiotropium bromide, telmisartan and atorvastatin; she did not take tamoxifen. Visual acuities were right 6/6, left 6/18. Fundus examination revealed bull's eye macular change bilaterally (Figure 1 A-C, right eye illustrated). HCQ retinal toxicity was diagnosed and HCQ was again recommended to be ceased. At follow-up in 2016 visual acuities were right 6/12 and left 6/24, and progressive macular atrophy was noted in both eyes.

Patient 2

A 69-year-old Caucasian woman complained of a blurred central patch in vision in both eyes. She had taken HCQ (500 mg/day, 11.4 mg/kg actual body weight, cumulative dose >440g) for 29 months for lichen planopilaris, but self-ceased this when she noted visual symptoms. She had no significant past ophthalmic or medical history, did not smoke cigarettes, and took no regular medications. Visual acuity was 6/6 both eyes. Fundus examination showed very mild macular granularity, however automated visual field testing (Humphrey, Zeiss Meditec, Germany) demonstrated a dense central scotoma and optical coherence tomography (Cirrus, Zeiss Meditec, Germany; OCT) scanning demonstrated parafoveal thinning in both eyes (Figure 1 D-F, left eye illustrated).

Main Text

Our two patients with dermatological conditions developed HCQ toxicity whilst being treated above the past and current dosing recommendations by ophthalmology societies,[3-5] dermatologists[1] and the manufacturer.[6] Patient 1 had HCQ restarted despite diagnosed toxicity, demonstrating the necessity of good communication between all practitioners involved in a patient's care. Patient 2 developed toxicity after only 29 months, similar to previous reports with very high doses of HCQ for cancer therapy,[7] raising the issues of the role of baseline screening and screening during the first five years of treatment.

Early ophthalmology reports suggested the risk of HCQ retinopathy was low,[8] approximately 0.5% after a mean of 8.7 years of treatment. However, a recent large study of 2361 patients who had received HCQ treatment for more than 5 years suggests much higher risk than previously recognised, with retinopathy occurring in around 7.5% patients, and up to 20% of patients who have received HCQ for 20 years.[9] This pivotal study led to revision of

international HCQ screening recommendations,[4, 5] although it should be noted that the study population was limited to members of the Kaiser Permanente Northern California health organisation.

The mechanism of HCQ toxicity is not understood. HCQ retinopathy is typically asymptomatic until late stages; occasionally patients report difficulty reading or positive scotomata (e.g. Patient 2). The condition is bilateral and usually symmetrical. Retinal damage is first noted parafoveal on automated field testing of macular function (10^{o} field), OCT scanning or fundus autofluorescence imaging (e.g. Patient 2). In late stages bull's eye pattern of macular atrophy, sparing the fovea, develops (e.g. Patient 1). Retinopathy in Asians may be more peripheral than in Caucasians. The sensitivity of field testing and OCT scanning are estimated to be 85.7% and 78.6% respectively, and specificity 92.5% and 98.1% respectively. Positive predictive values are less than 30% for all estimates of HCQ retinopathy prevalence. Negative predictive values are >99%.[10] Risk factors for toxicity include daily dose, cumulative dose, renal failure, concurrent use of tamoxifen and pre-existing macular disease. There is no data on cigarette smoking as a risk factor. The only available treatment is drug cessation, however progressive visual loss despite drug cessation occurs commonly (e.g. Patient 1), and has been well described when the diagnosis is made using OCT or visual fields, well before onset of late retinal changes on fundoscopy.

Until recently a dose of 400 mg daily, 6.5 mg/kg lean (ideal) body weight or cumulative dose <1000g was considered safe.[3] Both our patients were dosed above this level. Revised international ophthalmic guidelines,[4, 5] also adopted in Australia, recommend lowering of the maximum dose to 5 mg/kg actual body weight. The revised guidelines no longer consider cumulative dose as this was not found to be a predictor of toxicity. Due to the long action of HCQ, lower average daily doses can be achieved by alternate day dosing if necessary. Patients are recommended to have ophthalmic examination at baseline, and then annually after 5 years of treatment, with earlier review if symptoms develop earlier or risk factors are present. Minimum screening requires fundus examination, OCT macular scanning including vertical line scan, and automated macular perimetry.
Fundus photography, fundus autofluorescence and multifocal electroretinography are optional. Screening in Asian patients needs to consider more peripheral retinal involvement.

Conclusion

In an age where multidisciplinary care is evolving, all team members involved in monitoring disease and prescribing treatment should be self-informed about the ocular risks of HCQ and the role of contemporary retinal monitoring in reducing the risk of HCQ visual loss.

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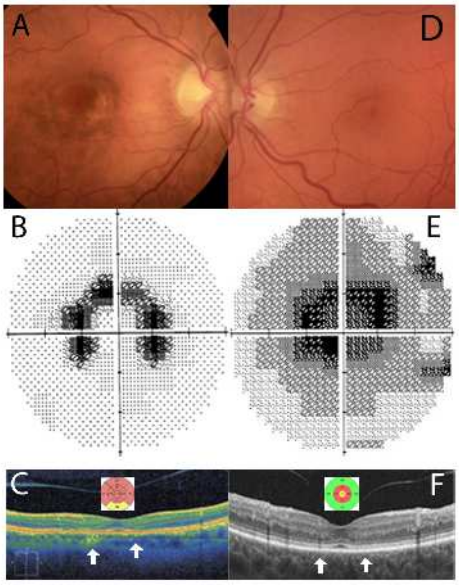
Figure Legend

Figure 1: *A-C, The right eye of a 58 year-old Caucasian female with lichen sclerosus and hydroxychloroquine retinopathy:* A) Colour fundus photograph showing bull's eye macular atrophy. B) Automated visual field testing (10^{o} field) showing a ring scotoma with inferior sparing. C) Optical coherence tomography (OCT, vertical cut) showing parafoveal retinal pigment epithelial and photoreceptor thinning (arrows, 'flying saucer sign'), with inset OCT *en face* view showing generalised macular thinning.
D-F, The left eye of a 69 year-old Caucasian female with lichen planopilaris and hydroxychloroquine retinopathy: D) Colour fundus photograph showing mild macular granularity. E) Automated visual field testing (10^{o} field) showing a central scotoma. F) OCT

scanning (vertical cut) showing parafoveal retinal pigment epithelial and photoreceptor thinning (arrows), with inset OCT *en face* view showing parafoveal retinal thinning.



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