Revisiting Ocular Effects of Hydroxychloroquine

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Hydroxychloroquine (HCQS), the antimalarialdrug is an invaluable drug used for the management of chronic rheumatic disease. The active component of drug is the quinoline alkaloids quinine and quinidine obtained from the bark of cinchona tree. The therapeutic efficacy of this drug for arthritis was confirmed during the time of World War II.[1] Recently, HCQS has been approved by the US Food and Drug Administration for the treatment of systemic lupus erythematosus (SLE), polymorphous light eruption, and rheumatoid arthritis.[2]

The adverse effects of HCQScan range from neuromyotoxicity, cardiotoxicity and ocular toxicity. Ocular toxicity can manifest as a non-significant keratopathy to a potentially blinding retinopathy.[3,4] Ocular toxicity was first reported by Cambiaggi in 1957[5] in a patient with SLE who was on treatment with chloroquine. The earlier reported prevalence of retinal toxicity was 1-3% using visual fields and fundoscopy as the diagnostic tools. However, with the advancement of the new diagnostic tools such as multifocal electroretinography (mfERG), optical coherence tomography (OCT), and fundus autofluorescence (FAF), the early changes can be detected often before the patient's symptoms. Therefore, the recent literature reported the prevalence of toxicity to be 7.5% in patients who were on HCQS for at least 5 years.[6]

Mechanism Of Ocular Toxicity:

The mechanism of HCQS toxicity is not well known. The slow and chronic damage caused by HCQS toxicity is still under research. HCQS bind to melanin in RPE leading to prolonged toxicity. However, clinically the primary site of damage is photo receptors followed by secondary disruption of RPE. The parafoveal and extramacular localization of damage could not be related to any anatomic pattern of retina. HCQS and chloroquine have bioavailability of approximately 70%. They are deposited in the tissues; which may persist for up to 5 years.[7]

Clinical Presentation:

Commonly affected ocular structures with HCQS include the cornea and retina.

Cornea: Corneal verticillata is more common with chloroquine than HCQS at recommended doses and is directly related to higher dosage. Patient may complaint of halos and photosensitivity with the corneal deposits all of which are reversible upon discontinuation of the drug.

Retina: The most dreaded complication however is the retinopathy which can result in permanent visual loss.[8] The patient is asymptomatic initially with no detectable fundal abnormalities. Initial screening tests i.e. visual fields examination may show decrease retinal sensitivity in central 10 degree area with perifoveal thinning of outer retinal layers on OCT suggestive of early retinopathic changes. In cases where initial screening tests are doubtful, the gold standard objective test mfERG may aid in early diagnosis. Characteristic findings include decreased photoreceptor function in a ring shaped pattern around the fovea.[9]

The advanced form of HCQS toxicity is characterized by a classical bilateral 'Bull's-eye maculopathy', an appearance caused by a ring of parafoveal RPE depigmentation that spares a foveal island. Attenuation of retinal arterioles and optic disc pallor may be evident in advanced cases.

The earliest functional changes occur paracentrally. As such the central vision is not affected so the patient is asymptomatic. The damage is progressive and irreversible; thus persisting even after the discontinuation of the drug[6]. However, the Asian population may not present with the classic bull's eye pattern of para central visual field loss. Visual field changes in these patients may extend beyond the central 10degree, thus emphasizing on the need of wider range of visual field testing.[10]

Dosage And Duration:

The daily dose recommendation for HCQS treatment of rheumatic diseases has recently changed from 6.5mg/kg lean body weight to 5 mg/kg total body weight for patients without additional risk factors, with a maximum of 400mg during the first 5 years of treatment.[6]

However, there has been a debate whether to use ideal or real body weight for calculation of the HCQS dose. Because HCQS distributes poorly in fatty tissues,[11] the initial literature shows that the risk happened to be much greater in thin/lean individuals whenever calculated with the ideal body weight. Thus, later it was suggested that the dosage should be calculated by ideal body weight to reduce the theoretical risk of

overdosing obese patients. Melles and Marmor in their case series showed that the risk at a given dose per kilogram was actually more closely correlated with actual weight than ideal weight.[6] According to their observation, the prevalence of retinal toxicity in relation to milligrams per kilogram of actual bodyweight was essentially independent of body habitus, whereas the risk multiplied in thin individuals if the dose was calculated using ideal body weight. Their study also concluded that there was an increased risk of developing retinal toxicity if the average daily dose exceeded 5mg/kg.

Risk Factors:

Since HCQS is excreted through the body majorly by kidneys, renal insufficiency accounts for the most important risk factor for increasing the ocular toxicity[12]. Melles and Marmor reported twice the risk of retinopathy in individuals who had glomerular filteration rate (GFR) of less than 50%.6 A multivariate analysis by a french PLUS study13 also showed a statistically significant lower blood concentration of HCQS in patients with higher Creatinine clearance (CrCl) as opposed to patients with renal insufficiency having low CrCl.

Tamoxifen, a selective estrogen receptor modulator(SERM) commonly used in the treatment of breast cancer has been known to cause central macular changes in dose dependent pattern.[14] HCQS if prescribed to a patient on treatment with tamoxifen can significantly increase the risk of retinopathy by their synergistic action on retinal cells.[15]

Pre-existing retinal and macular disease may impede early detection of the retinopathy thus increasing the risk of toxicity. However there is no conclusive evidence to suggest the increase risk of toxicity in these patients. Therefore, these patients should be screened more frequently.[6]

Screening Tools:

According to the current guidelines from the American Academy of Ophthalmology for screening patients on HCQS, the patient should be screened using one objective test in addition to visual field testing (subjective test), because recent literature shows that the central visual fields defects can present before any evidence of structural abnormalities.[16-17]

- Amsler Grid: Use of a red Amsler grid or red target for visual field testing is recommended for initial screening.

- HVF:The most sensitive and commonly used subjective test for monitoring HCQ toxicity is Automated Humphry visual field (HVF) testing using central 10-2 protocol.

The patient may show a paracentral scotoma early or a ring scotoma in advanced cases. As mentioned previously, a wider testing field using HVF 30-2 or 24-2 should be used in Asian population. Since visual field testing is a subjective test, the findings must be corroborated with an objective test.[18]

- SD-OCT: The most commonly used objective test is Spectral-domain OCT (SD-OCT) which enables early detection of the structural abnormalities by providing the cross-sectional images of the macula. Characteristics findings include parafoveal changes and thinning or loss of photoreceptor layers, a "preclinical" stage where the photoreceptor inner segment-outer segment (IS/OS) junction appears "moth-eaten" due to preferential loss of cone photoreceptors.[19]

'Flying saucer sign', has also been described as preservation of the outer retinal structures in the central fovea, perifoveal loss of the photoreceptor IS/OS junction, and outer retinal thinning.

A wide field SD-OCT should be used for screening the Asian population to detect the extramacular changes.

- mfERG : The most sensitive objective test for detecting the early HCQ retinopathy even before visual field changes is mfERG. It measures bioelectric signals from photoreceptors to elaborate depressed retinal sensitivity. It is now considered the gold standard for confirming HCQretinopathy in patients showing abnormal findings on other screening tests.[20]

Fundus auto flourescence (FAF): FAF is another objective test which can be used for screening.21An increased ring of signal within the parafoveal and perifoveal regions, which is indicative of photo receptor dysfunction and RPE abnormalities is noted on FAF.

Why To Screen?

HCQS is a widely used drug for various autoimmune and inflammatory conditions with fewer side effects than its available counterparts. The ocular damage caused by HCQS is irreversible even if the drug is discontinued. However, if the retinopathy is recognized at an earlier stage before RPE damage has occurred, the progression can be limited by discontinuing the drug and hence loss of visual acuity can be prevented. Thus the pattern of damage should be recognized at the earliest and verified either by different or repeated testing of the same screening modality.

Screening Guidelines:

The following screening guidelines should be followed as proposed by American Academy Of Ophthalmology in their 2016 revised guidelines[6] :

1. The patient should be screened within one year of starting HCQS to establish a baseline testing results using HVF and SD-OCT and any pre-existing retinal and macular diseases should be excluded after thorough fundus examination.

2. In high risk patients such as those with renal disease, Tamoxifen, pre-existing macular disease or daily dose greater than 5mg/kg of total body weight screening should be done annually.

3. In low risk patients, annual screening is recommended only after 5 years of HCQS usage.

Should Screening Be Continued After Cessation Of HCQS?

At present there are no accepted guidelines for screening in patients who have discontinued HCQS after diagnosis of retinal toxicity has been made. A study recommended an initial follow up after 3 months of diagnosis of HCQS retinopathy followed by annual screening.22In the absence of an established protocol it is generally recommended that a close surveillance should be kept of all such cases.

Management:

At present no medical or surgical treatment has been proven to be effective in treating or reducing the risk of HCQS retinopathy. Even after the stoppage of drug, the retinopathy continues to progress. However, the progression can be limited if retinopathy can be recognized before the damage to RPE cells. Once the diagnosis of retinopathy has been established, the decision to stop the drug should be taken in conjunction with the treating physician after weighing against the medical risks.

Similarly, there are no evidence based guidelines for dose reduction in patients with renal insufficiency and pre-existing macular pathology. Hence, newer methods for surveillance in the future are required to aid in safe usage of HCQS.

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