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Original Article

Spectral domain optical coherence tomography–based prevalence of hydroxychloroquine maculopathy in Indian patients on hydroxychloroquine therapy: A utopia of underdiagnosis

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ABSTRACT

Background: Spectral domain optical coherence tomography (SD-OCT) detects early structural damage to macula in patients on Hydroxychloroquine (HCQ) therapy. The current screening protocols emphasize concurrent use of both SD-OCT and Visual field analysis (VFA) which detects functional damage to detect Hydroxychloroquine maculopathy. However, VFA is a time-consuming and subjective test which is often neglected. This study gives the prevalence of Hydroxychloroquine maculopathy using SD-OCT alone which often fails to detect macular damage in peri-foveal and extra-foveal area of the retina.

Methods: Three hundred thirty four eyes of 167 patients taking systemic Hydroxychloroquine were studied with SD-OCT macular cube 512 x 128 to diagnose structural macular damage to detect prevalence of Hydroxychloroquine maculopathy.

Results: Out of 167 patients, only four patients showed features suggestive of Hydroxychloroquine maculopathy. One patient had ELM loss, two had para-foveal and one had peri-foveal IS-OS disruption. The SD-OCT gave prevalence as 2.4%.

Conclusion: SD-OCT alone can underdiagnose burden of Hydroxychloroquine maculopathy (prevalence = 2.4%) when compared to studies which use both SD-OCT and Visual field analysis (prevalence = 7.5%).

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Introduction

Hydroxychloroquine (HCQ) is a hydroxylated derivative of chloroquine, developed in 1955. It was initially developed as an anti-malarial but its mass use led to the serendipitious discovery of its anti-inflammatory action.[1] Chemically, it is an alkylated 4-aminoquinolines (4-AQ), hydroxyl derivative of 7-chloro-4(-4-diethylamino-1-methyl butyl amino) quinolone,[2] which is used as a disease modifying antirheumatic drug for the treatment of various inflammatory and connective tissue disorders. The exact mechanism of HCQ toxicity is unknown, but it is considered owing to 4-aminoquinoline nucleus of the chemical.[3] Its toxicity is a dose and duration-dependent definite phenomenon rather than an idiosyncracy. Binding of HCQ to lysosomes and endosomes via inhibition of activation of toll-like receptors (TLR3, TLR7, TLR9). It raises intra-organelle pH leads to ineffective degradation and storage of these toxic products and eventually cell damage. The toxic effects are due to accumulation of proteins ubiquinated by 4-AQs, which causes apoptosis, autophagy disruption, and oxidative damage.

This cross-sectional observational study was conducted on 334 eyes of 167 patients taking systemic HCQ. Patients taking HCQ rarely present with any ocular complaints until central loss of visual acuity has taken place owing to advanced retinopathy. Payne et al.[4] have reported decreased vision in 4.3%, flashing lights in 1.4%, and disappearing letters in 1.4% patients as presenting complaints. There are two main proposed classification systems for HCQ retinopathy. First, based on the probability of the retinopathy as: possible, probable, and definite.[5] Second classification system is based on the severity: premaculopathy, early maculopathy and advanced maculopathy.[6]

In present era of corona virus disease (COVID-19) pandemic, various health advisories recommend use of HCQ for prophylaxis of health-care workers and adult contacts of cases in a dose of 400 mg 2 doses 12 hours apart and then weekly and treatment of cases in a dose of 400 mg daily, which might exceed daily recommended dose of less than 5/ mg kg.[2]

Recent recommendations

The recent recommendations based on screening protocols suggested by American Academy of Ophthalmology 2016 revision[2] suggested that daily HCQ dosage of >5 mg/kg actual body weight, duration of more than 5 years of systemic HCQ therapy was considered a significant risk factor along with concomitant renal diseases, use of tamoxifen and pre-existing macular diseases. Pre-existing macular diseases can lead to increased susceptibility to toxicity and can hamper the screening tests.[2]

SD-OCT in HCQ retinopathy

OCT is an objective and reproducible tool to monitor for early signs of HCQ retinopathy and has been found to be more reliable than visual field analysis (VFA). Early retinal toxicity is characterized by loss of external limiting membrane (ELM), disruption of outer ellipsoid zone, parafoveal thinning of outer nuclear layer, and retinal pigment epithelium (RPE) damage.[7]

A recent study in patients using HCQ revealed:

- Decrease in outer segment (OS) and inner segment-outer segment (IS-OS) thickness
- A slight decrease in Ganglion cell inner plexiform layer measurements
- Increase in thickness of RPE-Bruch's complex[8]

Korahand et al, reported anatomical evidence of ganglion cell layer damage causing parafoveal region thinning.[9] The central macular thickness is affected later in the course of the disease, which starts thinning in parafoveal region over time to outer parafoveal region. Mititelu et al. reported the integrity of ELM in and around fovea on SD-OCT was associated with preservation and possibility of regeneration of ellipsoid zone. ELM disruption was associated with photoreceptor remodeling and its presence was a poor prognostic indicator for reversal of toxicity on stopping the medication.[10]

The baseline ophthalmological consultation is advised ideally, before starting the therapy or at least within first year of starting the therapy.[2] This helps in documenting any pre-existing macular conditions and documenting patient's baseline visual functions. If high-risk factors are present, the screening can begin sooner. The recent screening recommendations on HCQ retinopathy by American Academy of Ophthalmology has recommended SD-OCT and automated field analysis as primary screening tests.[2] The screening tests recommended in this protocol can further be divided into subjective and objective tests.

Subjective or functional tests

Visual field tests are sensible indicators of HCQ toxicity if reliable. In non-Asian patients, where parafoveal macula is more commonly involved, VFA 10–2 is recommended. In Asian patients, perifoveal and further peripheral involvement, which might me missed in central 10–2 fields, warrants VFA 24–2 or VFA 30–2. Perifoveal and extramacular involvement is not exclusive in Asians and is seen in 12% Asian population and 2% Caucasian population.[2] It should be emphasized that these patterns have only 4 central test spots representing central macula and reduced sensitivity even in 1 central spot is abnormal. The visual fields are highly variable, but when reliable, it provides an excellent tool to detect toxicity in perifoveal and extrafoveal areas. The parafoveal visual field defect involves 2–6 degrees of central field and perifoveal visual field defects may not be detectable in 10–2 visual field testing. The most commonly affected inferotemporal macular region in HCQ toxicity extrapolates as a superonasal field defect. If VFA is uncertain, it should be retested or other objective tests should be considered. About 10% patients have visual field abnormalities with normal SD-OCT. In such conditions, repeating the visual fields or mf-ERG is considered to detect any evidence of structural damage.

Objective or structural test

SD-OCT may show localized areas of photoreceptor layer thinning or loss in parafoveal areas in non-Asian eyes and perifoveal, reaching up to arcades in Asian eyes.[3] The wider angle SD-OCT which can take at least central 30° is the preferred modality of objective screening in Asian eyes. The findings in SD-OCT which are consistent with HCQ retinopathy are:[7,8,9]

1. IS-OS disruption
2. Photoreceptor layer disruption
3. Disruption of space between IS-OS layer and interdigitation zone
4. Interdigitation zone loss
5. Loss of RPE
6. Hyperreflective choroid due to loss of RPE

Eric Chen et al. found loss of perifoveal photoreceptor IS-OS junction with intact outer retina, including IS-OS junction, directly under fovea and called it 'Flying saucer sign'.[11] It was associated with thinning of outer nuclear layer, apparent posterior displacement of inner retinal structures toward RPE and loss of normal foveal depression.

Stepien et al. have described a 'moth-eaten appearance' of photoreceptor IS-OS junction due to preferential loss of cones in 'preclinical' stages of HCQ maculopathy.[12]

Sample size

Sample size is calculated to estimate 95% confidence interval for prevalence of retinopathy amongst patients on HCQ with 4% absolute error of margin, the sample size works out to be 167 assuming that prevalence to be 7.5% (2).

Inclusion criteria

a) Adult patients (more than 18 years of age) prescribed HCQ for non-ocular conditions such as rheumatoid arthritis, systemic lupus erythematosis, psoriasis, scleroderma, systemic sclerosis, ankylosing spondylosis, and so on. In a dosage as deemed adequate by respective treating physicians.
b) Duration of HCQ therapy more than one year.

Exclusion criteria

Patients with pre-existing retinal diseases, optic nerve diseases, uveitis, media opacities which preclude OCT and fundus examinations. Refractive error of more than ±6 D sphere or ±3 D cylinder, or best corrected visual acuity worse than 6/12 to rule out amblyopia or macular disorders.

Material and methods

This non-interventional cross-sectional observational study was conducted at a tertiary care teaching hospital between September 2017 to January 2019 on patients taking HCQ for more than one year for non-ocular conditions.

The study sample patients were selected from Rheumatology and Dermatology OPD of a tertiary care center, who were on HCQ dose for non-ocular indications.

The following parameters were measured in both eyes:

- BCVA with refraction, IOP, anterior segment examination using slit lamp biomicroscopy, general fundus examination using direct ophthalmoscope, indirect ophthalmoscope, +90D/78D examination and macular function tests including Amsler grid.
- Methods for OCT recording: SD-OCT was performed with Cirrhus HD-OCT (Carl Zeiss Meditech, Dublin, Calif, software ver. 3.0) and macular cube 512 x 128 protocol. The scans were repeated twice to ascertain higher signal strength and minimize the segmentation error and centration error. Ellipsoid layer and photoreceptor cell layer as analyzed on SD-OCT for presence of IS-OS abnormalities such as IS-OS disruption, IS-OS irregularities, and findings suggestive of very early HCQ retinopathy such as loss of ELM loss. Central subfield macular thickness (CMT in micrometers) indicating the foveal thickness was also documented. Presence or absence of IS-OS abnormalities was taken as the structural parameter to determine the presence or absence of HCQ retinopathy. Central subfield macular thickness was also noted to rule out central macular disorders.

Method of VFA 30–2 recording

VFA central 30–2 threshold test was carried out using Humphrey Field Analyzer 3 with SITA Standard strategy, white on white with background illumination 31.5 apostibls, stimulus size Goldmann III. The test was carried out with best corrected near vison correction, on mesopic pupil in a semi-dark room and repeated twice to maximize reliability indices. Even an isolated point of reduced sensitivity within 2–10° is considered suggestive of macular function abnormality. Scotomas in central 2–6° (sparing central 2°) are congruous with parafoveal and scotomas around 10° are congruous with perifoveal damage.

Other desirable tests such as fundus autofluorescence, mf-ERG were not included in the study.

Diagnosis of HCQ retinopathy

HCQ retinopathy (HCQ maculopathy) was diagnosed in cases where, at least 1 subjective (VFA 30-2 done twice) and 1 objective test (SD-OCT) is abnormal, and their findings are congruous. If only 1 of the subjective (VFA 30–2, carried out twice) or objective tests was abnormal or their findings were incongruous, such cases were labeled as – possible HCQ retinopathy and further evaluation was advised (including mfERG and wide-field OCT).

Results

This cross-sectional observational study included 334 eyes of 167 patients on systemic HCQ. The prevalence of HCQ

related structural macular defects based on SD-OCT findings and VFA-30-2 was measured using chi-square test. The statistical analysis was performed on SPSS statistical software. P-value less than 0.05 was considered statistically significant.

The study population was heterogenous based on age and gender, 85 males and 82 females with 4 were 30 years or less, 21 were 31–40 years, 60 were 41–50 years, 63 were 51–60 years, and 19 were more than 61 years in age (Chart 1).

Sixty-five had rheumatoid arthritis, 29 had ankylosing spondylosis, 26 had psoriasis, 18 had seronegative arthritis, 11 had SLE, 10 had scleroderma, 3 had discoid lupus, 2 had granuloma inguinale, 1 had granuloma faciale, and 1 had SLE with rheumatoid arthritis (Chart 2).

Based on duration, 110 patients were taking HCQ for five years or less, 52 were taking for 5–10 years, 5 were taking for more than 10 years. Based on daily dosing, 147 patients were taking 5 mg/kg/day or less HCQ, 20 were taking 5–10 mg/kg/day (Table 1).

SD-OCT detected normal macular morphology in 163 patients, ELM loss in 1 patient, parafoveal IS-OS disruption in 2 patients (Fig. 1), perifoveal IS-OS disruption in 1 patient (Fig. 2). Total 4 of 167 patients (2.4%) showed structural defects related to HCQ (Table 2). On VFA 30–2, of 167 patients, 159 (95.2%) patients did not have any features suggestive of HCQ retinopathy, 8 (4.8%) patients had VFA based HCQ retinopathy (Table 3). Of 334 eyes of 167 patients, 9 eyes (one patient had visual field defect in both eyes) had visual field findings consistent with HCQ retinopathy.

As per study design, the patients on HCQ who had SD-OCT based structural defect in either or both eyes which were consistent with visual field defects in congruous field were labeled as 'definite retinopathy' and those who had either structural macular defect on SD-OCT or functional defect in

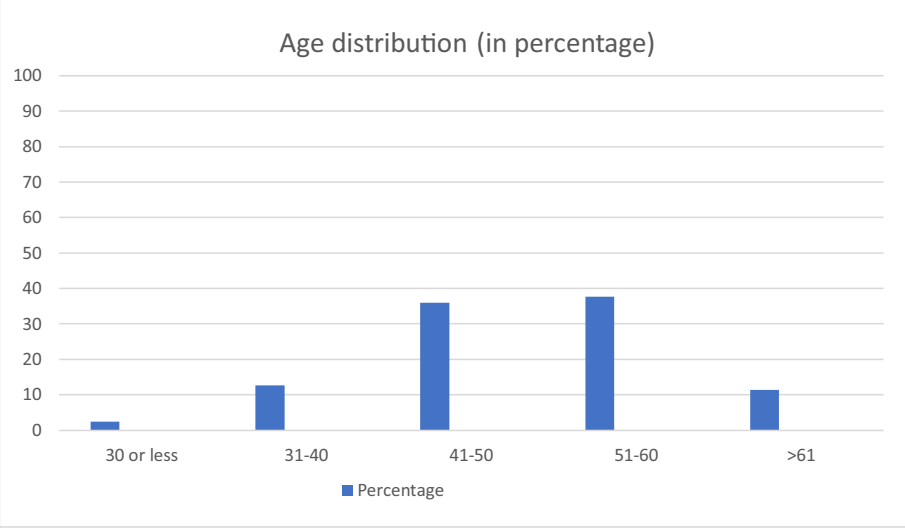

Chart 1 – Graph of age distribution of study population in percentage.

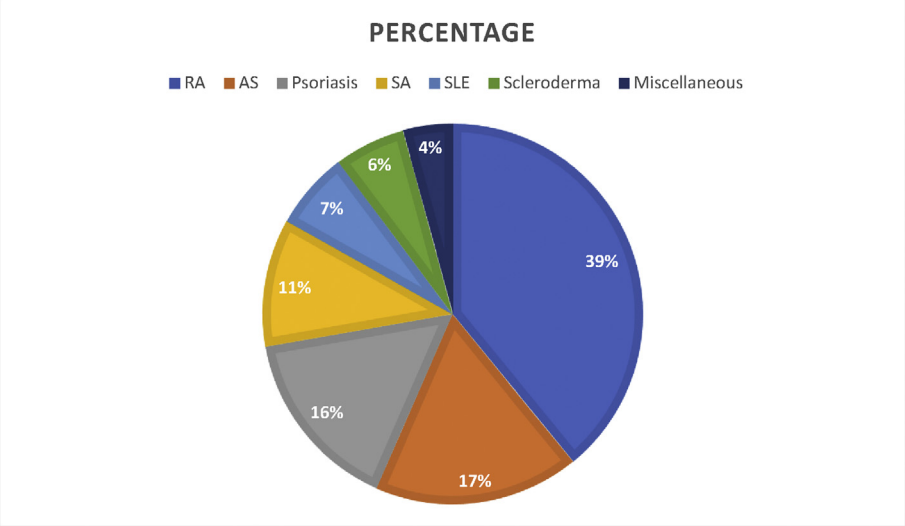

Chart 2 – Distribution of various diseases for which hydroxychloroquine is prescribed in study population.

Table 1 – Distribution of study population based on duration of therapy and daily dosing of hydroxychloroquine.

Duration in years	Number of patients	Percentage (%)
5 years or less	110	65.9
5–10 years	52	31.1
>10 years	5	3.0
Total	167	100.0
Daily dose (in mg/kg/day)	**Number of patients**	**Percentage (%)**
5 or less	147	88.0
5.01–10.00	20	12.0
Total	167	100.0

VFA 30–2 or both, but not congruous, were labeled as possible retinopathy'. Therefore, of 167 patients, 158 (94.6%) did not have any retinopathy, 3 (1.8%) had definite retinopathy (both SD-OCT and VFA abnormal and congruously so) and 6 (3.6%) had possible retinopathy (either SD-OCT or VFA was abnormal). SD-OCT alone was abnormal only in 4 cases (2.4%), and VFA alone was abnormal in 8 cases (4.8%).

The characteristics of use of HCQ based on duration, daily dosing and cumulative dose (Table 4) suggests that all 3 cases of IS-OS disruption were taking >5 mg/kg/day dose, with 2 of them for 5 years or more and 1 was of duration 1 year only in daily dose of 7.7 mg/kg. ELM loss was present at 4 years with daily dosing of 4 mg/kg/day.

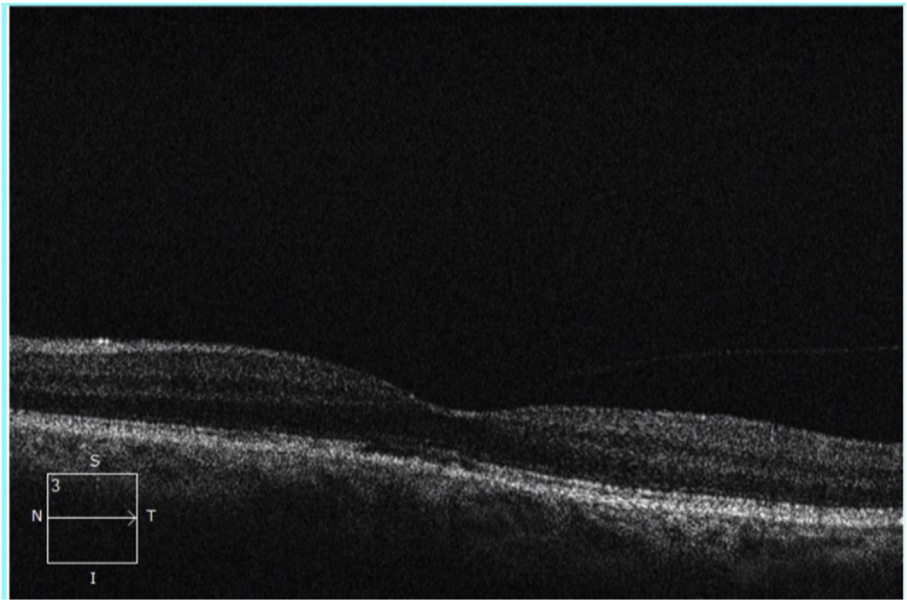

Fig. 1 – Parafoveal inner segment-outer segment (IS– OS) loss in SD-OCT of a patient on hydroxychloroquine. SD-OCT, spectral domain optical coherence tomography.

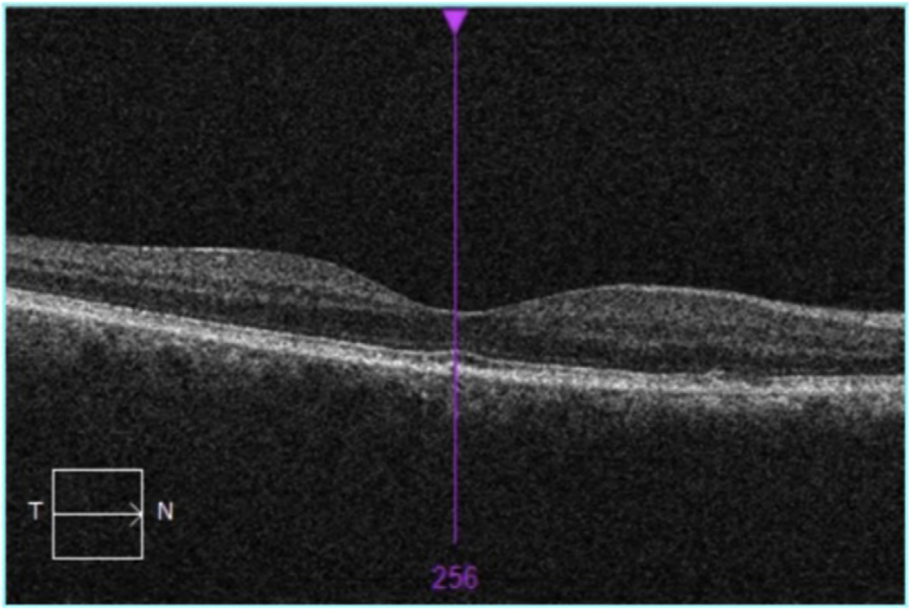

Fig. 2 – Perifoveal inner segment-outer segment (IS– OS) loss in SD-OCT of a patient on hydroxychloroquine. SD-OCT, spectral domain optical coherence tomography.

Table 2 – Distribution of SD-OCT findings in study population.

SD-OCT finding	Number of patients	Percentage (%)
Normal study	163	97.6
Abnormal	4	2.4
• External limiting membrane (ELM) loss	1	0.6
• Parafoveal inner segment-outer segment (IS-OS) disruption	2	1.2
• Perifoveal inner segment-outer segment (IS-OS) disruption	1	0.6
Total	167	100.0

SD-OCT, spectral domain optical coherence tomography.

Table 3 – Patient-wise distribution of VFA based findings consistent with hydroxychloroquine maculopathy.

VFA-based hydroxychloroquine retinopathy	Number of patients	Percentage (%)
Absent	159	95.2
Present	8	4.8
Total	167	100.0

VFA, visual field analysis.

Discussion

HCQ is one of the earliest immune-modulators developed and it has improved the quality of life of millions of patients suffering from autoimmune and connective tissue disorders. Recent recommendations of use of HCQ for treatment of cases and prophylaxis in COVID -19 contacts and involved health-care workers makes it imperative to revisit the dreaded irreversible adverse effect of the drug on central visual acuity due to maculopathy. The literature and clinical experience have proven without an iota doubt that exposure to systemic use of HCQ is a risk factor for toxic retinopathy, which is irreversible, and when advanced, can lead to permanent loss of central visual acuity. The screening for retinopathy will detect the earliest abnormalities associated with HCQ retinopathy and provide us with a fair idea about- 'if to stop', 'when to stop'. Various case series estimated that over 34–40% patients on HCQ are unscreened.

The most recently published 'Recommendations on screening for Chloroquine and HCQ Retinopathy (2016 Revision)' – American Academy of Ophthalmology statement and The Royal College of Ophthalmologists: Clinical Guidelines on 'Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on screening' (February 2018) are the latest revisions. The aim of this study was to detect the prevalence of SD-OCT and VFA-based detection of the prevalence of structural defects in macula following commencement of HCQ therapy as per American Academy of Ophthalmology screening guidelines.

The prevalence of HCQ retinopathy in this study was reported 2.4% with SD-OCT alone and 4.8% with VFA alone. However, when SD-OCT and VFA were combined, the prevalence of definite retinopathy was 1.8% and possible retinopathy was 3.6% making a total prevalence of 5.4% which is less compared to the prevalence of retinopathy which is 7.5% based on large population based studies.[2] This discrepancy can be possibly due to relatively small sample size of this study and the limitation of SD-OCT in detecting perifoveal and extrafoveal structural damage to macula which are more common in Asian population[2] which can be detected easily in a wide-field OCT or mf-ERG. The role of VFA 30–2 or 24–2 is valuable in detecting these defects in absence of SD-OCT findings and can be confirmed by other objective tests such as mf-ERG. Our study also found SD-OCT based macular defect in a case using HCQ at a dose 4 mg/kg/day and a case of definite retinopathy in duration of 1 year. Thus, a study with larger sample size or multicentric study is recommended to study the impact of dose and duration on prevalence of HCQ maculopathy in Indian population where a dose of 400 mg daily might often exceed recommended daily dose of less than 5 mg/kg/day.

Conclusion

SD-OCT is a valuable objective test for detection of early structural defects in HCQ screening but it alone may be insufficient to detect perifoveal and extrafoveal structural

Table 4 – Characteristics of patients with hydroxychloroquine retinopathy.

S. No	Retinopathy	Duration in years	Daily dose in mg/kg/day	Cumulative dose in grams	SD-OCT (IS-OS disruption)	VFA-30-2 scotoma
1	Definite	8	7.8	1168	Parafoveal RE	Paracentral RE
2	Definite	5	8.16	730	Parafoveal RE	Paracentral RE
3	Definite	1	7.7	146	Perifoveal RE	Peri-central RE
4	Possible	10	2.8	730	NAD	Peri-central BE
5	Possible	2	6.6	292	NAD	Peri-central LE
6	Possible	2	5.9	292	NAD	Peri-central RE
7	Possible	4.5	4	328.5	ELM loss, IS-OS disruption	NAD
8	Possible	5	6.8	730	NAD	Pericentral RE
9	Possible	3	4.1	219	NAD	Pericentral LE

VFA, visual field analysis; SD-OCT, spectral domain optical coherence tomography, NAD, no abnormality detected.

damage keeps it from remaining an exclusive screening tool for HCQ retinopathy and might contribute to underdiagnosis of this serious adverse effect in Indian population. VFA which establishes functional defect is complementary to SD-OCT for definite diagnosis but it is time-consuming, cumbersome, and at times unreliable. This study reflects the need of incorporating wide-field OCT or mf-ERG to detect objective changes in the screening protocol for Indian population, as the gap in the knowledge still exists about prevalence of parafoveal, perifoveal, and extrafoveal maculopathy among HCQ users.

Disclosure of competing interest

The author have none to declare.

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