Original Article

Assessing the Risk of Retinopathy in Indian Patients using Hydroxychloroquine for Rheumatic and Musculoskeletal Diseases: A Retrospective Observational Study

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Abstract

Background: To assess the prevalence and risk factors associated with hydroxychloroquine (HCQ) retinopathy in patients with rheumatic and musculoskeletal diseases (RMD).

Methods: Retrospective observational study was conducted on 984 patients using HCQ for RMD to detect prevalence of retinopathy by Humphrey visual field, spectral-domain optical coherence tomography, fundus autofluorescence test, and multifocal electroretinography (mfERG).

Results: The patients' age ranged between 13 and 79 years and 85.8% were female. The prevalence of retinopathy was 13.5% in cases treated with HCQ. It was significantly more in the higher age group (>60 years) compared to lower age (<30 years), P = 0.033, but not significantly associated with gender, body mass index, hypertension, diabetes mellitus, hypothyroidism, and various RMD. In addition, retinopathy was not significantly associated with HCQ dose/day (P = 0.101), but was significantly associated with duration of HCQ treatment (12.2% prevalence with < 5 years treatment, while 19.8% with 5–10 years HCQ use; P = 0.017). A statistically significant difference was found between median duration of patients with and without retinopathy (36 vs. 30 months; P = 0.046). The mean cumulative HCQ dose in retinopathy patients was significantly high compared to nonretinopathy patients (283.79 g vs. 231.33 g; P = 0.006). Among the individual (possible retinopathy) tests, mfERG had the highest detection rate (11.4%) for retinopathy screening, whereas Humphrey visual field analyzer test (HVF) + mfERG had the highest detection rate among the combination (definite retinopathy) tests (12.8%).

Conclusions: The high prevalence of retinal toxicity in patients with 1–5 years of HCQ therapy prompts the need for frequent ophthalmic screening, even before completion of 5 years of treatment.

Key Words: *Humans, hydroxychloroquine retinopathy and age, hydroxychloroquine retinopathy and cumulative dose, hydroxychloroquine retinopathy and duration, hydroxychloroquine, modern screening modalities, retinal diseases, retrospective studies, rheumatic and musculoskeletal diseases*

Introduction

Hydroxychloroquine (HCQ) is an anti-malarial drug with immunomodulatory properties. It has also shown benefits in treating rheumatic and musculoskeletal diseases (RMD) such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and scleroderma.[1] Its potential to act as a disease-modifying antirheumatic drug[2] in these immune-mediated diseases[3] can be explained by its inhibitory effect on several activities of the immune system such as antigen presentation, chemotaxis, and cell activation.[2] Majority of the patients with RMD like SLE often require long-term therapy. However, the risk of developing irreversible retinopathy and consequent vision loss is a possible serious complication with HCQ use.[3] HCQ increases the permeability of retinal pigment epithelium (RPE) disrupting the blood–retinal barrier

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contributing to retinopathy. However, visual function loss can occur before these biomicroscopic changes are evident in screening. The spectrum of retinal toxicity ranges from fine mottling to a typical bull's-eye presentation.[3]

Retinopathy is not reversible; furthermore, discontinuing the drug does not prevent progression of retinopathy. The American Academy of Ophthalmology (AAO) statement (2016 revision) affirms that all patients initiated on long-term HCQ therapy should have a baseline ophthalmologic examination within the 1st year of starting the drug and recommends annual screening only after 5 years of drug exposure in patients who are on acceptable doses of HCQ without major risk factors.[4] The 2019 update of the European League against Rheumatism recommendations for the management of SLE recommends HCQ in all patients at a dose not exceeding 5 mg/kg real body weight.[5]

Aims and objectives

This study was conducted with the objective of finding the prevalence of retinopathy among Indian patients by modern screening methods. In addition, this study further assessed whether patients with any particular RMD have an increased risk of retinal toxicity due to HCQ and the risk factors in these patients.

Materials and Methods

Design, setting, and participants

We conducted a retrospective observational study in the Department of Rheumatology, Yashoda Hospital, Secunderabad, among Indian patients who had used HCQ for various RMD. Case reports between July 2017 and March 2019 were systematically searched. The baseline characteristics of age, gender, body mass index (BMI), and comorbidities were noted. The ophthalmology tests were reviewed by the second author Samala V.

Inclusion criteria

Patients were included in the study if they had used HCQ for at least 1 year for any of the following RMD: SLE, RA, mixed connective tissue disease (MCTD), primary Sjogren's syndrome (pSS), systemic sclerosis, and others; their HVF analyzer report was available.

HCQ retinopathy was defined as presence of a single consistent abnormal test result (in case of HVF-repeated results) with normal findings in others (possible retinopathy) or presence of definite abnormalities in two tests (one subjective- and one objective-definite retinopathy).

Patients were prescribed HCQ as per their actual body weight (ABW). Institutional ethics committee approval was taken for collection of data and informed consent was taken from each patient.

Exclusion criteria

Retinopathies other than that due to HCQ were excluded. History of diabetes, hypertension, and other systemic diseases and medications was taken. Preliminary vision testing and refraction, intraocular pressure recording, and slit-lamp biomicroscopy were done to rule out any anterior segment anomalies followed by 90D fundus examination. Retinopathy secondary to diabetes, hypertension, age-related macular degeneration, glaucoma, and other maculopathies were excluded by fundoscopy. Optical coherence tomography (OCT), field analysis, and other investigations were done wherever necessary.

In the absence of reliable HVF findings, patients without either one of the following tests to diagnose retinopathy were excluded: spectral-domain optical coherence tomography test (SD-OCT), fundus autofluorescence test (FAF), and multifocal electroretinography test (mfERG).

Diagnostic tools

The details of the screening modalities used for the study are as follows:

- HVF
  - Humphrey field analyzer; Model 720i-manufactured by Carl Zeiss Meditec
  - 10-2, 24-2, and 30-2 field patterns were used in HVF. Abnormality was defined as the presence of reproducible central or paracentral scotomas within or beyond the macula[4]
  - Glaucomatous scotomas with optic nerve cupping with or without raised IOP were excluded.
- SD-OCT
  - PRIMUS 200; manufactured by Carl Zeiss Meditec
  - Abnormality was defined as presence of localized thinning of the photoreceptor layers in the parafovea or near the arcades.[4]
- FAF
  - o Manufactured by Topcon Europe Medical BV
  - o Abnormality was defined as an area of increased or decreased autofluorescence in the parafoveal or extramacular regions.[4]
- mfERG
  - Vision monitor mono 2012H Manufactured by metro vision
  - Abnormality was defined as the presence of parafoveal or extramacular depression in mfERG.[4]
- A complete eye examination including visual acuity, color vision, intraocular pressure, anterior segment evaluation, and fundus examination was done as a routine practice in all patients.

Statistical methods

In this study, statistical analysis was performed using 10.0 version of statistical software. Statistical Package for Social Science for Windows, Version 10.0. (Chicago, IL,USA) SPSS Inc.., Chicago.

- Descriptive analysis
  - Continuous variables were summarized using summary statistics (number of observations, mean, and standard deviation with range)
  - Categorical values were estimated using frequencies and percentages.
- Tests of significance
  - In this study, association between prevalence of retinopathy with variables such as RMD diagnosis, dosage of HCQ, and comorbidities such as hypertension and diabetes was analyzed using Chi-square test for categorical data and Student's *t*-test for continuous variables
  - All values were reported based on two-sided analysis and all the statistical tests results were considered significant at $P < 0.05$ (5% level of significance).

Results

Demographic characteristics

A total of 984 patients were included in the study. The range of age of the patients included was from 13.00 to 79.00 years. The demographic characteristics of the group are listed in Table 1.

Table 1: Demographical data

Parameters	Numbers (SD)
Number of cases	984
Average age (years)	45.03±13.32
Mean weight (kg)	61.74±11.91
Mean BMI (kg/m^2)	26.29±05.58
Sex (%)	
Male	140 (14.2)
Female	844 (85.8)
Comorbidities (%)	
HTN	178 (18.1)
DM	89 (09.0)
HYP	167 (17.0)
CKD	008 (00.8)
Liver disease	002 (00.2)
Average HCQS dose/day (mg)	210.77
Average duration of HCQ treatment (months)	38.58
RMD (%)	
RA	666 (67.5)
SLE	203 (20.6)
pSS	37 (3.8)
MCTD	36 (3.7)
Others including SSc, sarcoidosis, etc.	42 (4.4)

BMI: Body mass index; CKD: Chronic kidney disease; DM: Diabetes mellitus; HCQ: Hydroxychloroquine; HTN: Hypertension; HYP: Hypothyroidism; MCTD: Mixed connective tissue disease; pSS: Primary Sjogren's syndrome; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis, SD = Standard Deviation

Prevalence of hydroxychloroquine-related retinopathy

Out of 984 patients in our study, 133 had retinopathy. The prevalence was 13.5% by any one of the aforementioned screening modalities.

Assessment of risk factors

Association of age group and retinopathy

We analyzed the prevalence of retinopathy seen in various age groups. As age increased, the prevalence of retinopathy also increased and the difference was statistically significant [$P = 0.033$, Figure 1 and Table 2].

Association of gender with development of retinopathy

There was no significant association of gender with development of retinopathy in this study [Table 2].

Association of body mass index and retinopathy

We evaluated the number of patients developing retinopathy according to their BMI; however, the difference was statistically insignificant ($P = 0.289$) [Table 2].

Association of various comorbidities with development of retinopathy among hydroxychloroquine users

No significant association was found between comorbid hypertension, diabetes mellitus, hypothyroidism, chronic kidney disease (CKD), chronic liver disease, and development of retinopathy [Table 2].

Association between rheumatic and musculoskeletal diseases and development of retinopathy

We studied the proportion of patients developing retinopathy according to their underlying RMD. The prevalence of retinopathy in patients with MCTD, RA, SLE, pSS, and other RMD was 8.3%, 14.0%, 13.8%, 10.8%, and 11.9%, respectively, but the difference was statistically insignificant ($P = 0.865$).

Association of hydroxychloroquine dose with development of retinopathy

We examined the association of daily dose of HCQ on the development of retinopathy. There was no significant association between dose/day and development of

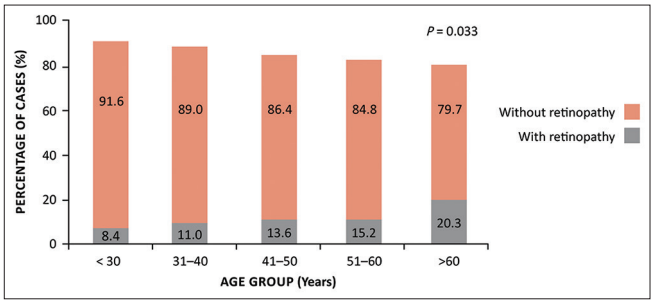

Figure 1: Association between age and retinopathy

retinopathy [Table 2]. On further analysis, the mean daily dose of HCQ among those who developed retinopathy (*n* = 133) was 210.53 ± 37.46 mg, which was comparable to 210.81 ± 32.55 mg among patients who did not develop retinopathy (*n* = 851).

We also examined the mean dose/day/kg body weight and no statistically significant difference was found between the retinopathy (3.41 ± 1.0 mg/kg) and nonretinopathy (3.56 ± 0.84 mg/kg) group (*P* = 0.101).

Table 2: Association of risk factors with development of retinopathy

Risk factor	With retinopathy *n* (%)	Without retinopathy *n* (%)	*P*
Age group (years)			
<30	13 (8.4)	141 (91.6)	0.033*
31-40	24 (11)	194 (89)	
41-50	36 (13.6)	228 (86.4)	
51-60	32 (15.2)	178 (84.8)	
Gender			
Male	14 (10)	126 (90)	0.189
Female	119 (14.1)	725 (85.9)	
BMI			
<18	3 (8.3)	33 (91.7)	0.289
18.0-22.9	26 (11.1)	208 (88.9)	
23.0-24.9	17 (11.9)	126 (88.1)	
>25	87 (15.2)	484 (84.8)	
HTN			
Yes	28 (15.7)	150 (84.3)	0.340
No	105 (13)	701 (87)	
DM			
Yes	13 (14.6)	76 (85.4)	0.752
No	120 (13.4)	775 (86.6)	
HYP			
Yes	23 (13.8)	144 (86.2)	0.915
No	110 (13.5)	707 (86.5)	
CKD			
Yes	2 (25)	6 (75)	-
No	131 (13.4)	845 (86.6)	
Liver disease			
Yes	-	2 (100)	-
No	982 (13.5)	849 (86.5)	
Dose/day (mg)			
200	122 (13.8)	763 (86.2)	0.171
300	8 (8.7)	84 (91.3)	
400	3 (42.9)	4 (57.1)	
Duration of treatment (years)			
1-5	103 (12.2)	739 (87.8)	0.017*
5-10	26 (19.8)	105 (80.2)	
>10	4 (36.4)	7 (63.6)	

*Chi-square test, significant. BMI: Body mass index; CKD: Chronic kidney disease; DM: Diabetes mellitus; HTN: Hypertension; HYP: Hypothyroidism

The mean cumulative dose among retinopathy cases was 283.79 g, which was significantly more as compared to 231.33 g among nonretinopathy cases (*P* = 0.006).

Duration of hydroxychloroquine treatment and development of retinopathy

The duration of HCQ use among patients who developed retinopathy ranged between 12 and 204 months (median = 36 months), whereas in the nonretinopathy group, the range was 12 to 108 months (median = 30 months); the difference was statistically significant (*P* = 0.046). A statistically significant association was found between duration of HCQ treatment (<5 years and 5–10 years) and development of retinopathy [Table 2].

Evaluating the ability of visual tests to detect hydroxychloroquine-related retinopathy

Vision (*n* = 984): The best-corrected visual acuity in 984 subjects was 6/6 (92.47%), 6/9 (3.65%), 6/12 (2.64%), 6/18 (1.12), and 6/24 (0.1%).

Fundoscopic findings (*n* = 984): Only 2.6% of patients had fundoscopic evidence of HCQ retinopathy. The findings include retinal pigment epithelial changes in 2.54% and bull's-eye retinopathy in 0.1% patients. The rest of patients had a normal fundus.

Comparing prevalence of retinopathy detected by subjective or objective tests (possible retinopathy).

The prevalence of retinopathy detected by different screening modalities is listed in Table 3. When considering tests in isolation, mfERG tests had the highest detection rate of retinopathy (11.4%) followed by HVF (10.8%).

HVF (*n* = 963; 21 unreliable) findings include reproducible central (6.43%) and paracentral (4.36%) nonglaucomatous scotomas. SD-OCT (*n* = 980) showed inner retinal layer thinning (1.84%), parafoveal thinning (1.32%), changes in inner/outer segment (*n* = 0.51%), and flying saucer sign (0.1%). mfERG (*n* = 525) findings include decreased

Table 3: Prevalence of retinopathy with tests

Screening modalities	Number of cases	Percentage of cases with retinopathy	
		Yes, *n* (%)	No, *n* (%)
HVF	963	104 (10.8)	859 (89.2)
SD-OCT	980	37 (3.8)	943 (96.2)
mfERG	525	60 (11.4)	465 (88.6)
FAF	522	8 (1.5)	514 (98.5)
HVF + SD-OCT	980	112 (11.4)	868 (88.6)
HVF+ mfERG	525	67 (12.8)	458 (87.2)
HVF + FAF	522	46 (8.8)	476 (91.2)

FAF: Fundus autofluorescence; HVF: Humphrey visual field; mfERG: Multifocal electroretinography; SD-OCT: Spectral-domain optical coherence tomography

amplitude (6.09%) and diminished waveforms (5.33%). FAF (*n* = 522) showed reduced fluorescence in 1.53% of patients. Fundus fluorescein angiography was also done in 519 subjects; all of which had normal findings.

Comparing prevalence of retinopathy detected by combination of tests (definite retinopathy)

The prevalence of retinopathy detected by the combination of HVF and mfERG was 12.8%. Similarly, a combination of HVF and SD-OCT could detect retinopathy in 11.4% of patients, whereas HVF and FAF could detect only 8.8% of such patients [Table 3].

Comparing prevalence of retinopathy detected by different Humphrey visual field patterns

The prevalence of retinopathy detected by 10-2 HVF pattern was 9.9%, which was significantly less as compared to prevalence detected by 24-2 (25.3%) and 30-2 (53.1%) patterns [Table 4]. Twenty-one patients with unreliable findings in HVF reports were excluded from this analysis.

Table 4: Prevalence of retinopathy as detected by different Humphrey visual field patterns

HVF results	Number of cases* (*n*=963)	Percentage of cases with retinopathy	
		Yes, *n* (%)	No, *n* (%)
10-2	836	83 (09.9)	753 (90.1)
24-2	95	24 (25.3)	71 (74.7)
30-2	32	17 (53.1)	15 (46.9)
P		0.000*	

*Chi-square test, significant. HVF: Humphrey visual field

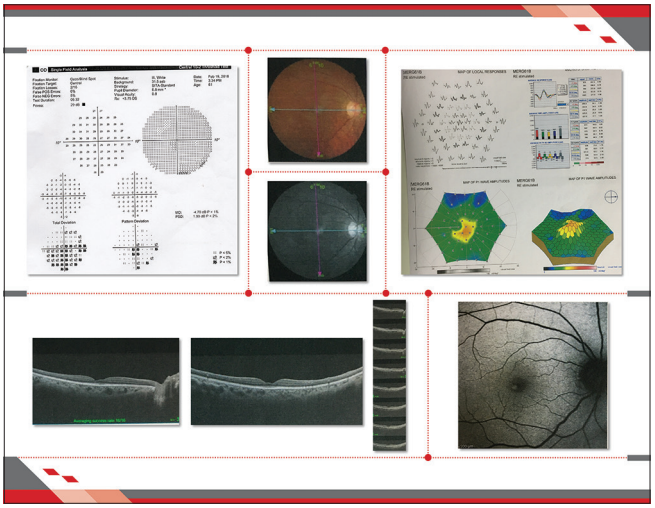

Figure 2: A 61-year-old female of systemic lupus erythematosus on hydroxychloroquine 200 mg/day for 120 months showing central scotomas in visual field (10-2), altered foveal contour, and early IS/OS junction changes in spectral-domain optical coherence tomography test, decreased amplitude in multifocal electroretinography, and increased autofluorescence inferotemporal to fovea in fundus autofluorescence (right eye), but fundoscopy is still normal

Discussion

The prevalence of retinopathy among 984 patients using HCQ for various RMD in this study was found to be 13.5%. The high prevalence of retinopathy in our study points to the unidentified burden of retinal toxicity in Indian patients using HCQ. Modern highly sensitive screening modalities have enabled detection of early signs of HCQ retinopathy, which has resulted in increased overall prevalence. In the largest retrospective analysis by Melles and Marmor, among 2361 patients who used HCQ for at least 5 years continuously, the prevalence of HCQ retinopathy was 7.5%. The prevalence rose to 20% with 20 years of therapy.[6] It is known that a pericentral pattern of HCQ retinopathy is common among patients of Asian origin rather than perifoveal.[7,8] In our study, we used wider HVF test patterns namely 24-2 and 30-2, which can possibly explain a higher pick-up rate of pericentral scotomas, which may be missed by routine10-2 pattern.

Interesting findings typical of HCQ retinopathy found in a 61-year-old female patient from our study are depicted in Figure 2. In this patient, all the modern screening tests showed abnormal findings, yet fundoscopy was normal. This highlights the importance of modern screening modalities for early diagnosis of HCQ retinopathy.

The objective changes of HCQ retinopathy often precede visual symptoms. In the early stages of this condition, patients are usually asymptomatic. In our study, only one patient who had bull's-eye retinopathy was symptomatic. Visual field testing is an important subjective method to screen patients for retinopathy. It is important to look for even subtle defects when performing visual field tests. Further, mfERG is the most sensitive test for detecting early changes of retinopathy.[9] In this study, mfERG was done in 525 patients. Among cases of possible retinopathy, mfERG had the highest detection rate (11.4%). HVF and mfERG could detect 12.8% of definite retinopathy cases. Various studies have concluded that mfERG is the most sensitive objective test to recognize early changes of retinopathy, with a good correlation to 10-2 visual field testing.[9,10] Three patients in our study for whom mfERG was repeated after 6 months demonstrated reversibility. This reversibility reiterates the significance of mfERG as a sensitive functional indicator for early retinal abnormalities induced by HCQ as well as changes observed after treatment withdrawal.[11,12]

The common risk factors for developing HCQ retinopathy as per recommendations on screening for chloroquine and HCQ retinopathy (2016 revision) by the AAO are high daily dose, long duration of use, and concomitant renal disease.[4] In our study group, only eight patients had comorbid CKD; hence, a significant association could not be drawn. Similarly, no association was found between daily dose- and HCQ-induced retinopathy; however, the duration of HCQ treatment positively correlated with the development of retinopathy.

Increased age was significantly associated with development of retinopathy in our study (P = 0.033). Various studies have similarly reported increasing age as a risk factor for the development of retinopathy. Espandar *et al*. found a similar association between advancing age and retinal toxicity (P = 0.006).[13] However, there are other studies which have demonstrated that retinal toxicity due to HCQ was unrelated to age.[14] The 2016 revision of AAO guidelines now consider age as a "lesser factor" as opposed to "major risk factor" in the 2011 version.[4,15]

There was no particular vulnerability of patients with any specific RMD to develop HCQ-related retinopathy. RA was the most common diagnosis in our study group (n = 666), followed by SLE (n = 203). The association between various RMD and retinopathy was statistically insignificant (0.865). In a recent study by Singh *et al*. who evaluated 2867 patients treated for RMD with HCQ, there was no association of specific RMD with development of vision loss.[16] There was no preponderance of patients with any particular RMD to develop retinal toxicity. Further, there was no association of comorbidities such as hypertension, diabetes mellitus, or hypothyroidism with retinopathy among HCQ users. An association between chronic liver disease and CKD with the development of retinopathy could not be analyzed due to an insufficient number of patients with these comorbidities.

The patients in our study were prescribed HCQ based on their ABW rather than ideal body weight. The latest AAO guidelines also recommend dosing based on ABW.[4] In our patients, there was no significant association between dose/day and development of retinopathy. There was no statistical difference in the mean dose/day/kg body weight in the retinopathy and nonretinopathy group. However, the mean cumulative dose of patients who developed retinopathy was significantly higher than those who did not (283.79 g vs. 231.33 g, P = 0.006). Espandar *et al*. also found a significant correlation of HCQ retinopathy with cumulative dose.[13]

Among patients treated with HCQ for less than 5 years, 12.2% developed retinopathy, whereas 19.8% of patients in the 5–10-year duration group had retinopathy, and the difference was statistically significant (P = 0.017). Further, an increasing trend toward the development of retinopathy was noted among patients using HCQ for 1–5 years; however, it was not found to be statistically significant. Furthermore, a statistically significant difference was noted in the median duration of HCQ treatment between patients who developed retinopathy and those who did not (36 vs. 30 months; P = 0.046). Espandar *et al*. also found a significant correlation of HCQ retinopathy with duration of use.[13] Although the AAO recommends annual screening in patients without major risk factors only after 5 years of HCQ use, the prevalence of retinopathy in patients using HCQ for 1–5 years was 12.2% even without presence of major risk factors. This highlights the need for ophthalmologic screening even before completion of 5 years of HCQ therapy. A recent study has seen good correlation of high blood HCQ level with retinopathy and can be used wherever available.[17] Finally, we need to be cautious when interpreting these modern screening methods lest we overdiagnose patients with retinopathy and stop important drug like HCQ.

Limitations

The retrospective nature of this study is a limitation because need for screening was decided on an individual basis. Further, only those patients with modern screening results available were included, which could have led to a selection bias. Further, this study was based in a single center and thus does not truly represent the entire Indian population.

Conclusions

This study highlights the unidentified burden of retinopathy in Indian patients using HCQ. The risk factors identified are increasing age, higher mean cumulative dose, and longer duration of treatment. Given the high prevalence of HCQ toxicity in Indian patients, we strongly recommend screening more frequently after baseline examination using wider test patterns.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ruberto G, Bruttini C, Tinelli C, Cavagna L, Bianchi A, Milano G. Early morpho-functional changes in patients treated with hydroxychloroquine: A prospective cohort study. Graefes Arch Clin Exp Ophthalmol 2018;256:2201-10.
2. Haładyj E, Sikora M, Felis-Giemza A, Olesinska M. Antimalarials – Are they effective and safe in rheumatic diseases? Reumatologia 2018;56:164-73.
3. Korthagen NM, Bastiaans J, van Meurs JC, van Bilsen K, van Hagen PM, Dik WA. Chloroquine and hydroxychloroquine increase retinal pigment epithelial layer permeability. J Biochem Mol Toxicol 2015;29:299-304.
4. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF, American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology 2016;123:1386-94.
5. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, *et al*. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78:736-45.
6. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol 2014;132:1453-60.
7. Lee DH, Melles RB, Joe SG, Lee JY, Kim JG, Lee CK, *et al*. Pericentral hydroxychloroquine retinopathy in Korean patients.

Ophthalmology 2015;122:1252-6.

8. Jorge A, Ung C, Young LH, Melles RB, Choi HK. Hydroxychloroquine retinopathy – Implications of research advances for rheumatology care. Nat Rev Rheumatol 2018;14:693-703.
9. Pandya HK, Robinson M, Mandal N, Shah VA. Hydroxychloroquine retinopathy: A review of imaging. Indian J Ophthalmol 2015;63:570-4.
10. Lai TY, Ngai JW, Chan WM, Lam DS. Visual field and multifocal electroretinography and their correlations in patients on hydroxychloroquine therapy. Doc Ophthalmol 2006;112:177-87.
11. Moschos MM, Nitoda E, Chatziralli IP, Gatzioufas Z, Koutsandrea C, Kitsos G. Assessment of hydroxychloroquine maculopathy after cessation of treatment: An optical coherence tomography and multifocal electroretinography study. Drug Des Devel Ther 2015;9:2993-9.
12. Kellner U, Renner AB, Tillack H. Fundus autofluorescence and mfERG for early detection of retinal alterations in patients using chloroquine/hydroxychloroquine. Invest Ophthalmol Vis Sci 2006;47:3531-8.
13. Espandar G, Moghimi J, Ghorbani R, Pourazizi M, Seiri MA, Khosravi S. Retinal toxicity in patients treated with hydroxychloroquine: A cross-sectional study. Med Hypothesis Discov Innov Ophthalmol 2016;5:41-6.
14. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2010;62:775-84.
15. Yusuf IH, Sharma S, Luqmani R, Shah VA. Hydroxychloroquine retinopathy. Eye (Lond) 2017;31:828-45.
16. Singh DK, Muhieddine L, Einstadter D, Ballou S. Incidence of blindness in a population of rheumatic patients treated with hydroxychloroquine. Rheumatol Adv Pract 2019;3:rkz009.
17. Petri M, Elkhalifa M, Li J, Magder LS, Goldman DW. Hydroxychloroquine blood levels predict hydroxychloroquine retinopathy. Arthritis Rheumatol 2020;72:448-53.