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Original Article/นิพนธ์ต้นฉบับ

Patterns of Hydroxychloroquine and Chloroquine Retinopathy in Thai Patients

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Abstract

Purpose: To evaluate patterns of Hydroxychloroquine (HCQ) and Chloroquine (CQ) retinopathy in Thai patients.

Methods: Retrospective observational study. We reviewed the medical records of patients taking HCQ and CQ who visited ophthalmology department at Ramathibodi Hospital for retinopathy screening during 1st January 2016 to 31st December 2016. The baseline characteristics and imaging tests consisting of spectral domain optical coherence tomography (SD-OCT), computed tomography visual fields (CTVF), and fundus autofluorescence (FAF) were reviewed for evidence of drug-induced retinopathy. Retinopathy patterns were classified as parafoveal (retinal changes within 2-7 degrees from fovea or within central 2.5mm), perifoveal (retinal changes> 8 degrees from fovea), and combined (retinal changes in both parafoveal and perifoveal area).

Results: Among 933 patients screened in 2016, 2.59% (20 of 773) and 20.63% (33 of 160) were diagnosed with toxicity in HCQ and CQ group, respectively. Of total 20 patients with HCQ retinopathy, 70% (14 of 20) had typical parafoveal pattern, and 30% (6 of 20) had perifoveal pattern. Of 33 patients with CQ

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retinopathy, 6 patients with Bull's eye retinopathy were excluded due to advanced lesion, 81.48% (22 of 27) had parafoveal pattern, 11.11% (3 of 27) had perifoveal pattern, and 7.41% (2 of 27) had combined pattern. We also noticed that patients with perifoveal pattern, though were the minority, were often delayed diagnosed due to previously unrecognized pattern of retinal damage.

Conclusions: Parafoveal pattern was predominant among Thai patients in both HCQ and CQ group. Perifoveal pattern was more prevalent in HCQ than CQ group. Appropriate screening exam with wide-angle image would help in early detection of perifoveal retinopathy.

Introduction

Hydroxychloroquine (HCQ) and chloroquine (CQ) have been effective drugs for treating autoimmune diseases such as Rheumatoid arthritis (RA), Systemic Lupus Erythematosus (SLE), and other skin related autoimmune diseases.[1,2] Drug-induced macular toxicity is their well-known side effect and the most important risk factors for toxicity are excessive daily dose (HCQ>5.0 mg/kg real weight and CQ>2.3 mg/kg real weight), renal disease, concomitant Tamoxifen use, and macular disease.[1,2] The retinopathy can progress from mild disruption of outer layer and RPE with ring scotoma in visual field test to end stage Bull's eye maculopathy, even EMM and CME after drug cessation.[1,3] Thus, it is important to detect the toxicity early enough to prevent extensive damage to photoreceptors and RPE.[3,4]

It has been well established that visible lesions in clinical fundus examination represent late stage of the retinopathy.[2] Multiple screening procedures including SD-OCT, CTVF, FAF, and multifocal ERG (mf-ERG) provide early and correct diagnosis of toxicity. [2,4] Although the classic parafoveal pattern (retinal changes within 2-7 degrees from fovea) was the most common appearance of HCQ and CQ retinopathy. [2,5] According to recent studies, perifoveal pattern (lesion further than 8 degrees from fovea) was recently found to be particularly frequent in Asian patients in the US and South Korea. [2,5,6] Therefore, AAO screening guideline in 2016 [2] recommended screening tests with wider than central 10 degrees field for Asian patients. [2]

Currently, there has not been reports about patterns of HCQ and CQ retinopathy in Thai patients. This study aimed to evaluate patterns of HCQ and CQ retinopathy in Thai patients.

Subjects and Methods

This retrospective observational study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by Center of Ethical Reinforcement for Human Research, Mahidol University. The inclusion criteria involved patients who took HCQ or CQ and visited ophthalmology department at Ramathibodi Hospital for retinopathy screening during 1st January 2016 to 31st December 2016. There were 2,134 patients included. The medical records and imaging studies were reviewed separately.

Patients with optic neuropathy or maculopathy that can interfere with the imaging findings were excluded. Patients with diabetic macula edema, glaucoma, age-related macular degenerations, macular scar from previous inflammation, and history of optic neuropathy were excluded. Patients who came for baseline screening before starting the medicine in 2016 were also excluded.

The medical records were reviewed for baseline characteristics and risk factors associated with toxicity [2,7] including age, gender, body weight, primary indications (SLE, RA, others), drug daily dose (mg/kg/day) , drug duration (months) and cumulative dose (g).

Drug duration was counted from the 1st day of recorded drug prescription to the day of retinopathy diagnosis at ophthalmology department (regardless of patients' actual drug cessation). And cumulative dosage was the summation of the drug used during drug duration.

The imaging studies comprised of spectral domain optical coherence tomography (SD-OCT) by Heidelberg Engineering, computed tomography visual fields (CTVF) by Humphrey perimeter; Carl Zeiss Meditec Inc), and fundus autofluorescence (FAF) by Heidelberg engineering for evidence of drug-induced retinopathy. The imaging findings that were interpreted as positive were

1. Disruption of photoreceptor, ellipsoid layer, or RPE layer in SD-OCT
2. Ring/partial ring scotoma in CTVF
3. Hyperfluorescence or hypofluorescence at parafoveal/ perifoveal area in FAF

The diagnosis of drug-related retinopathy was made when there were at least 2 out of 3 positive corresponding imaging studies. Retinopathy patterns were classified as parafoveal (retinal changes within 2-7 degrees from fovea or within central 2.5mm), perifoveal (retinal changes> 8 degrees from fovea), and combined pattern (retinal changes in both parafoveal and perifoveal area with normal retina in between). Bull's eye maculopathy, which was visible by clinical fundus examination, was defined as extensive ring area of macular change without normal retina between parafoveal and perifoveal area.

We reviewed the OCT macula, and FAF results (both were accessible from the same program) prior to the CTVF. Patients without both OCT and FAF were excluded. Because without 2 out of 3 tests, the diagnosis of toxicity could not be made, according to mentioned criteria above. Raster scan OCT images of both eyes and every visit in the past were reviewed by the researchers. Hospital numbers of patients with suspected structural damages were noted and later used to look for CTVF results. Cases with uncertain diagnosis were consulted with our retina specialist staff.

Comparisons between groups of different patterns in each drug were performed using the independent t-test for continuous measures and Fisher exact test for categoric measure. Drug duration were compared using Mann-Whitney U test in HCQ group, and Kruskal-Wallis test in CQ groups.

Results

There were 2,134 patients who visited ophthalmology department at Ramathibodi Hospital for HCQ and CQ retinopathy screening

in 2016. There were 1897 females and 237 males. Age of the patients were between 19-76 years (average 54.2 years). The drug duration was between 1-133.5 months. One thousand, two hundred, and one patient were excluded. They consisted of 967 patients with no OCT macula or FAF, 148 with first-time baseline screening investigation in 2016, 80 with other macular diseases (wet age-related macular degeneration, epiretinal membrane, diabetic macular edema, and central serous chorioretinopathy), 6 with glaucoma and optic neuropathy. Among 933 patients who met with the criteria, 773 patients used HCQ, and 160 patients used CQ.

We noticed that only 54.69% of the patients screened for retinopathy at Ramathibodi hospital in 2016 were tested with OCT macula (Figure 1) or FAF (Figure 2). There were 17 in 53 patients (32%) with retinopathy who tested positive for all 3 imaging studies. Thirty-three patients (62%) were diagnosed with 2 tests consisting of OCT and CTVF. And 3 patients were diagnosed with FAF and CTVF.

The prevalence of retinal toxicity in HCQ and CQ group were 2.59% (20 of 773) and 20.63% (33 of 160), respectively. Of total 20 patients with HCQ retinopathy, 70% (14 of 20) had typical parafoveal pattern, and 30% (6 of 20) had perifoveal pattern.

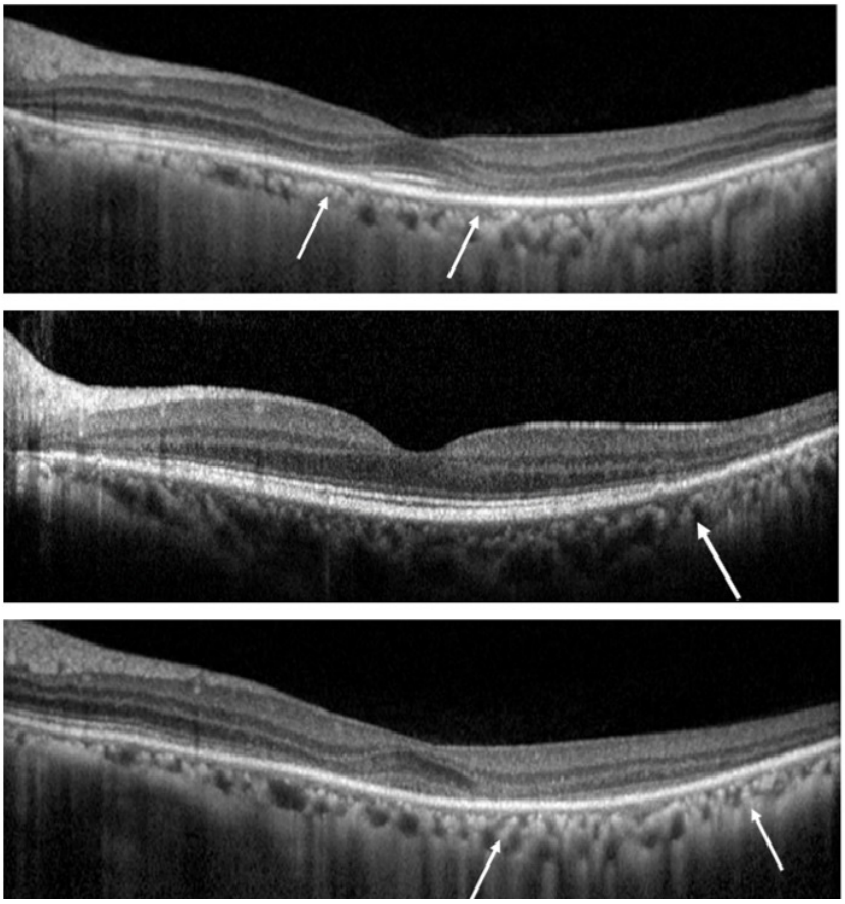

Figure 1 SD-OCT images showing loss of ellipsoid layer in the parafoveal (top), perifoveal (middle), and combined pattern (bottom)

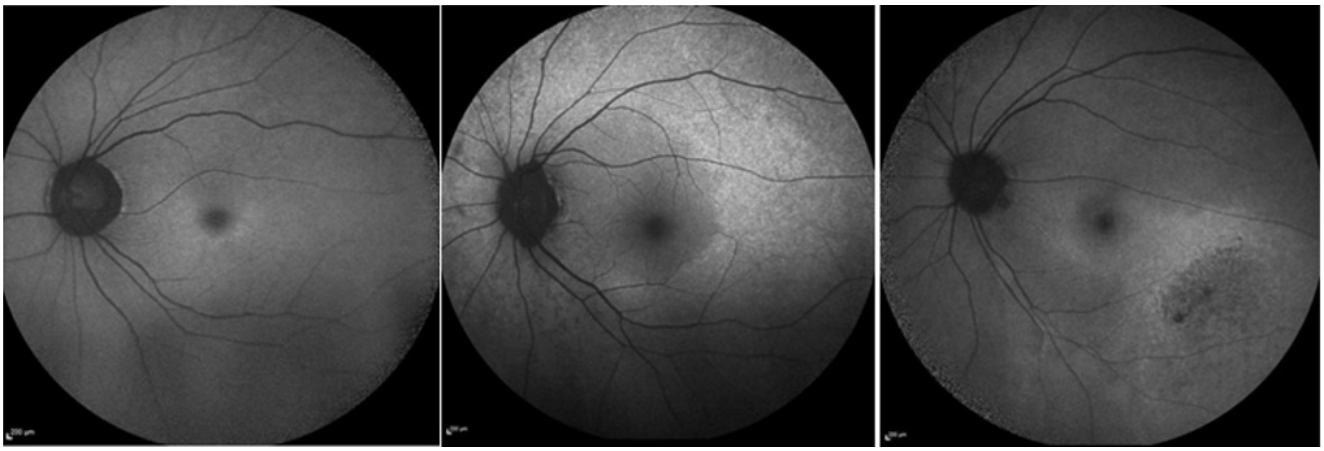

Figure 2 FAF images showing abnormal circumferential hyperfluorescence ring lesions in the parafoveal (left), perifoveal (middle), and combined pattern (right)

(as Figure 1) We did not find patients with combined pattern or Bull's eye retinopathy in HCQ group. Patients with Bull's eye retinopathy in CQ group (6 of 33) were excluded from patterns calculation due to advanced stage of damage precluding previous classified pattern. In CQ group, 81.48% (22 of 27) had parafoveal pattern, 11.11% (3 of 27) had perifoveal pattern, and 7.41% (2 of 27) had combined pattern. (as Table 1, Figure 3)

Parafoveal pattern was more common than perifoveal or combined pattern in both HCQ and CQ groups. Bull's eye retinopathy is found only in CQ but not in HCQ group in this study.

Table 1 Number of patients with different patterns of toxicity in HCQ and CQ groups

Patterns	HCQ	CQ	total
Parafoveal	14	22	36
Perifoveal	6	3	9
Combined	0	2	2
Bull's eye	0	6	6
Total	**20**	**33**	**53**

The difference of baseline characteristics (including; age, sex, primary diagnosis, drug dosage, cumulative doses and drug duration) were not statistically significant in patients taking either HCQ

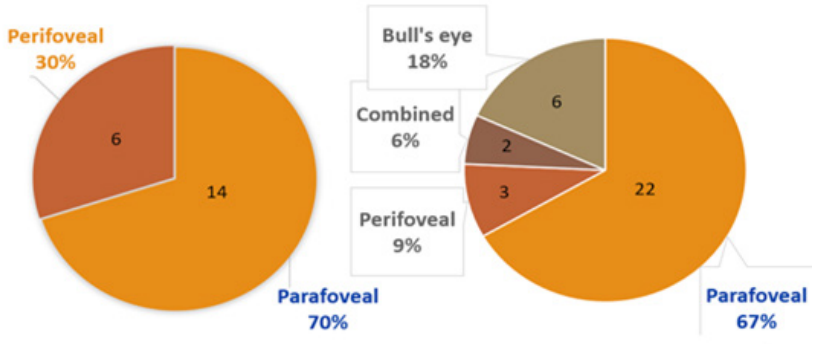

Figure 3 Proportion of patients with different patterns of toxicity in HCQ group (left) Proportion of patients with different patterns of toxicity in CQ group (right)

or CQ. In HCQ patients, mean daily doses are 2.94 and 3.06 mg/kg/day in parafoveal and perifoveal group, respectively. All patients were using drugs at daily dosage below 5mg/kg/day. (Table 2) In CQ patients, daily doses are 3.89, 2.88, 4.08 mg/kg/day in parafoveal, perifoveal, and combined groups, respectively. Almost all of the patients received more than 2.3 mg/kg/day. (Table 3)

The earliest time to presentation of HCQ and CQ toxicity were 6, 10.8, and 46 months, for parafoveal, perifoveal, and combined pattern, respectively. The majority of both HCQ and CQ patients developed retinopathy within 5 years of drug usage. HCQ median duration seemed to

Table 2 Baseline characteristics of the patients with HCQ toxicity (n= 20 cases)

Risks	Parafoveal	perifoveal	P value
Age (yrs)	58.07 (± 12.09)	47.17 (± 14.39)	0.09
Sex: female	13/14 (92.86%)	6/6 (100%)	
Autoimmune diseases:			
- SLE	7 (50%)	3 (50%)	
- Rheumatoid	7 (50%)	1 (16.67%)	
- others	0	2 (33.33%)	
Kidney disease	1/14 (7.14%)	2/6 (33.33%)	
HCQ daily dose (mg/kg/day)	2.94 (± 1.22)	3.06 (± 1.15)	0.84
Duration of HCQ use (months) (median)	20.8 (± 25.80)	43.8 (± 19.84)	0.18
HCQ cumulative dose (g)	150.35 (± 163.40)	204.89 (± 114.69)	0.47
Duration > 5 years	2/14 (1.43%)	1/6 (16.67%)	
Daily dose > 5mg/kg/day	0	0	

Table 3 Baseline characteristics of the patients with CQ toxicity (n= 27 cases)

Risks	Parafoveal	perifoveal	Combined	P value
Age (yrs)	53.82 (± 10.65)	53.33 (± 8.15)	53.50 (± 3.54)	0.99
Sex: female	20/22 (91%)	3/3 (100%)	2/2 (100%)	
Autoimmune diseases:				
- SLE	6 (27.27%)	2 (66.67%)	2 (100%)	
- Rheumatoid	10 (45.45%)	1 (33.33%)	0	
- others	6 (27.27%)	0	0	
CQ daily dose (mg/kg/day)	3.89 (± 1.07)	2.88 (± 1.27)	4.08 (± 1.17)	0.32
Duration of CQ use (months) (median)	48.0 (± 67.05)	133.60 (± 52.17)	49.60 (± 4.53)	0.47
CQ cumulative dose (g)	453.22 (± 460.11)	599.77 (± 466.26)	372.00 (± 33.94)	0.83
Duration >5years	6/22 (27.27%)	2/3 (66.67%)	0/2	
Daily dose >2.3 mg/kg/day	20/22 (90.90%)	2/3 (66.67%)	2/2 (100%)	

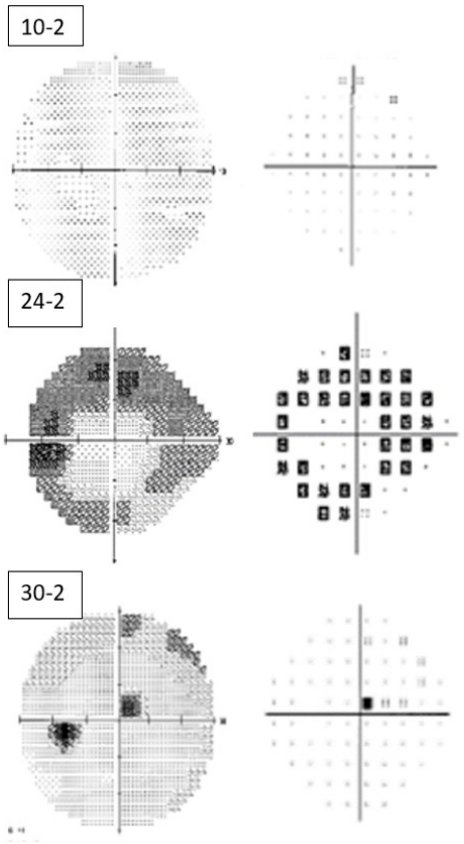

Figure 4 Automated visual field: 3a(left) paracentral ring scotoma in CTVF 24-2 in patient with perifoveal pattern and 3b(right) normal appearance of CTVF 10-2 in the same patient

be longer in perifoveal group (43.8 months) than in parafoveal group (20.8 months) (p= 0.18). CQ median duration were also longer in perifoveal group (133.60 months) compared to parafoveal (48 months) and combined group (49.6 months), though not statistically significant (p=0.47).

We noticed that the diagnosis in perifoveal pattern were delayed in most of the patients. Overall, 6 out of 9 patients with perifoveal pattern already had evidence of perifoveal ellipsoid layer loss in OCT macula at least a few years before the year of diagnosis by the researchers. While a ring scotoma was apparent in CTVF 24-2 in these patients, CTVF 10-2 mostly showed some mild peripheral losses. Two patients even presented with a normal CTVF 10-2. (Figure 4)

Discussion

In the US, the incidence for HCQ toxicity is less than 1% in the first 5 years of therapy, less than 2% up to 10 years, and increases to approximately 20% after 20 years. The most important risk factor for toxicity appeared to be excessive daily dose (HCQ>5.0 mg/kg real weight and CQ>2.3 mg/kg real weight), renal disease, concomitant Tamoxifen use, and macular disease.[2] It has been established that the prevalence of HCQ maculopathy was much lower than CQ.[2]

Lee DH et al performed a retrospective study in 218 South Korean patients who used HCQ and visited the department for eye screening in 2011 to 2014. They found that 9 in 218 (4.1%) were diagnosed with toxicity.[6]

A previous retrospective study from Ramathibodi hospital, Thailand, Puavilai et al. reviewed record of patients receiving CQ during 1987–1997. They found 22 of 155 patients (14.2%) developed retinopathy. There were no correlations between corneal deposits or retinopathy and age, sex, duration of treatment, or cumulative dose of CQ. According to the study, the retinopathy can be detected as early as 9 months after starting CQ therapy.[7]

In Thailand Leecharoen S. et al reviewed medical records of patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and scleroderma (Scl), who received CQ for their treatment, at the Division of Rheumatology,

Faculty of Medicine, Chiang Mai University between 1 January 1992 and 31 August 2005. The found 37 of 139 patients (26.61%) had retinopathy.[8]

Another study at Siriraj hospital by Chiowchanwisawakit P. et al reported the prevalence of CQ retinopathy among rheumatoid patients taking CQ for at least 6 months during 2010-2011 to be 13.5% .[9] The also reported that age > 60 years, duration of CQ usage > 5 years and current CQ dose ≥2.5 mg/kg ideal body weight/ day were the risk factors for CQ retinopathy.[9]

N. Tangtavorn et al reported the prevalence of HCQ and CQ retinopathy to be 3.24% and 8.09%, accordingly, over 10 years. [10] They also found that retinopathy in Thai patients usually develop before 5 years duration of drug usage, and the damage could be detected as early as 6 months and also with a lower cumulative dose. [10] Fixed manufactured doses and lower body weight may contribute to the higher incidence in Asians.[2,6,10]

In this study, the HCQ retinopathy prevalence was 2.59% which was similar to previous studies in Thailand, and South Korea. [6,10] The CQ prevalence was 20.63%, higher than HCQ group and varied in previous studies.[8,9,10]

Despite the dosage of more than 5mg/kg/day being one of the known risk factors for developing HCQ retinopathy according to AAO 2016[2], none of the HCQ patients with retinopathy in this study were daily overdosed. On the contrary, almost all of the CQ patients with retinopathy in this study received dosage exceeding recommended 2.3 mg/kg/day. Higher prevalence of toxicity in CQ was maybe due to the different nature in drugs deposition at RPE and fixed manufactured doses (200mg/tab for HCQ and 250mg /tab for CQ).[2,10] CQ was also more primitive than HCQ and was prescribed mainly in the era while multi model imaging such as OCT macula, FAF, or multifocal ERG were not available.[9] The time of diagnosis was also detected at later stage of diseases. As we found Bull's eye in 6 patients of CQ group but none in HCQ group.

In 2015, Melles and Marmor have found that other than classic parafoveal pattern of HCQ retinopathy, perifoveal and mixed pattern were found more commonly in Asians than in Caucasians in the US.[2,5] In the study by Lee DH et al in South Korea, 9 in 218 were diagnosed with HCQ retinopathy and perifoveal was even predominant; 8 patients had perifoveal pattern toxicity while only 1 had classic parafoveal pattern.[6] Thus, they recommended that screening protocols for Asian patients involve wide-field examinations.[2,5,6]

In this study, parafoveal was the predominant pattern among Thai patients in both HCQ and CQ groups. Perifoveal pattern was found in higher proportion of 30% in HCQ group than 9% in CQ groups. The difference of baseline characteristics: age, sex, primary indications between parafoveal and perifoveal patients are not statistically significant in both HCQ and CQ groups.

Duration and cumulative dose seemed to be longer and higher in perifoveal pattern, though not statistically significant. Furthermore, we noticed that the diagnosis in perifoveal pattern were delayed for at least a few years in most of the patients. We suspected that because the pattern

in OCT was not expected, and the initial CTVF10-2 appeared normal, patients were followed until OCT showed more apparent damage and CTVF 24-2 or 30-2 were performed. Screening exam with wide-angle image and regard for the potential of perifoveal pattern would help in early detection.

Researchers have found CTVF (subjective test) to be more sensitive with less specificity than OCT macula (objective test).[2,11,12] FAF can show early retinal changes preceding damage in OCT, thus, help detect perifoveal pattern.[2] Multifocal electroretinography (mf ERG) is similar in sensitivity to visual fields and provides objective detection of decreased sensitivity in the macula.[2] However, mf ERG requires experience in interpreting and is available only in large clinical centers. In 2014, David J Browning and Chong Lee, reported that all 3 tests (SD-OCT, 10-2VF, and mf ERG) are most useful when all are negative and help rule out retinopathy especially in overdosed cases (negative predictive values were >99%).[12]

At Ramathibodi hospital, CTVF, OCT macula, and FAF are readily available. Only small number of patients were testes with mf ERG. This study found that CTVF is the most common test used for screening drug related retinopathy. However, only 54.69% of the patients screened for retinopathy were tested with OCT macula and/or FAF. This reflected that our screening program can be improved by using both subjective and objective tests.

Considering that CTVF 10-2 might not cover lesions for perifoveal area, CTVF 24-2 or 30-2 would be more appropriate in cases with perifoveal pattern. However, we need to be aware that CTVF24-2 or 30-2 provides decreased sensitivity per spot-to-spot distance compared to CTVF10-2 test. A single point scotoma in these tests may be very significant.[12]

In conclusion, classic parafoveal pattern was more prevalent than perifoveal or combined pattern among Thai patients in both HCQ and CQ group. Perifoveal pattern was more common in HCQ than CQ group and was often delayed in diagnosis. Thai patients usually develop retinopathy earlier than 5 years of drug duration. Using combinations of appropriate screening exams with wide-angle image (CTVF of at least 24-2, OCT, and FAF of at least 30 degrees) would help in early detection of retinopathy. And it is important that examiners can recognize the different patterns of defects shown on CTVF tests.

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