Fundus auto fluorescence and spectral domain ocular coherence tomography in the early detection of chloroquine retinopathy

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Purpose: To determine the sensitivity of spectral domain ocular coherence tomography (SD-OCT) and fundus auto fluorescence (FAF) images as a screening test to detect early changes in the retina prior to the onset of chloroquine retinopathy.

Method: The study was conducted using patients taking chloroquine (CQ), referred by the Rheumatology Department to the Ophthalmology Department at Tygerberg Academic Hospital. Group A consisted of 59 patients on CQ for less than 5 years, and Group B consisted of 53 patients on CQ for more than 5 years. A 200 × 200 macula thickness map, 5-line raster SD-OCT on a Carl Zeiss Meditec Cirrus HD-OCT and FAF images on a Carl Zeiss Meditec Visucam 500 were recorded for 223 eyes. Images were reviewed independently, and then those of Groups A and B compared.

Results: There were no statistically significant differences between Groups A and B. The criteria included the internal limiting membrane and the retinal pigment epithelium (ILM-RPE) thickness, interdigitation zone integrity ($p = 0.891$, $df = 1$, $\chi^2 = 0.1876$), ellipsoid zone integrity ($p = 0.095$, $df = 2$, $\chi^2 = 4.699$) and FAF image irregularities ($p = 0.479$, $df = 1$, $\chi^2 = 4995978$).

Conclusion: The inclusion of SD-OCT and FAF as objective tests into the prescribed screening guidelines does not appear to simplify the detection of subclinical injury in patients on chloroquine treatment.

Introduction

Antimalarials such as chloroquine (CQ) and hydroxychloroquine (HCQ) have been used to treat rheumatoid illnesses since the 1950s. Both these agents are thought to cause ocular toxicity.[1,2,3] It has been shown that HCQ has a lower incidence of toxic retinopathy than CQ.[4] However, a retrospective case control study using 2361 patients showed a prevalence of toxicity in 7.5% of patients taking HCQ for ≥ 5 years.[5]

The safe daily dose and cumulative dose of CQ use is unclear[6,7] as there is a high variability regarding which cumulative dosage leads to retinopathy.[8] Information published by the American Academy of Ophthalmology (AAO) in February 2011 stated that (1) a daily dose > 400 mg of HCQ (> 6.5 mg/kg ideal body weight for short individuals) and > 250 mg daily of CQ (> 3.0 mg/kg ideal body weight for short individuals), (2) a cumulative dose > 1000 g of HCQ and 460 g of CQ, (3) therapy duration > 5 years, (4) patient age, (5) other retinal and macula diseases, (6) renal and kidney disease and (7) genetic factors are known to modify patient risk.[9]

There has been a decrease in retinopathy in Western countries where HCQ has been used as a replacement for CQ. However, in South Africa, HCQ is not available to patients attending public clinics and hospitals.

Literature review

Antimalarials are excreted from the body very slowly and are melanotropic drugs. These drugs accumulate in structures such as the retinal pigment epithelium (RPE) and choroid. Photoreceptor degeneration is seen owing to increased deposits in the RPE, which in turn leads to increased phagocytic activity and lipofuscin accumulation.[10]

Five stages of chloroquine retinopathy have been described by Kanski.[11] Pre-maculopathy is the first stage where there is a normal visual acuity but also a paracentral scotoma to a red target between 4 and 9 degrees. This stage is then followed by a slight reduction in visual acuity and a subtle 'bull's eye' lesion; these changes may be reversed if the drug is discontinued. Screening

techniques have been implemented to detect early changes so as to prevent progression of the disease.

Fundus auto fluorescence (FAF) records RPE lipofuscin deposition, which is a mixture of fluorophores.[12] Lipofuscin has the characteristic of autofluorescence when exposed to UV or blue light.[10] The retina exhibits visible changes in patients taking CQ or HCQ, such as a pericentral ring of increased intensity as seen in patients with mild retinopathy, whilst patients with more advanced retinopathy have a more mottled appearance with variations in intensity in the pericentral macula. The image of a healthy macula on FAF has low autofluorescence at the fovea owing to low lipofuscin concentration. Autofluorescence increases minimally to about 7 degrees – 13 degrees from the fovea.[13,14] Generally, FAF is not symmetrically distributed around the fovea.

Changes in the RPE visible on FAF are also associated with alterations of the photoreceptor inner and outer segment boundary (IS/OS), and thinning of the outer nuclear layer of the retina is seen on SD-OCT.[15]

In 2002, the AAO published preferred practice patterns (PPP) for CQ and HCQ retinopathy. The suggested screening examinations included a dilated fundus examination, visual field assessment with either an Amsler grid or Humphrey Visual Field Analyser, measuring the central 10 degrees of vision, colour vision testing and fundus photography. Both fluorescein angiography and multifocal electroretinography (mfERG) are considered optional.[16] Revisions as published (AAO, February 2011) recommended that the Amsler grid be removed from the list of tests and that a 10–2 Humphrey visual field be supplemented with sensitive objective tests such as the mfERG, FAF and SD-OCT.[9]

Importance of the study

At present, there is no gold standard for CQ retinopathy diagnosis; however, as per the revised recommendations, a dilated fundus examination and visual field testing are considered compulsory examination procedures for a patient taking CQ. Whilst clinical examination is vitally important, small changes are difficult to record and recall. Visual field testing is subjective, leaving room for error, as the patient's cooperation and understanding are vitally important for a reliable result. FAF and SD-OCT are relatively new imaging devices for the ophthalmologist. The tests are objective and serial images can be taken and recorded over time.

The AAO guideline[9] recommends that a baseline examination and record keeping of fundus images should take place within the first year of starting CQ treatment, and follow-up should be annually after 5 years of treatment. Despite this recommendation, follow-up currently in South Africa takes place either bi-annually or annually throughout the course of treatment, without a five-year delay as suggested. For this reason, we compared retinal changes in patients taking CQ for more than 5 years with those using CQ for less than 5 years.

Objectives of the study

The study evaluated FAF and SD-OCT as screening tests to prophylactically detect early changes in the retina leading to CQ retinopathy. The primary aim was to determine whether there were any differences in the number of visible retinal changes suggestive of CQ retinopathy between patients on CQ treatment for more than 5 years compared with those on less than 5 years, using FAF images and SD-OCT.

Methods

The study was conducted using patients taking CQ chronically for various diseases, referred by the Rheumatology Department at Tygerberg Hospital to the Ophthalmology Department at the same hospital. The process included a current review of FAF images and SD-OCT images of these patients. FAF imaging was performed on the Carl Zeiss Meditec Visucam 500, and SD-OCT imaging on the Carl Zeiss Meditec Cirrus HD-OCT. Tygerberg Academic Hospital is a tertiary hospital, the second biggest of its kind in South Africa. Currently, screening includes a 10–2 Humphrey visual field examination, a dilated fundus examination, and FAF and SD-OCT imaging. All patients were referred as standard practice, and not solely on complaint or deterioration of visual acuity, on request of the rheumatologist.

Information regarding dosage, cumulative dosage, weight and years on treatment was obtained from both the patient and the patient's hospital file.

Consent was obtained from 112 patients (223 eyes [111 right eyes {one patient was monocular owing to a previous evisceration from trauma} and 112 left eyes]); 101 (90.2%) female participants and 11 (9.8%) male participants. The age range was 5.6–87.8 years.

Results

Group A consisted of 59 patients on CQ for less than 5 years, and Group B consisted of 53 patients on CQ for more than 5 years.

Table 1 shows various participant characteristics as well as primary diagnosis and cumulative dosage of CQ.

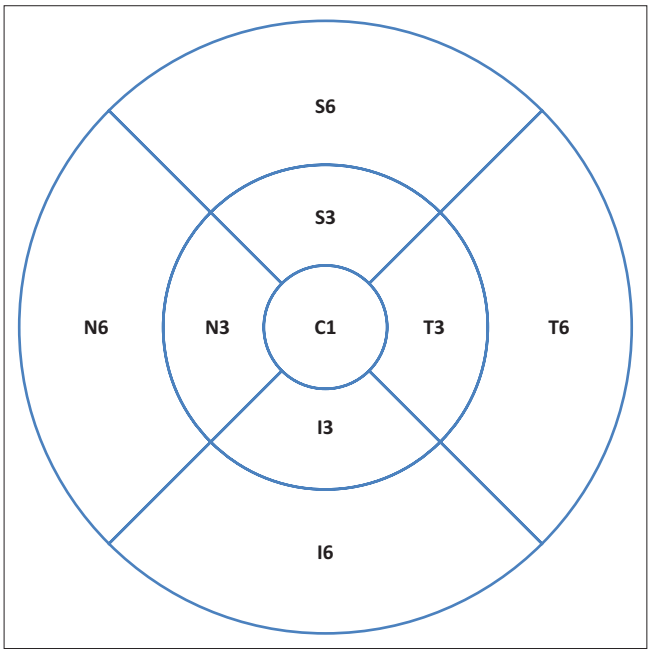
For the macular map, the four quadrants of the outer, 6 mm diameter ring around the fovea were labelled S6, T6, I6, and N6 to represent the superior, temporal, inferior and nasal regions, respectively. The inner, 3 mm diameter ring was labelled analogously. C1 represents the innermost 1 mm diameter ring around the fovea[17] (Figure 1).

Figure 2 shows a box and whisker plot of the C1 ring in Groups A and B measured with SD-OCT, and Figure 3 shows the correlation between C1 and cumulative dosage.

Tables 2 and 3 compare macula thickness between Groups A and B.

TABLE 1: Patient characteristics in Groups A and B using chloroquine for less than or more than 5 years.

Patient characteristics	Duration on chloroquine	
	< 5 years	> 5 years
Age		
Mean age and standard deviation (years)	50.04 ± 15.67	54.59 ± 9.8
Gender		
Male	6 (10.17)	5 (9.44)
Female	53 (89.83)	48 (90.56)
Race		
Mixed race	44 (74.58)	41 (77.36)
Somalian	1 (1.69)	0
White	4 (6.78)	4 (7.56)
Black	8 (13.56)	6 (11.32)
Unknown	2 (3.39)	2 (3.76)
Primary diagnosis		
Rheumatoid arthritis	32 (54.24)	32 (60.39)
Systemic lupus erythematosis (SLE)	15 (25.43)	15 (28.30)
Discoid lupus erythematosis (DLE)	5 (8.47)	2 (3.77)
Osteoarthritis	1 (1.69)	2 (3.77)
Mixed connective tissue disease	1 (1.69)	2 (3.77)
Systemic sclerosis	3 (5.09)	0 (0.00)
Sarcoidosis	2 (3.39)	0
Cumulative dosage		
2 days	1 (1.69)	0
4 days	14 (23.74)	16 (30.18)
5 days	42 (71.19)	34 (64.16)
6 days	1 (1.69)	2 (3.77)
7 days	1 (1.69)	1 (1.89)



Note: The inner, 3 mm diameter ring is labelled analogously. C1 represents the innermost 1 mm diameter ring around the fovea.[17]

FIGURE 1: Macular map: the four quadrants of the outer, 6 mm diameter ring around the fovea are labelled S6, T6, I6 and N6 to represent the superior, temporal, inferior and nasal regions, respectively.[17]

Spectral domain ocular coherence tomography

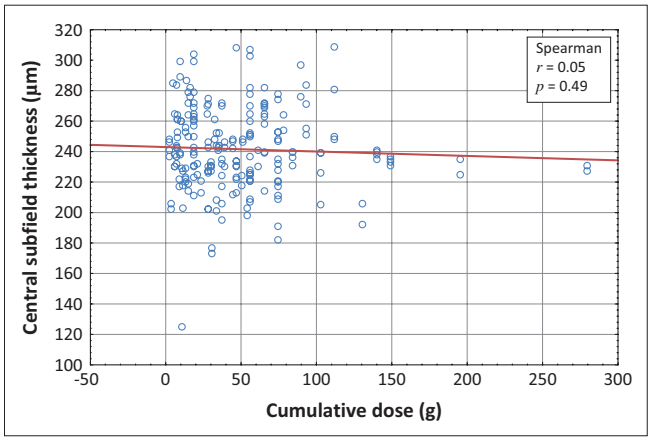
Ellipsoid zone

Analysis of the ellipsoid zone revealed 186 normal ellipsoid zones (98 in Group A; 88 in Group B). Three were classified as questionably abnormal (3 in Group A; 0 in Group B) and 26 were classified as abnormal (10 in Group A; 16 in Group B) (Table 4).

Of the abnormal and questionable images seen in Group A, 7 had focal abnormalities (viz. confined to one specific area), 4 had diffuse abnormalities and 1 had both focal and diffuse

ILM-RPE, internal limiting membrane and retinal pigment epithelium.

FIGURE 2: Box and whisker plot of central 1 mm thickness of the ILM and RPE (C1) in Group A and Group B measured with SD-OCT.



Note: There was no correlation between central subfield thicknesses (C1) and cumulative dosage of chloroquine ($r = 0.05$, $p = 0.49$).

FIGURE 3: Correlation between central subfield thickness (C1) (µm) on SD-OCT and cumulative dosage (g).

TABLE 2: Comparisons of all retinal thickness layers as per the macula map with the chi-square statistic between Group A (< 5 years on chloroquine) and Group B (> 5 years on chloroquine) ($df = 4$).

Layer	Pearson chi-square statistic	*p* value
S6	5.863	0.209
T6	3.776	0.437
I6	4.096	0.393
N6	4.724	0.317
S3	3.024	0.554
T3	3.97	0.41
I3	3.542	0.472
N3	8.577	0.073
C1	1.413	0.842

TABLE 3: Macula map thickness distributions compared with a *t*-test for independent samples between Groups A (107 values) and B (103 values).

Variable	Mean < 5 years (Group A)	Mean ≥ 5 years (Group B)	*t*-value	*df*	*p*
S6 (distribution)	2.96	3.11	1.609	208	0.109
T6 (distribution)	3.02	3.12	1.253	208	0.212
I6 (distribution)	3.07	3.16	0.903	208	0.368
N6 (distribution)	2.99	3.08	1.04	208	0.299
S3 (distribution)	3.18	3.13	-0.582	208	0.561
T3 (distribution)	3.21	3.19	-0.239	208	0.815
I3 (distribution)	3.18	3.2	0.296	208	0.768
N3 (distribution)	3.16	3.15	-0.156	208	0.876
C1 (distribution)	3.18	3.17	-0.148	208	0.882

TABLE 4: Ellipsoid zone integrity analysis.

Integrity	Group A	%	Group B	%	Total
Normal	98	84.62	88	88.29	186
Questionable	3	2.7	0	0	3
Abnormal	10	9.01	16	15.38	26
Total	**111**	-	**104**	-	**215**

TABLE 5: Interdigitation zone integrity analysis.

Integrity	Group A	%	Group B	%	Total
Normal	106	95.50	97	95.10	203
Abnormal	5	4.50	5	4.90	10
Total	**111**	-	**102**	-	**213**

abnormalities. Those with focal abnormalities had a distinct blurring below the foveal dip. This blurring was the most common abnormality detected in the study.

Of the abnormal images seen in Group B, 8 had focal abnormalities and 6 had diffuse abnormalities. Two were not classified.

Interdigitation zone

Analysis of the interdigitation zone revealed 203 normal-looking interdigitation zones (106 in Group A; 97 in Group B), and 10 abnormal (5 in Group A; 5 in Group B). Of the abnormal images seen in Group A, 2 had focal abnormalities and 3 had diffuse abnormalities (Table 5).

In Group B, 2 eyes had focal abnormalities and 2 had diffuse abnormalities. The 5th eye was classified as abnormal in this area owing to CHRPE (congenital hypertrophy of the retinal pigment epithelium).

Retinal pigment epithelium

Analysis of the RPE revealed the lowest number of visible changes, with 1 abnormal image and 1 questionable image.

Other abnormalities

In Group A, 3 images with unusually shaped macula dips were seen and 1 epi-retinal membrane was found. In Group B, 1 image with an unusually shaped macula dip was seen, 1 intra-retinal cyst, 1 epi-retinal membrane, 1 with oedema, and 2 with high myopia.

When comparing the occurrence of other abnormalities on SD-OCT between Group A and Group B with a paired *t*-test, a non-statistically significant result was produced (p = 309, $df = 4$, $\chi^2 = 4.79$).

Macula cube

Two hundred and fourteen 200 × 200 macula thickness cube images were assessed. Group A consisted of 111 images, and Group B of 103. However, only 107 in Group A had assigned distributions (4 images were of 2 patients under 18 years of age and no normative values were available). The value of the distribution was thought to be most relevant, as the distribution was compared with normative data in relation to age. For each area of the macula cube, both in Group A and B, the mean distribution was 'green', indicating that 90% of the measurements fell within those values. As seen in the analysis, when comparing the distribution profile between Groups A and B individually for all 9 areas (S6, T6, I6, and N6, S3, T3, I3, and N3 and C1), the p values showed no statistical significance, which indicates that the distribution profile does not differ between those on CQ for more or less than 5 years. This finding is therefore not a clear indicator of subclinical macula pathology.

Fundus auto fluorescence

Images of 213 (109 in Group A and 104 in Group B) FAF images were assessed for any visible changes (Table 6). At present, there is no standardised or known grading system for interpretation or zoning of FAF irregularities or abnormalities. For this reason, we stated that any changes occurring within the arcades would be regarded as 'central' and those outside the arcades as 'peripheral'. Our impression is that the appearance of an FAF image differs depending on the race, and therefore the pigmentation, of the patient. Those with more pigmentation had an overall darker-looking image, in comparison with those with less pigmentation.

The proportion of normal images in Group A (85.3%) is slightly greater than that in Group B (81.7%) but, when compared by a paired *t*-test, the difference was not statistically significant (p = 0.477). Most abnormalities were found centrally (Group A 81.2%; Group B 55.5%), some were found both centrally and peripherally (Group A 6.3%; Group B 22.2%) and only in Group B were abnormalities found at the fovea (Group A 0%; Group B 16.7%) (Table 7).

Most of the abnormalities seen were small localised areas of hypo auto fluorescence (Group A 37.5%; Group B 17.7%).

TABLE 6: Fundus auto fluorescence – retinal pigment epithelium integrity analysis.

Integrity	Group A	%	Group B	%	Total
Normal	93	85.32	85	81.73	178
Abnormal	16	14.68	19	18.27	35
Total	**109**	-	**104**	-	**213**

TABLE 7: Fundus auto fluorescence – retinal pigment epithelium analysis of location of abnormality (central, central and peripheral, and fovea).

Location	Group A	%	Group B	%	Total
Central	13	81.25	10	55.56	23
Central and peripheral	1	6.25	4	22.22	5
Fovea	0	0.00	3	16.67	3
Other (CHRPE)	2	12.50	1	5.56	3
Total	**16**	-	**18**	-	**34**

CHRPE, congenital hypertrophy of the retinal pigment epithelium.
Note: The inner, 3 mm diameter ring is labelled analogously. C1 represents the innermost 1 mm diameter ring around the fovea.[17]

Discussion

The 2011 revised AAO screening guidelines for CQ and HCQ retinopathy suggest a Humphrey 10–2 visual field, dilated fundus examination and the use of an objective test such as SD-OCT and FAF.[9] In our study using these tests on 223 eyes, we found a low incidence of CQ retinopathy, probably indicating a fairly low degree of ocular toxicity.

After extensive review of all images, there were no signs from SD-OCT or FAF that required a decision to be made regarding cessation of CQ treatment in any of the patients. The changes seen in those on CQ treatment for less than 5 years did not differ significantly from those on CQ for more than 5 years, which may suggest that the 5-year cut-off for more intensive screening is premature. These investigations may assist us at baseline prior to initiating CQ therapy to investigate underlying retinal disease.

The use of a 5-line raster with SD-OCT as an assessment for early CQ retinopathy detection did not prove to provide us with additional insight. It is interesting to note that the most common change seen was a 'blurry' central area under the macula dip.

At the present stage of retinal imaging, it may be more difficult to detect early abnormalities with FAF as it is less quantitative than other methods.

Recent publications have demonstrated that the cumulative dosage related to real body weight is a large factor in development of retinopathy, together with other factors such as kidney disease and additional medication use.[5]

Conclusion

Future studies comparing more disparate groups, such as those on treatment for only 1 year to those on treatment for 10 years or more, may be useful to determine at which stage the occurrence of CQ retinopathy increases, and assist in determining an appropriate stage at which more intensive screening becomes valuable. Additional research is needed to determine whether our population group, which was mostly that of mixed-race ethnicity (see Table 1), has a lower incidence of CQ retinopathy, as well as studies with a larger sample size, to detect changes with greater power.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

M.B.G. (Stellenbosch University) was the project leader and undertook this study as part contribution toward a MSc Clinical Epidemiology degree. A.Z (Stellenbosch University) was the supervisor.

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