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Reliability of Optical Coherence Tomography Angiography in Detection of Early Hydroxychloroquine Toxicity

Nesma Sayed Mohammed
Ophthalmology Department, Faculty of Medicine (For Girls), Al-Azhar University, Cairo, Egypt
Corresponding author: Nesma Sayed Mohammed, **Mobile:** (+20)1014852522, **E-mail:** nesma7@live.com

ABSTRACT

Background: Chloroquine is an antimalarial drug, while hydroxychloroquine is an analogue of chloroquine. Hydroxychloroquine (HCQ) is used to treat autoimmune diseases in addition to malaria. They have toxic effects on retina**.** Different screening protocols were described to detect HCQ toxicity**.**

Objective: The aim of the current work was to study the ability of optical coherence tomography angiography (OCTA) to detect early retinal changes that may occur after HCQ treatment in patients with rheumatoid arthritis.

Patient and Methods: This prospective cross-sectional study included a total of 40 eyes of 20 patients who were newly or previously prescribed HCQ for rheumatoid arthritis, recruiting from the Department of Ophthalmology, Al-Zahraa University Hospital. This study was conducted between May 2018 to Dec 2019. OCTA imaging was performed via Angiovue software.

Results: The superficial whole vascular density, superficial parafoveal vascular density, superficial perifoveal vascular density, deep whole vascular density, deep parafoveal vascular density, and deep perifoveal vascular density were thinner in treatment groups compared to the control group ($p<0.05$).

Conclusion: OCTA could be a beneficial tool for screening of HCQ retinal affection. It could detect the decrease in the deep capillary plexus at the parafoveal and perifoveal regions in patients who were receiving HCQ treatment.

Keywords: Hydroxychloroquine toxicity, Optical coherence tomography angiography, Rheumatoid arthritis.

INTRODUCTION

Chloroquines (CQ) and its analogue hydroxychloroquine (HCQ) were known as antimalarial drugs. They are now being widely used in the treatment of autoimmune diseases [1, 2]. They are also used as emerging treatment options for skin, oncologic, and pediatric inflammatory disorders [3]. Surprisingly, they are now widely used as a first-line drug in the treatment of new coronavirus infection COVID-19 [4]. At first the Food and Drug Administration (FDA) granted an emergency use authorization for use of oral formulations of CQ and HCQ in the treatment of COVID-19 [5, 6].

Chloroquines have toxic effects on retina and eventually lead to so-called bull's eye maculopathy. Both the actual body weight and the duration are two important factors for toxicity [7]. The optimum safe dose of the drug is still debatable. The doses of < 5 mg/kg/day were considered safe [3].

The exact mechanism of retinal toxicity still unclear. Toxic effects on retinal pigment epithelium (RPE) cells, accumulation of HCQ in pigmented ocular tissues, and degeneration of rods and cones are among the purposed mechanisms of HCQ toxicity [8].

Screening is recommended in the first year and annually thereafter. The 10-2 visual field testing, spectral domain optical coherence tomography (OCT), and autoflu orescence (AF) imaging are accepted as the main screening tools [3]. In some special circumstances, multifocal electroretinography (mfERG) might be essential also [9, 10].

Optical coherence tomography angiography (OCTA) is a new noninvasive tool which can assess the retinal vascular system quantitatively, and the efficacy of OCTA in HCQ retinopathy was previously evaluated by several authors [11, 12].

The aim of this work was to study the efficacy of OCTA in detecting the early changes in retinal vasculature by comparing the quantitative OCTA parameters in patients who were using HCQ for different durations.

PATIENTS AND METHODS:

This prospective cross-sectional study included a total of 40 eyes of 20 patients, recruiting from the Department of Ophthalmology, Al-Zahraa University Hospital. This study was conducted between May 2018 to Dec 2019.

Ethical Consideration:

An informed written consent was obtained from each participant after receiving a full explanation about the study. **Approval was obtained from the Ethics Board of Al-Azhar University committee.** All procedures were conducted in accordance with the Helsinki Declaration guidelines.

The included subjects were divided into three groups: **Group 1 (control)** included 16 eyes of 8 patients, who were not taking any medication, **Group (2)** included 14 eyes of 7 patients,. who were under HCQ treatment for ≤ 5 years, and **Group (3)** included 10 eyes of 5 patients, who were under HCQ treatment

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for HCQ > 5 years. The main outcome measure of the study was OCTA parameters of the patients who were under HCQ treatment.

Inclusion criteria were patients who were prescribed HCQ for treatment of rheumatoid arthritis.

Exclusion criteria were patients who had a retinal disease, intraocular inflammation, media opacity, and history of systemic conditions that could alter the microvasculature (including diabetes, hypertension, cardiovascular disease, and renal disease).

All the patients underwent a complete ophthalmological examination, including best-corrected visual acuity (BVCA), slit-lamp biomicroscopy, and dilated fundus examination. Optical coherence tomography imaging was performed via OCT RT XR Avanti with Angiovue software (Optivue Inc, Fermont, CA).

Structural OCT parameters and OCTA parameters for fovea were analyzed. 6×6 scan size was used for OCTA imaging, all of the scans were automatically segmented, and the quantitative values were all calculated via the built-in automated software of the device. The scans with a signal strength index of <37 with motion artifacts and segmentation errors were accepted to have a poor quality and were not analyzed.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 25.0. Numerical variables were expressed as the mean and standard deviation. One-way analysis of variance (ANOVA) which was used to test the difference between the means. P values<0.05 was considered statistically significant.

RESULTS

A total of 40 eyes of 20 patients were enrolled in this study. Group (1) included 16 eyes of 8 patients (7 females and 1 male), Group (2) included 14 eyes of 7 patients (5 females and2 males) and Group (3) included 10 eyes of 5 patients (all were females).

There was a statistically significant difference between group 2 and group 3 as regard the HCQ duration. The difference in age was statistically insignificant (Table 1).

Table (1): Difference in age and HCQ druation among the study groups.

Group / Parameters	Group (1)	Group (2)	Group (3)	P-Value
Age (years)	42.06± 8.31	38.38 ±15.4	45.47±12.4	>0.05
Duration (months)	-	27.17 ±8.2	117.9 ±17.2	<0.001

The mean values for the OCTA parameters are summarized in Table 2&3. The superficial whole vascular density, superficial parafoveal vascular density, superficial perifoveal vascular density, deep whole vascular density, deep parafoveal vascular density, and deep perifoveal vascular density were lower in the Group (2) & (3) than the control group. There was statistically insignificant difference as regard the foveal vessel density in both the superficial and deep plexus in group (2) and group (3) when each one was compared to group (1) (Table 2 & 3).

Table (2): Comparison between Group (1) (control) and Group (2) as regard the optical coherence tomography angiography outcomes.

Vessel density (%)	Group (1)	Group (2)	P value
Superficial whole image	56.09 ± 3.63	40.80 ± 3.49	< 0.001
Superficial foveal density	20.43±8.23	21.67 ± 5.77	0.35
Superficial parafoveal density	54.21 ± 2.78	42.97 ± 10.13	< 0.001
Superficial perifoveal density	54.26 ± 2.79	43.23 ± 9.41	< 0.001
Deep whole density	56.48 ± 3.84	39.50 ± 4.71	0.001
Deep foveal density	21.77 ± 5.43	21.35 ± 23.6	0.38
Deep parafoveal density	54.26 ± 2.79	43.23 ± 9.41	< 0.001
Deep perifoveal density	54.25 ± 2.80	42.97 ± 10.13	< 0.001

FAZ foveal avascular zone

Table (3): Comparison between Group (1) (control) and Group (3) as regard the optical coherence tomography angiography outcomes.

Vessel density (%)	Group (1)	Group (3)	P value
Superficial whole image	56.09 ± 3.63	40.76 ± 3.42	< 0.001*
Superficial foveal density	20.43±8.23	20.02 ± 9.2	0.39
Superficial parafoveal density	54.21 ± 2.78	41.51 ± 9.43	< 0.001*
Superficial perifoveal density	54.26 ± 2.79	44.96 ± 8.40	< 0.001*
Deep whole density	56.48 ± 3.84	47.0 ± 4.0	< 0.001*
Deep foveal density	21.77 ± 5.43	20.79 ± 12.89	0.36
Deep parafoveal density	54.26 ± 2.79	46.0 ± 4.0	< 0.001*
Deep perifoveal density	54.25 ± 2.80	46.1 ± 5.1	< 0.001*

DISCUSSION

In this study, we evaluated the patients who were using HCQ for the treatment of rheumatoid arthritis via OCTA. The exact mechanism of HCQ retinal toxicity is still debatable. A possible mechanism is the inhibition of uptake of all-trans-retinol leading to a negative effect on the visual cycle [(13)]. The accumulation in RPE cells seems to be important as the retinal toxicity might continue even after the cessation of the drug [(14)]. Optical coherence tomography is an extremely useful tool in the screening examinations of the patients using HCQ [(3)]. Structural OCT was widely studied to reveal the early findings of HCQ toxicity.

OCTA , another noninvasive tool that has been used to show the retinal circulation, is being studied to detect early HCQ toxicity. OCTA studies regarding the changes in vascular density in patients who are under HCQ treatment showed variable outcomes. The retinal thickness decrease was common finding in most of the OCT-based studies; however, there is not a consensus in the differences in vascular density detected via OCTA [(15, 16)].

There is an ongoing debate regarding the primary site of the toxicity. Some studies suggest RPEs might be the primary affected tissue; some other suggest the outer retina/photoreceptor complex as the primary affected tissue [(17)]. Screening guidelines are very important in the follow-up examinations of the patients who are under HCQ treatment.

The first changes in HCQ toxicity begin from the perifoveal and parafoveal regions; therefore, if some change is expected in vascular density, it should be in this area. Foveal affection is generally affected late. Our results showed no difference between the three groups as regard the foveal vascular density. This was consistent with **Tarakcioglu *et al.*** [(12)] who found that in patients who receiving HCQ treatment for > 5 years, the changes did not occur centrally at the fovea; instead they occurred at both parafoveal and perifoveal areas. However, **Goker *et al.*** [(11)] showed that the vascular density in fovea was significantly lower in patients who were under HCQ treatment than the patients who were not.

Also, **Forte *et al.*** [(16)] compared the OCTA findings between the patients who were under HCQ treatment for > 5 years (20 eyes of 10 patients) and a control group (36 eyes of 18 healthy volunteer). They reported that the vascular density in fovea in deep capillary plexus and choriocapillaris was decreased. The main affected zone was reported to be central fovea in this study.

Bulut *et al.* [(15)] conducted a study to evaluate the additional benefit of OCTA in the screening of HCQ-induced retinal alterations. They divided the patients into two groups as low risk (receiving HCQ for < 5 years) and high risk (receiving HCQ for > 5 years). It also showed some controversial outcomes. Surprisingly, the thickness results did not show statistical difference between the low-risk and high-risk groups. Foveal, parafoveal, and perifoveal retina thickness values were similar, and only choroidal thickness was found to be decreased in the group of high-risk patients. In contrast to thickness outcomes, all of the vascular density parameters (whole, superficial, deep foveal, parafoveal and perifoveal) were found to be decreased in the high-risk group of patients which was consistent with our results apart from foveal involvement where our study showed foveal sparing.

Ozek *et al.* [(18)] evaluated the OCTA findings in rheumatoid arthritis patients receiving HCQ treatment. This study had also controversial outcomes. Nearly none of the retinal thickness outcomes differed between the three study groups except for inferior superficial plexus and hemi-inferior deep capillary plexus thickness values which were lower in the group of patients who were receiving HCQ treatment for > 5 years. The vessel density analysis showed some positive outcomes, and deep temporal and hemi-inferior vascular density was found to be decreased in patients who were receiving HCQ treatment for > 5 years. This was in agreement with our results where we found the fovea vascular density showed no difference among the three study groups .Also, the decreased vascular density occurred at the parafoveal and perifoveal deep plexus. Although these changes could be noted at the groups under HCQ treatment, they were seen more when the duration was more than 5 years.

In our study, using OCTA, we found some retinal changes occurred at the retinal vascular density after HCQ use, these changes could be seen at parafoveal

and perifoveal areas at the level of deep capillary plexus. The foveal area was not affected.

CONCLUSION

It could be concluded that OCTA could be a beneficial tool for screening of HCQ retinal affection. It could detect the decrease in the deep capillary plexus at the parafoveal and perifoveal regions in patients who were receiving HCQ treatment. These findings are needed to be confirmed in more longitudinal studies.

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