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Clarissa dos Reis Pereira
Hospital das Clínicas,
Universidade de São Paulo,
São Paulo, SP, Brazil

Vinicius Sande Miguel
Unigranrio, Rio de Janeiro,
RJ, Brazil

Thiago Sande Miguel
Universidade Federal
Fluminense, Niterói, Rio de
Janeiro, RJ, Brazil

Daniel Almeida da Costa
UNIFAA - Centro
Universitário de Valença,
Brazil

Bruna Sande Miguel
Unigranrio, Rio de Janeiro,
RJ, Brazil

Maurício B Pereira
Universidade Federal
Fluminense, Niterói, Rio de
Janeiro, RJ, Brazil

Early and progressive hydroxychloroquin retinal toxicity: 9-year follow-up with multimodal retinal imaging

Clarissa dos Reis Pereira, Vinicius Sande Miguel, Thiago Sande Miguel, Daniel Almeida da Costa, Bruna Sande Miguel and Maurício B Pereira

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Abstract
Retinopathy secondary to the use of hydroxychloroquine sulfate can cause irreversible central visual loss and progress even after stopping the drug. The pathophysiological mechanism by which this phenomenon occurs is unclear. Periodic eye exams associated with multimodal imaging exams help in the early recognition of this pathology, being essential for the realization of an early diagnosis in order to minimize adverse visual sequelae. Patients must be aware of the risk of toxicity and its possible consequences, so the use of this medication must be well-founded. Detecting early and subtle changes in visual perception can minimize damage, but not necessarily to prevent it. Medications should be discontinued, if possible, when toxicity is recognized or strongly suspected, but this is a decision to be made together with patients and their physicians, as it is indicated by an underlying pathological condition that can also lead to irreversible sequelae for patients.

Keywords: Retina, Visual acuity, hydroxychloroquine, maculopathy, visual field, retinal diseases, scotoma, drug toxicity

Introduction

Antimalarials, especially hydroxychloroquine sulfate (HCQ), are widely used in patients with rheumatic diseases, such as Systemic Lupus Erythematosus and Rheumatoid Arthritis, for long periods [1-6]. Despite the low incidence of serious systemic side effects resulting from of its chronic use, there is a risk of irreversible retinal damage (1), which can evolve even after the drug is discontinued [7, 8].

It is believed that macular toxicity by HCQ is a rare condition, but still underestimated, especially when only the fundoscopic aspect is considered for the diagnosis (2, 3, 8). Prevalence is variable in the literature, ranging from 4.3 to 13.8%, depending on the detection method used [9, 10].

In general, it is difficult to predict the occurrence of retinotoxicity and there is no treatment after the onset of target maculopathy [2,6]. Therefore, screening these patients is essential for early detection of retinal involvement, considering that there is a risk of progression when the macula has already been visibly affected, resulting in permanent visual impairment [3, 8].

Although infrequent, the early manifestation of the disease can occur [8]. The present clinical case is an example of this, in which a patient without risk factors and using HCQ at an appropriate dosage for her weight, showed signs of retinal toxicity less than 2 years after starting the drug. There was progression of the condition for 9 years, even after discontinuing the medication. The documentation of this case by color retinography, autofluorescence and, in particular, by fluorescein angiography, allowed demonstrating the evolution of the maculopathy over this period.

Case report

A 49-year-old female patient, Caucasian, with polymyositis, used hydroxychloroquine 400mg/day (daily dose of 4.7 mg/kg of actual weight) for 19 consecutive months.

She had a past pathological history of ovarian cancer with colonic metastasis, treated with intravenous chemotherapy and surgical resection at the age of 27. He denied the use of Tamoxifen or other oral chemotherapy. He did not have renal or hepatic insufficiency.

After showing retinal pigmentary changes suggestive of HCQ toxicity, accompanied by campimetric and electroretinogram changes, the medication was discontinued.

Corresponding Author:
Daniel Almeida da Costa
UNIFAA - Centro
Universitário de Valença,
Brazil

Despite the suspension, there was a progressive reduction in visual acuity and an increase in the area of perifoveal pigmentary atrophy, progressively assuming a pattern of target maculopathy ("bull's eye").

In the first year after medication discontinuation, the patient had a VA of 20/25 in AO. Fundoscopy showed a slight AO macular pigmentary alteration (figure 1), and fluorescein angiography showed a defect in AO macular transmission, due to RPE atrophy (figure 2).
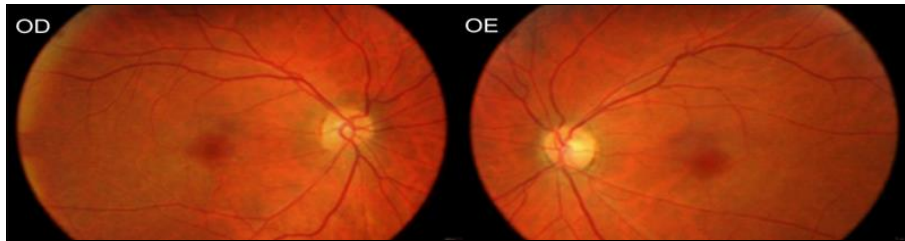

Fig 1: Color retinography of the RE and LE. We observed a slight alteration of the foveal reflex and hypopigmentation temporal to the fovea in the BE

Fig 2: Fluorescein angiography of the RE and LE. Spots of pigmentary atrophy represented by transmitted hyperfluorescence around the BE fovea

In the second year after discontinuing medication, computerized visual perimetry showed central and paracentral scotomas in the BE (figure 3) and optical coherence tomography (OCT) revealed retinal atrophy, with attenuation of the foveal profile and reduced thickness, with measurements of 101 microns in the RE and 148 in the OS (figure 4). The electroretinogram was also bilaterally subnormal, both scotopic and photopic.
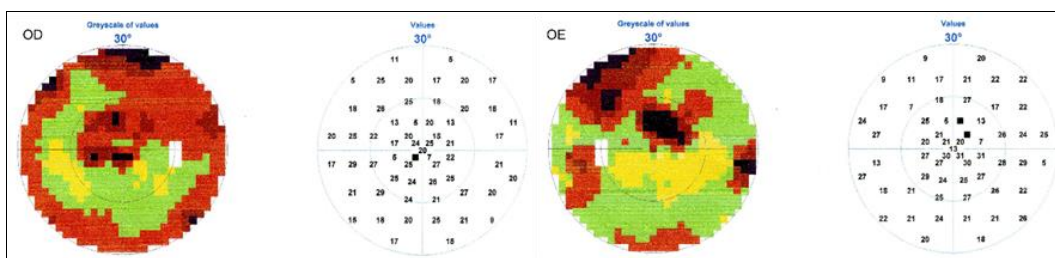

Fig 3: Central computerized perimetry (30º) by Octopus 123 (Haag-Streit, USA). The images show the presence of central and paracentral scotomas with decreased sensitivity, extending to the limits of the tested area in BE
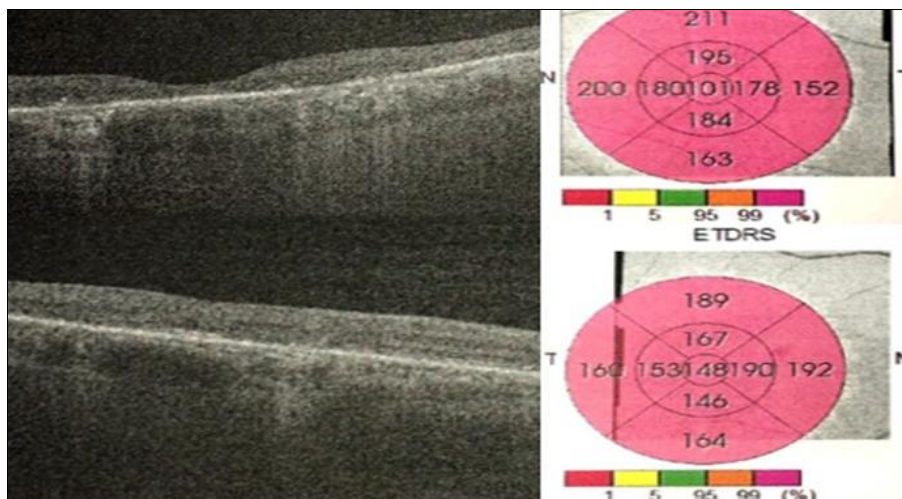

Fig 4: Optical coherence tomography images

The patient was followed up for 9 years after discontinuing the drug, showing progression of retinotoxicity, which culminated in macular atrophy with a classic bull's eye appearance (Figures 5 and 6), with evolution of the central scotomas to the visual field. The VA remained at 20/25 in the RE, and there was a worsening in the LE to 20/40, with the updated correction. The autofluorescence performed showed the presence of hypoautofluorescent images correlated with areas of pigmentary atrophy (figure 7), similar in appearance to other conditions with a maculopathy pattern in the "bull's eye" [11].

The patient continues on regular ophthalmological follow-up to monitor the progression of retinal damage and possible complications.
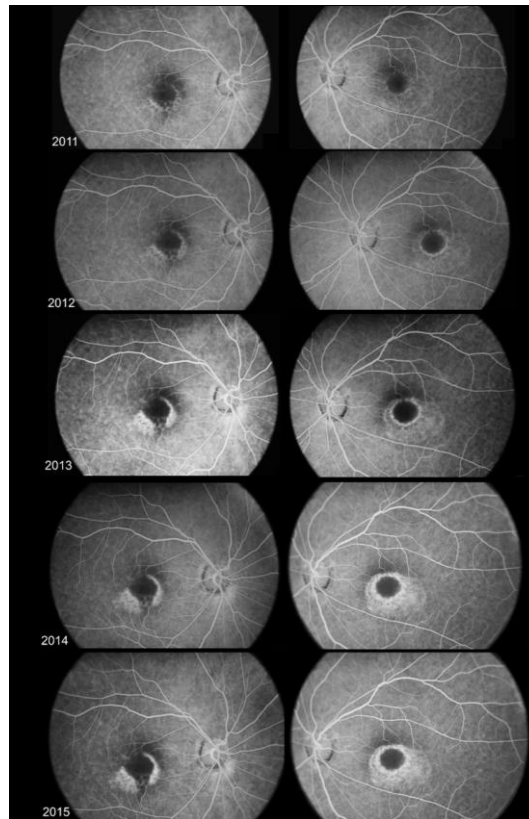

Fig 5: Fluorescein angiography images of the RE and LE, from 2011 to 2015, showing the progression of pigmentary atrophy in the perifoveal region of the BE
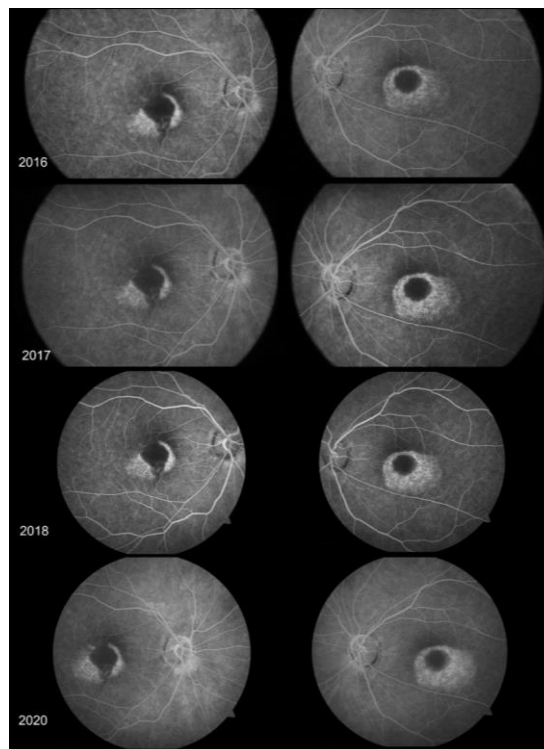

Fig 6: Fluorescein angiography images of the RE and LE, from 2016 to 2020, showing the progression of pigmentary atrophy in the perifoveal region of the BE until it assumes a "bull's eye" pattern
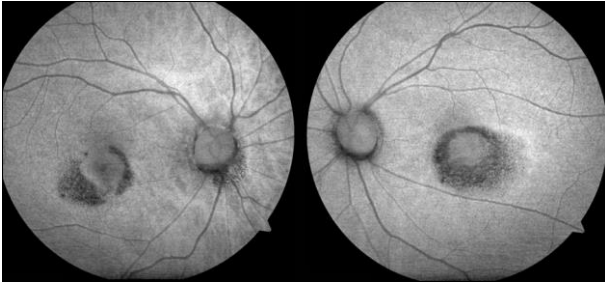
Fig 7: Autofluorescence images, showing the hypoautofluorescence pattern in pigmentary atrophy lesions

Discussion

The use of HCQ has been consolidated in the treatment of rheumatological conditions for many years, but recently it has also been studied in patients infected with the new SARS-Cov-2, the virus responsible for the 2020 pandemic [12, 13]. In cases associated with COVID-19, the initial recommendation of HCQ treatment doses was well above the recommended safe limits by current therapeutic guidelines [2, 10, 14].

It has already been observed that high doses can accelerate the occurrence of retinal toxicity, but in the studies carried out so far, a period of at least 11 months was necessary for the appearance of subtle changes in the macular Optical Coherence Tomography (OCT) and 15 months for the onset of maculopathy.

Even in chronic users of the drug at dosages considered safe, the risk of retinotoxicity is variable, increasing with time of use and with the presence of other risk factors [2, 3, 16]. In the last 10 most recent studies, the risk ranged from 2.9 to 30.5%. [16] Melles *et al.* [3] suggest an initial risk of less than 1% in the first 5 years of use, with doses equal to or less than 5mg/kg of actual weight, at day [3]. This rate remains below 2% for up to 10 years, rising to around 20% after 20 years of use [3].

The main risk factors for retinopathy are dosage above 5.0mg/kg of actual weight per day and the cumulative dose [3, 10]. As the drug is excreted in the urine, renal failure with a considerable reduction in the glomerular filtration rate increases significantly the risk [17]. The use of tamoxifen has also come to be considered a predisposing factor, as it can accelerate photoreceptor intoxication by HCQ [3].

Some studies suggest that there may also be a genetic predisposition for the development of retinotoxicity caused by HCQ [17, 18]. It is believed that polymorphisms in the cytochrome P450 gene may influence the blood concentration of the drug, inducing the onset of the disease [18], while polymorphisms in the ABCA4 gene would have a protective role [19].

Determining HCQ blood levels could help monitor both its clinical effect and the risk of toxicity, but these measures are not yet universally available [10, 20]. In addition, in more recent studies, there is still great variability between the prescribed dose and the drug dosage in the blood, possibly caused by the aforementioned genetic polymorphisms, but especially by poor adherence to treatment [20].

The pathogenic mechanism of HCQ on the retina has not yet been fully understood [21]. In 1978, Rosenthal *et al.* [22] demonstrated initial damage to retinal ganglion cells (GCC) with the use of chloroquine in rhesus monkeys [22]. Clinical studies recent studies have also demonstrated involvement of the inner retina by HCQ well before the classic damage to the outer layers and the retinal pigment epithelium (RPE) [23, 24]. It has also been proven that HCQ is capable of binding to the melanin present in the RPE in such a way that it remains deposited for many years, which could justify the perpetuation of retinopathy, even after discontinuing the drug [5, 25].

More recently, Mondal *et al.* [21] used an animal model in rats to evaluate the ocular effects of prolonged use of HCQ, observing an impairment of lysosomes and sphingolipid metabolism [21]. In addition, they showed early damage to the inner retina, especially to GCC, affecting visual functions well before they lead to "bull's eye" maculopathy [21].

With regard to the clinical picture, the visual decline can be underestimated, as most patients do not present a reduction in VA in the early stages of the disease or perceive only small central or paracentral scotomas [2-6]. Perceptible funduscopic changes represent an advanced stage and irreversible end of the disease that should no longer occur, as retinotoxicity can be detected much earlier by macular OCT, showing thinning of the retinal layers or discreet ruptures of the ellipsoid zone [10].

However, the phenotype of central maculopathy is not universal and the retina closest to the vascular arcades may be affected in some patients, especially those of Asian origin [26]. Although they are rarer, the investigation of these cases should include the performance of tests. with wider fields [27].

With regard to screening, the AAO suggests starting with a previous examination or in the first months of HCQ use [2, 10]. This initial examination should exclude the presence of severe maculopathy of another etiology that could affect retinal function or confuse the diagnosis of toxicity [10]. If there are no risk factors, the next ophthalmological evaluation can be postponed for 5 years, with annual follow-up thereafter [2].

Currently, the main test for early detection is macular OCT, if available [10]. Visual campimetry should also be part of the screening, especially the evaluation of the central 10°, but it is more subject to individual variations and can be a challenging test for many patients [2, 10].

Other exams can help in the screening of retinotoxicity by HCQ, such as multifocal electroretinogram (mfERG) [25] and microperimetry (MP) [28]. PM would be the most sensitive test between the two, but more evidence is still needed to corroborate its routine use in the screening of these patients [28]. In addition to these, AAO also suggests autofluorescence as another diagnostic tool in these cases [2]. Although these recommendations cover the vast majority of patients who will develop macular damage, there are reports in the literature of cases of premature target maculopathy, with low cumulative doses of up to 57g [29], and others before 5 years of treatment [8, 30, 31]. The patient in the reported case fits into this group, as she had no risk factors and developed macular changes after only 19 months of using HCQ, within the proposed dosage of 5 mg/kg of actual weight per day.

As already mentioned, from the moment that the damage to the RPE is visible, there is no way to reverse the situation and the risk of worsening remains even with the suspension of the medication [2, 6]. According to Marmor *et al.*, cases patients with severe retinal damage may continue to progress for at least 3 years after stopping the drug [6].

Thus, it is essential to improve our screening to detect toxicity in the early stages, thus avoiding severe visual sequelae [6]. It is important to consider expanding the investigative arsenal for chronic users of HCQ, with macular OCT [10, 32], including assessment of the thickness of the retinal ganglion cell complex, in addition to mfERG in selected cases [25, 28].

Conclusion

HCQ has been an effective drug in the treatment of rheumatological diseases with a chronic course for decades [2]. On the other hand, its prolonged use can cause irreversible macular damage, so that early detection of retinal toxicity is essential to preserve the vision of these patients [16]. Recognition of the effects of HCQ before any funduscopic changes are perceptible, with tests such as the visual field, and especially with OCT, is the best way to prevent the occurrence of serious and progressive lesions, such as the one observed in this case reported.

Care must be taken when observing inconclusive macular lesions that suggest retinotoxicity, as the suspension of HCQ in rheumatological patients may cause the reactivation of their underlying disease, even increasing their risk of death [33]. Upon confirmation of retinal involvement, discontinuation of the drug should be recommended, but this should be discussed with the patient and his or her attending physician [33].

Patients should be informed that the maculopathy may progress despite discontinuation of the drug, but also that there are risks related to possible reactivation of its underlying pathology with discontinuation of treatment. It is not always an easy decision, but a detailed screening associated with the use of appropriate dosages brings security so that HCQ can be used for long periods without causing visual damage.

References

1. Carr RE, Henkind P, Rothfield N, Siegel IM. Ocular toxicity of antimalarial drugs. Long-term follow-up. Am J Ophthalmol. 1968;66(4):738-44.
2. Murray JJ, Lee MS, Marmor RE, *et al*. American Academy of Ophthalmology Statement: Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 Revision). (Ophthalmology. 2016;123:1386-1394). Ophthalmology. 2017;124(3):e28-e9.
3. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol. 2014;132(12):1453-60.
4. Sebba AI, Weisman M, Welch KE, Yocum D, Furst DE, T M, *et al*. Hydroxychloroquine concentration-response relationships in patients with rheumatoid arthritis. Arthritis and rheumatism; c2002, 46(6).
5. 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(6):775-84.
6. Marmor MF, Hu J. Effect of disease stage on progression of hydroxychloroquine retinopathy. JAMA Ophthalmol. 2014;132(9):1105-12.
7. Brinkley JR, Dubois EL, Ryan SJ. Long-term course of chloroquine retinopathy after cessation of medication. Am J Ophthalmol. 1979;88(1):1-11.
8. Michaelides M, Stover NB, Francis PJ, Weleber RG. Retinal toxicity associated with hydroxychloroquine and chloroquine: risk factors, screening, and progression despite cessation of therapy. Arch Ophthalmol. 2011;129(1):30-9.
9. Singh DK, Muhieddine L, Einstadter D, Ballou S. Incidence of blindness in a population of rheumatic patients treated with hydroxychloroquine. Rheumatol Adv Pract. 2019 Apr 15;3(1).
10. Rosenbaum JT, Costenbader KH, Desmarais J, Ginzler EM, Fett N, Goodman SM, *et al*. American College of Rheumatology, American Academy of Dermatology, Rheumatologic Dermatology Society, and American Academy of Ophthalmology 2020 Joint Statement on Hydroxychloroquine Use With Respect to Retinal Toxicity. Arthritis Rheumatol. 2021;73(6):908-11.
11. Pereira CR, Pereira MB, Damasceno EF. Autofluorescência em um caso de distrofia macular anular concêntrica benigna. Revista Brasileira de Oftalmologia. 2019;78(4):260-3.
12. Yazdany J, Kim AHJ. Use of Hydroxychloroquine and Chloroquine During the COVID-19 Pandemic: What Every Clinician Should Know. Ann Intern Med. 2020 Jun 2;172(11):754-755.
13. Gautret P, Lagier JC, Honoré S, Hoang VT, Colson P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial revisited. Int J Antimicrob Agents. 2021 Jan;57(1):106243.
14. Marmor MF. COVID-19 and Chloroquine/Hydroxychloroquine: Is There Ophthalmological Concern? Am J Ophthalmol. 2020 Aug;216.
15. Leung LS, Neal JW, Wakelee HA, Sequist LV, Marmor MF. Rapid Onset of Retinal Toxicity From High-Dose Hydroxychloroquine Given for Cancer Therapy. Am J Ophthalmol. 2015 Oct;160(4):799-805.
16. Jorge A, Sharan KR, Choi HK. The Risk of Hydroxychloroquine Toxic Retinopathy and Its Risk Factors in the Treatment of Rheumatic Diseases: A Systematic Review - ACR Meeting Abstracts. American College of Rheumatology Meeting Abstracts; c2017, 1964.
17. Jallouli M, Galicier L, Zahr N, Aumaître O, Francès C, Le Guern V, *et al*. Plaquenil Lupus Systemic Study Group. Determinants of hydroxychloroquine blood concentration variations in systemic lupus erythematosus. Arthritis Rheumatol. 2015 May;67(8):2176-84.
18. Lee JY, Vinayagamoorthy N, Han K, Kwok SK, Ju JH, Park KS, *et al*. Association of Polymorphisms of Cytochrome P450 2D6 With Blood Hydroxychloroquine Levels in Patients With Systemic Lupus Erythematosus. Arthritis Rheumatol. 2016 Jan;68(1):184-90.
19. Grassmann F, Bergholz R, Mändl J, Jägle H, Ruether K, Weber BH. Common synonymous variants in ABCA4 are protective for chloroquine induced maculopathy (toxic maculopathy). BMC Ophthalmol. 2015 Mar 6;15:18.
20. Petri M, Elkhalifa M, Li J, Magder LS, Goldman DW. Hydroxychloroquine blood levels predict hydroxychloroquine retinopathy. Arthritis & rheumatology. 2020 Mar;72(3):448-53.
21. Mondal K, Porter H, Cole J, Pandya HK, Basu SK, Khanam S, *et al*. Hydroxychloroquine Causes Early Inner Retinal Toxicity and Affects Autophagosome-Lysosomal Pathway and Sphingolipid Metabolism in the Retina. Mol Neurobiol. 2022;59(6):3873-87.

22. Rosenthal AR, Kolb H, Bergsma D, Huxsoll D, Hopkins JL. Chloroquine retinopathy in the rhesus monkey. Invest Ophthalmol Vis Sci. 1978 Dec;17(12):1158-75.

23. De Sisternes L, Hu J, Rubin DL, Marmor MF. Localization of damage in progressive hydroxychloroquine retinopathy on and off the drug: inner versus outer retina, parafovea versus peripheral fovea. Invest Ophthalmol Vis Sci. 2015 May;56(5):3415-26.

24. Aw J MG, Anderson HR, Gardiner TA, McFarlane S, Archer DB, et al. Chloroquine causes lysosomal dysfunction in neural retina and RPE: implications for retinopathy. Current eye research; c2004, 28(4).

25. 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 Nov;256(11):2201-2210.

26. Melles RB, Marmor MF. Pericentral retinopathy and racial differences in hydroxychloroquine toxicity. Ophthalmology. 2015 Jan;122(1):110-6.

27. Marmor MF. Hydroxychloroquine Screening Alert: Change is in the Wind. Ophthalmic Surg Lasers Imaging Retina. 2017 Feb 1;48(2):96-98.

28. Alghanem H, Padhi TR, Chen A, Niziol LM, Abalem MF, Dakki N, et al. Comparison of Fundus-Guided Microperimetry and Multifocal Electroretinography for Evaluating Hydroxychloroquine Maculopathy. Transl Vis Sci Technol. 2019 Sep 27;8(5):19.

29. Rüther K, Foerster J, Berndt S, Schroeter J. [Chloroquine/hydroxychloroquine: variability of retinotoxic cumulative doses]. Der Ophthalmologe: Zeitschrift der Deutschen Ophthalmologischen Gesellschaft. 2007;104 10:875-9.

30. Chiang E, Jampol LM, Fawzi AA. Retinal toxicity found in a patient with systemic lupus erythematosus prior to 5 years of treatment with hydroxychloroquine. Rheumatology (Oxford). 2014 Nov;53(11):2001.

31. Phillips BN, Chun DW. Hydroxychloroquine retinopathy after short-term therapy. Retin Cases Brief Rep. 2014 Winter;8(1):67-9.

32. Cabral RTS, Klumb EM, Couto MINN, Carneiro S. Evaluation of toxic retinopathy caused by antimalarial medications with spectral domain optical coherence tomography. Arq Bras Oftalmol. 2019 Jan-Feb;82(1):12-17.

33. Daftarian N, Lima A, Marozoff S, Ojo D, Levasseur SD, Maberley DAL, et al. Investigators of INTACT study group. RetINal Toxicity And HydroxyChloroquine Therapy (INTACT): protocol for a prospective population-based cohort study. BMJ Open; 2022 Feb 17, 12(2).