ORIGINAL ARTICLE

Role of optical coherence tomography in the early detection of macular thinning in rheumatoid arthritis patients with chloroquine retinopathy

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Background: Chloroquine and hydroxychloroquine are drugs that are primarily used for the treatment of malaria and are also recommended for treating connective tissue disorders, autoimmune diseases, and some dermatological and inflammatory diseases. Treatment with these drugs has potential risk for the development of retinopathy, clinically characterized by bilateral pigment changes in the macula, as one serious ocular complication. The aim of this research was to evaluate the parafoveal and perifoveal macular retinal thickness, as central foveal thickness in adult patients with rheumatoid arthritis (RA) on chloroquine therapy using optical coherence tomography (OCT). **Materials and Methods:** In this cross-sectional study, 56 RA patients (56 eyes) were included and examined. All patients were treated with chloroquine (tablets resochin or delagil) at a dose of 250 mg/day without treatment with steroids and other immunosuppressive drugs. Patients were divided into two groups, namely, Group I patients - no visible changes in the macula (26 patients) and Group II patients- with visible changes in the macula (30 patients). The central fovea thickness and parafoveal and perifoveal retinal thickness in all quadrants were measured by OCT and compared in both groups. **Results:** There are a significantly higher number of eyes without thinning of the macula in Group I patients than in Group II ($P < 0.001$) patients. There are a higher number of patients with recorded parafoveal thinning in Group II patients, especially in the inferior, nasal, and temporal sectors, respectively ($P < 0.05$). **Conclusion:** Maculopathy is the main side effect of chloroquine therapy in RA patients that can be detected by OCT in the early stages of the macular involvement.

Key words: Chloroquine, optical coherence tomography, retina, rheumatoid arthritis

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INTRODUCTION

Chloroquine (4-aminoquinoline) and hydroxychloroquine are drugs that are primarily used for the treatment of malaria. They cause a mild suppression of the immune system and have been used for long in treating of connective tissue disorders in some autoimmune disorders such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[1] Furthermore, they can be used for some dermatological and inflammatory diseases, with potential risk for the development of retinopathy as a serious ocular complication.[1,2]

Although it is well-known that chloroquine may have a toxic effect on the retina and macular region, it is commonly used as the only available drug in some countries, because of socioeconomic reasons, for the treatment of RA and SLE.[1] The first changes occur in the cytoplasm of ganglion cells and photoreceptors of the retina. Lately retinal pigment epithelium (RPE) is affected, where the drug binds to melanin, which adversely affects the retina cell metabolism and leads to slow and chronic toxic effects.[3-5]

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Chloroquine or hydroxychloroquine retinopathy is clinically characterized by bilateral pigment changes in the macula, due to atrophy of the RPE, with sparing the foveal area. It is known as a "bull's eye" maculopathy. Retinal toxicity can selectively affect the periphery of the retina without significant changes in the macular area. In the late stages of retinopathy, RPE atrophy and the atrophy of neurosensory retina can occur. These changes are spreading centrifugally and cover the entire retina. Patients often complain of central vision loss, visual field defects, lack of color vision, and night blindness.[6,7] Patients in the chloroquine treatment can develop asymptomatic relative scotoma without any visible changes in the retina.[1,8]

The risk factors for toxic retinopathy are the daily dose of hydroxychloroquine >5.0 mg/kg of actual weight, chloroquine >2.3 mg/kg of actual weight, duration of therapy > 5 years (without other risk factors), kidney disease, concomitant use of tamoxifen, and macular disease. Even patients who use the recommended dose have a significant risk after decades of use. Earlier literature suggested that a "cumulative dose" (which combines daily dose and duration) may be a simple risk indicator; nowadays, it is known that is more accurate to determine the risk based on the duration of use relative to the daily dose/weight.[9]

The aim of this study was to evaluate the parafoveal and perifoveal macular retinal thickness as the central foveal thickness (CFT) in adult patients with RA from south-eastern Serbia on chloroquine therapy using optical coherence tomography (OCT).

PATIENTS AND METHODS

This cross-sectional study included 56 RA patients (56 eyes) referred for ophthalmological examination by the rheumatologist. All patients involved in the trials met the criteria of the American College of Rheumatology from 2010 as well as other criteria described in the previous study.[10-14] The patients were divided into two groups: Group I patients - no visible changes in the macula (26 patients) and Group II patients - with visible changes in the macula (30 patients). Patients with glaucoma, ocular hypertension, optic nerve diseases, diabetes, diseases of the retina and the macula, uveitis, chorioretinitis, defects in the visual field, including the central 10 degrees, prior ophthalmic surgery, and larger refractive errors (greater than ± 6D spheres and/or greater than ± 3D cylinder) were excluded from the study.[6] If both eyes of the patients met the inclusion criteria, only one eye was randomly selected. All patients signed the informed consent.

The basic demographic data, as well as data on the therapeutic daily dose, duration of treatment, and duration of the disease, were recorded. All of our patients were treated for early RA (patients who started taking therapy in the first 3–6 months of the onset of symptoms) with chloroquine tablets (Tablet Resochin, Bayer Schering, Bulgaria or Tablet Delagile, Pharma Swiss, Hungary), for different lengths of time (6.11 ± 5.85 years; 4.00), at a dose of 250 mg/day, without steroids and other immunosuppressive drugs usage.

All patients underwent a standard ophthalmological examination, including determination of visual acuity by Snellen, biomicroscopy examination of the anterior segment of the eye, measurement of intraocular pressure by Goldmann applanation tonometry, ophthalmoscopy, wide pupil fundoscopy with + 90D lens, standard automated perimetry (Humphrey Visual Field Analyzer, HFA, SAD; Carl Zeiss Meditec, Inc., Treshold Test, Sita Standard 24-2 and 10-2), and OCT (Stratus OCT, Carl Zeiss Meditec, Inc.). OCT protocols "fast mac" - fast macular thickness map and "retinal thickness/volume tabular (OU)" were used for testing.

CFT and parafoveal and perifoveal retinal thickness in all quadrants (9: fovea, superior inner, nasal inner, inferior inner, temporal inner, superior outer, nasal outer, inferior outer, and temporal outer) in both groups were measured and compared using the Fisher's exact test.[2] The data were collected, tabulated, and analyzed. A value of $P < 0.05$ was considered statistically significant.

RESULTS

The demographic characteristics of all participants were determined and are presented in Table 1. Among the examined patients, there were significantly more women (male–female, 6 (10.71%): 50 (89.29%), $P < 0.001$).

Furthermore, Table 2 shows the collected and analyzed clinical parameters. The visual acuity of the eyes without visible changes in the macula region (Group I patients) was better than in eyes with visible changes (Group II patients), ($P < 0.01$).

There is no statistically significant difference in the length of chloroquine therapy between the eyes without visible changes and with visible changes, which means that there is no statistically significant association of the changes in correlation with the length of therapy [Table 2].

The thickness of the retinal nerve fibers was determined in nine macular fields (fovea, superior inner, nasal inner, inferior inner, temporal inner, superior outer, nasal outer, inferior outer, and temporal outer) [Table 3]. In the whole sample, the highest number of patients had normal macular thickness, i.e., without thinning, 39 (69.64%): 17 (30.36%) ($P < 0.01$). Furthermore, there is a significantly

Table 1: Demographic characteristics, duration of therapy, and basic clinical parameters of rheumatoid arthritis patients

Number of patients	56
Demographic characteristics	
Number of eyes	56
Number of females (%)	50 (89.29)
Number of males (%)	6 (10.71)
Age (years)	49.50±14.73 (49.00)
Therapy	
Average length of therapy (years)	6.11±5.85 (4.00)
Clinical parameters	
Average visual acuity (Snellen)	0.89±0.19 (1.00)
IOP (mmHg)	17.11±2.01 (17.50)
Group I (patients without changes)	26 (46.43)
Group II (patients with changes)	30 (53.57)

Age (years)=Age of patients with early RA; Average length of therapy (years)=Average length of therapy (mean value±SD [median]); Average visual acuity (Snellen)=Average visual acuity determined by Snellen chart (mean value±SD [median]); IOP (mmHg)=Intraocular pressure is presented as mean value±SD (median); Group I (patients without changes)=Group of patients without visible changes in macula; Group II (patients with changes)=Group of patients with visible changes in macula; SD=Standard deviation; RA=Rheumatoid arthritis

Table 2: Clinical characteristics of rheumatoid arthritis patients by groups

Clinical parameters	Group I	Group II	*P*
Visual acuity (Snellen)	0.96±0.12 (1.00)	0.82±0.21 (0.9)	0.0011
IOP (mmHg)	17.23±2.08 (17.00)	17.00±1.97 (18.00)	0.8678
Length of therapy (years)	6.08±6.49 (4.00)	6.16±4.27 (5.00)	0.0039

Visual acuity (Snellen)=Visual acuity determined by Snellen chart (mean value±SD [median]); IOP (mmHg)=Intraocular pressure is presented as mean value±SD (median); Length of therapy (years)=Length of therapy (mean value±SD [median]); SD=Standard deviation

Table 3: Thickness distribution of the retinal nerve fibers in nine macular sectors

Sector	Normal, *n* (%)	Higher, *n* (%)	Thinning, *n* (%)
Fovea	52 (92.86)	0	4 (7.14)
Superior inner	51 (91.07)	4 (7.14)	1 (1.79)
Nasal inner	48 (85.71)	2 (3.57)	6 (10.71)
Inferior inner*	46 (82.14)	3 (5.36)	7 (12.50)
Temporal inner	49 (87.50)	1 (1.79)	6 (10.71)
Superior outer	49 (87.50)	7 (12.50)	0
Nasal outer	49 (87.50)	5 (8.93)	2 (3.57)
Inferior outer	48 (85.71)	3 (5.36)	5 (8.93)
Temporal outer	53 (94.64)	1 (1.79)	2 (3.57)

*P<0.05 (P=0.0128) versus superior outer. Sector=Macular region and nine sectors; *n*=Number of eyes with retinal thickness distribution by macular normative base (Fast Mac)

higher number of eyes without thinning of macula in Group I patients than in Group II patients (25 [96.15%]: 1 [4.85%] vs. 14 [46.67%]: 16 [53.33%]) (Group I [$P < 0.001$] vs. Group II [$P = 0.715$]). The thinning of the retinal nerve fibers in the macula, looking at all nine fields together, are statistically more common in Group II patients than in Group I patients ($P < 0.001$) [Table 3].

As shown in Table 3, most of the eyes had macular thinning in the inferior inner sector (12.50%), statistically significantly higher than in the superior outer sector, where the thinning does not exist at all ($P < 0.05$, Fisher's exact test). Frequency is followed by nasal inner (10.71%) and temporal inner (10.71%) quadrants of the macula. There were more eyes with the thinning of macular nerve fibers in all of these nine sectors in Group II patients, except for superior outer sector where there were no pathological findings in any of the examined groups. A statistically significantly higher presence of pathological values was in Group II patients than Group I patients for inferior inner and temporal inner sectors [$P < 0.05$, Fisher's exact test, Table 4].

DISCUSSION

Chloroquine retinotoxicity is a serious ophthalmological concern because it cannot be treated. If the damage is detected before the RPE changes, it is possible to maintain a good central visual acuity.[9] In clinical practice, photoreceptors are primarily damaged, and as the outer nuclear layer degenerates, secondary RPE is also disturbed.[9]

As far as we know, it has not been proven that the anatomical properties of the retina and RPE correlate specifically with parafoveal or extramacular region if chloroquine toxicity develops. Although most European patients show initial damage to photoreceptors in the classical parafoveal region, most patients with Asian background will show initial damage in the peripheral extramacular region near the arcades.[9]

This present study results show that there were significantly more women (89.29%) among the participants. Furthermore, the visual acuity was better in the eyes without fundoscopically visible changes in the macula ($P < 0.01$). This is in line with the other authors' opinion that the first changes in chloroquine retinopathy can be completely asymptomatic, and the retina can remain normal for a long time before the onset of maculopathy.[2] Therefore, the most important are screening and detection of the first changes in the phase of early maculopathy.[2] In practice, the ophthalmic examination has to cover fundoscopy and standard automated perimetry 10-2 threshold vision field testing, and at least one of the objective tests multifocal electroretinogram, fundus autofluorescence, and OCT,[9,15-17] as recommended by the American Academy of Ophthalmology (AAO).[4,9]

In this study, all of our patients took a fixed daily dose of chloroquine, i.e., 250 mg/day. However, we did not find the connection between macula thinning and the length of chloroquine therapy. Our research recorded that thinning occurred primarily in the inferior inner and

Table 4: Group's comparison of retinal nerve fibers thickness in nine macular sectors

Sector	Group I			Group II			*P*
	Normal, *n* (%)	Higher, *n* (%)	Thinning, *n* (%)	Normal, *n* (%)	Higher, *n* (%)	Thinning, *n* (%)	
Fovea	26 (100.00)	0	0	26 (86.67)	0	4 (13.33)	0.1153
Superior inner	24 (92.31)	2 (7.69)	0	27 (90.00)	2 (6.67)	1 (3.33)	0.9424
Nasal inner	24 (92.31)	1 (3.85)	1 (3.85)	24 (80.00)	1 (3.33)	5 (16.67)	0.2002
Inferior inner*	25 (96.15)	1 (3.85)	0	21 (70.00)	2 (6.67)	7 (23.33)	0.0116
Temporal inner*	26 (100.00)	0	0	23 (76.67)	1 (3.33)	6 (20.00)	0.0254
Superior outer	23 (88.46)	3 (11.54)	0	26 (86.67)	4 (13.33)	0	/
Nasal outer	24 (92.31)	2 (7.69)	0	25 (83.33)	3 (10.00)	2 (6.67)	0.4935
Inferior outer	24 (92.31)	2 (7.69)	0	24 (80.00)	1 (3.33)	5 (16.67)	0.0545
Temporal outer	26 (100.00)	0	0	27 (90.00)	1 (3.33)	2 (6.67)	0.4935

*$P<0.05$, Group I versus Group II (Fisher exact). Sector=Macular region and nine sectors; *n*=Number of eyes with retinal thickness distribution by macular normative base (Fast Mac); / - Undefined *P* value, because none of the groups has Thinning and it is impossible to do a statistical test

temporal inner quadrants, without any connection to the treatment durations. In line with those results, Allam *et al*.[2] documented in their study that clinically asymptomatic patients using chloroquine in RA therapy had reduced CFT and also reduced parafoveal thickness in all quadrants compared to the healthy controls. They believe that this change is not correlated with either cumulative doses or the duration of the treatment.[2]

In the present study, we have evaluated the retinal thickness of macula and found that macula thinning, observing all nine fields, is significantly more common in the group of patients with fundoscopically visible changes ($P < 0.001$). Our research has shown that there are a higher number of patients with recorded parafoveal thinning in Group II, especially in the inferior, nasal and temporal sectors, respectively. There was no thinning in a superior outer sector in any patient. Rarely, the thinning occurred in the peripheral region which is contrary to the study of some authors,[7,9] that hydroxychloroquine retinopathy does not always develop in the parafoveal area, especially in Asian patients, where the dominant pericentral damage is present.[18,19] Spectral-domain OCT (high-resolution OCTs) shows localized thinning of the retinal layers in the parafoveal region and confirm early toxicity stage, much before symptomatic visual field loss occurs.[7,20] Our findings are in accordance with the recent results that there are changes in the thickness of the retina and loss of outer retinal layers, which could be detected by OCT in patients with initial chloroquine maculopathy, even with normal findings on retina and perimetry.[21] Most patients with vision loss were on therapy for >5 years.[22] Although Brandao and Palmowski-Wolfe[23] described a case of chloroquine maculopathy identified exclusively by OCT thickness analysis in a patient in whom cumulative and daily doses were below the high risk of screening and under-reported doses in other studies.

If chloroquine maculopathy is diagnosed, therapy is usually stopped immediately, clinical improvement occurs.[9,24] However, reversibility of vision loss decreases over time, which is why early detection of these changes is the most important. To date, there is no medical treatment for chloroquine and hydroxychloroquine retinopathy, except the cessation of therapy. Before the discontinuation of the medicinal product, the patient's systemic condition should be considered and done in agreement with a rheumatologist or other physician, since the cessation of therapy may lead to deterioration of the systemic disease.[9] It must be noted that loss of vision is possible several months after the discontinuation of the drug. In addition, chloroquine retinopathy may progress long after cessation of the drug and may be complicated by cystoid macular edema, the formation of epiretinal membranes, and involving the retinal periphery.[9,24-27]

Chloroquine and hydroxychloroquine are useful drugs and have little systemic side effects in relation to other drugs for the treatment of immunological and inflammatory diseases. When retinopathy is recognized early before the RPE is damaged, there is a slight and limited progression after the treatment is stopped, and the fovea is not compromised. Screening cannot "prevent" the damage but allows the detection of toxicity before the vision is endangered. It can help patients to continue with therapy and prevent serious retinal damage.[9]

The major limitation of this study is the small number of patients included who immediately start the therapy within the 6 months of the symptoms appearances but our results are consistent; therefore, we recommend conducting studies with a larger number of RA patients. Furthermore, to the best of our knowledge, this is the first such research in Serbian population that includes the OCT parameters, so it would be nice to expand this research with data from the visual field 10-2 test in future.

CONCLUSION

In summary, this study finds that the side effect of RA chloroquine therapy is maculopathy that can be detected

very early on OCT even in the case of thinning in the macula without clinically obvious changes. We recommend OCT, as a noninvasive, highly accurate, and reproducible method, for the follow-up of patients using chloroquine derivatives, regardless of duration with or without visible macular changes. Furthermore, we can propose that screening protocols for chloroquine maculopathy must include the study of thinning in the parafoveal and peripheral macular zone due to the indicated racial differences.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Moschos MM, Nitoda E, Chatziralli IP, Gatzioufas Z, Koutsandrea C, Kitsos G, *et al.* Assessment of hydroxychloroquine maculopathy after cessation of treatment: An optical coherence tomography and multifocal electroretinography study. Drug Des Devel Ther 2015;9:2993-9.
2. Allam RS, Abd-Elmohsen MN, Khafagy MM, Raafat KA, Sheta SM. Spectral-domain optical coherence tomography of preclinical chloroquine maculopathy in Egyptian rheumatoid arthritis patients. J Ophthalmol 2015;2015:292357.
3. Geamănu Pancă A, Popa-Cherecheanu A, Marinescu B, Geamănu CD, Voinea LM. Retinal toxicity associated with chronic exposure to hydroxychloroquine and its ocular screening. Review. J Med Life 2014;7:322-6.
4. 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;15:18.
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;62:775-84.
6. Pasadhika S, Fishman GA, Choi D, Shahidi M. Selective thinning of the perifoveal inner retina as an early sign of hydroxychloroquine retinal toxicity. Eye (Lond) 2010;24:756-62.
7. Pasadhika S, Fishman GA. Effects of chronic exposure to hydroxychloroquine or chloroquine on inner retinal structures. Eye (Lond) 2010;24:340-6.
8. Rodríguez-Hurtado FJ, Sáez-Moreno JA, Rodríguez-Ferrer JM. Maculopathy in patient with systemic lupus erythematosus treated with hydroxychloroquine. Reumatol Clin 2012;8:280-3.
9. 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.
10. Pavlovic V, Dimic A, Milenkovic S, Krtinic D, Aleksic I. Relation between bone mineral density and IL-17 serum levels in Serbian patients with early rheumatoid arthritis. Open Med (Wars) 2015;10:106-12.
11. Karimzadeh H, Karami M, Bazgir N, Karimifar M, Yadegarfar G, Mohammadzadeh Z, *et al.* Ultrasonographic findings of rheumatoid arthritis patients who are in clinical remission. J Res Med Sci 2018;23:38.
12. Karimzadeh H, Rafiei R, Sayedbonakdar Z, Karami M. Agreement of clinical examination and ultrasound methods for detection of joints involvements in rheumatoid arthritis. J Res Med Sci 2017;22:87.
13. Javadi F, Eghtesadi S, Ahmadzadeh A, Aryaeian N, Zabihiyeganeh M, Foroushani AR, *et al.* The effect of quercetin on plasma oxidative status, C-reactive protein and blood pressure in women with rheumatoid arthritis. Int J Prev Med 2014;5:293-301.
14. Rahnama N, Mazloum V. Effects of strengthening and aerobic exercises on pain severity and function in patients with knee rheumatoid arthritis. Int J Prev Med 2012;3:493-8.
15. Bergholz R, Rüther K, Schroeter J, von Sonnleithner C, Salchow DJ. Influence of chloroquine intake on the multifocal electroretinogram in patients with and without maculopathy. Doc Ophthalmol 2015;130:211-9.
16. Kelmenson AT, Brar VS, Murthy RK, Chalam KV. Fundus autofluorescence and spectral domain optical coherence tomography in early detection of plaquenil maculopathy. Eur J Ophthalmol 2010;20:785-8.
17. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol 2014;132:1453-60.
18. Korah S, Kuriakose T. Optical coherence tomography in a patient with chloroquine-induced maculopathy. Indian J Ophthalmol 2008;56:511-3.
19. Melles RB, Marmor MF. Pericentral retinopathy and racial differences in hydroxychloroquine toxicity. Ophthalmology 2015;122:110-6.
20. Stepien KE, Han DP, Schell J, Godara P, Rha J, Carroll J. Spectral-domain optical coherence tomography and adaptive optics may detect hydroxychloroquine retinal toxicity before symptomatic vision loss. Trans Am Ophthalmol Soc 2009;107:28-33.
21. Chen E, Brown DM, Benz MS, Fish RH, Wong TP, Kim RY, *et al.* Spectral domain optical coherence tomography as an effective screening test for hydroxychloroquine retinopathy (the "flying saucer" sign). Clin Ophthalmol 2010;4:1151-8.
22. Bergholz R, Schroeter J, Rüther K. Evaluation of risk factors for retinal damage due to chloroquine and hydroxychloroquine. Br J Ophthalmol 2010;94:1637-42.
23. Brandao LM, Palmowski-Wolfe AM. A possible early sign of hydroxychloroquine macular toxicity. Doc Ophthalmol 2016;132:75-81.
24. Lai WW, Lam DS. Chloroquine-induced bull's eye maculopathy. Hong Kong Med J 2005;11:55-7.
25. Nika M, Blachley TS, Edwards P, Lee PP, Stein JD. Regular examinations for toxic maculopathy in long-term chloroquine or hydroxychloroquine users. JAMA Ophthalmol 2014;132:1199-208.
26. Kellner S, Weinitz S, Farmand G, Kellner U. Cystoid macular oedema and epiretinal membrane formation during progression of chloroquine retinopathy after drug cessation. Br J Ophthalmol 2014;98:200-6.
27. Turgut B, Turkcuoglu P, Serdar Koca S, Aydemir O. Detection of the regression on hydroxychloroquine retinopathy in optical coherence tomography. Clin Rheumatol 2009;28:607-9.