Evaluation of Macular Changes in the Pre-symptomatic Stage and the Effect of Hydroxychloroquine Duration on These Changes in Patients Using Hydroxychloroquine

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ABSTRACT

Purpose: To evaluate the alterations in retinal layer thickness within the central macula in patients treated with hydroxychloroquine (HCQ) based on the duration of drug use.

Materials and Methods: The 70 eyes of 35 patients (Systemic Lupus Erythematosus(SLE) 5.7%, Rheumatoid Arthritis(RA) 68.6%, Sjogren Syndrome(SS) 25.7%) who had been using the medication for five years or less were classified as group I and the 70 eyes of 35 patients (SLE 14.2%, RA 60.0%, SS 25.8%) who had been using the medication for more than five years were classified as group II. Optical coherence tomography, fundus autofluorescence (FAF), and 10-2 visual field tests conducted on patients using HCQ were reviewed retrospectively.

Results: The full retinal thickness (FRT), nerve fiber layer (NFL), inner plexiform layer (IPL), outer nuclear layer (ONL) and inner retinal layers (IRL) values in Group II are lower compared to those in Group I, the difference is not significant ($p > 0.05$). There were a statistically significant differences in ganglion cell layer (GCL), retina pigment epitelium (RPE) and outer retinal layers (ORL) values among the two groups ($p < 0.05$). In group II periferic visual field mean deviation (pvf-md) and periferic visual field pattern standart deviation (pvf-psd) values are higher than in group I but the difference is not significant ($p > 0.05$). FAF was evaluated as normal in all patients except one.

Conclusion: HCQ use may cause subfoveal retinal layer thickness alterations in GCL, RPE, ORL even without evident retinal toxicity. Regular retinal imaging should be performed before it leads to vision loss.

Keywords: Antimalarial drugs, hydroxychloroquine, macula, retinal imaging, retinal toxicity.

INTRODUCTION

Hydroxychloroquine sulfate (Plaquenil®; Sanofi-Aventis, Bridgewater, NJ) is an antimalarial drug widely prescribed for connective tissue disorders such as Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA) and Sjogren Syndrome (SS) because of its anti-inflammatory properties. It is used both independently and alongside other medications to improve their effectiveness and allow for lower dosages.[1] Hydroxychloroquine's (HCQ) affordability, its role in improving survival rates in SLE, and its ability to alleviate synovitis and physical disabilities in RA contribute to its popularity.[2,3] Nonsteroidal anti-inflammatory drugs are frequently used in rheumatologic conditions but they tend to have more side effects than HCQ.[4] It is slowly eliminated from the body.[5] With prolonged use, it accumulates in melanin-rich eye structures like the choroid and retina pigment epithelium (RPE), causing progressive photoreceptor cell death and irreversible damage in the outer retinal layers.[6]

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published guidelines for screening hydroxychloroquine retinopathy in 2016.[7] A fundus examination must be performed on patients before starting the medication. This way, any pre-existing maculopathy can be detected if present. Patients who are on acceptable doses and do not have significant risk factors should begin annual screenings after 5 years. Annual examinations are recommended for high-risk groups. High-risk criteria include treatment duration over 5 years, a daily dose more than 6.5 mg/kg, a high body mass index, patient age over 60, and liver or kidney dysfunctions affecting drug metabolism. Primary screening tests consist of a visual field test and spectral-domain optical coherence tomography (SD-OCT). Multifocal electroretinogram (mfERG) is a valuable tool for objectively verifying visual field tests, while fundus autofluorescence (FAF) is utilized to illustrate topographic retinal damage. The guideline supported by other studies.[8] A study by Melles and Marmor [9] involving 2500 patients indicated that the HCQ dosage calculated as less than 5 mg per kg per day, according to the individual's actual body weight is linked to less than a 2% risk of toxicity within the first 10 years. Early detection of retinal toxicity through patient monitoring can occur before visual symptoms manifest.[10] The goal of modern screening techniques is to identify retinopathy before any fundus abnormalities become apparent. In many cases, toxic damage tends to affect the parafoveal region; however, extramacular damage patterns are more frequently observed in Asian patients. It is advised that the medication dosage should not more than 5.0 mg/kg/day, determined according to the patient's true body weight. The risk of toxicity depends not only on the daily dose but also on the duration of use. When HCQ is used at recommended doses, the toxicity rate is less than 1% within the first 5 years, under 2% within 10 years, however, when used for more than 20 years, this rate increases to up to 20%. Interestingly, if no toxicity develops after 20 years, the risk for the next year is just 4%. Pre-symptomatic retinopathy can be identified early, preventing vision loss if the medication is stopped.[7,11] Early detection is vital as toxicity can progress even post-discontinuation.[12]

Fundus Autofluorescence (FAF) imaging allows topographic mapping of natural or pathological intrinsic fluorophores of fundus and it is noninvasive. It evaluates the fluorescence emitted by fluorophores, known as lipofuscin, stored in the lysosomes of postmitotic RPE cells under short-wavelength light. FAF intensity increases with age from the fovea.[13,14] When lipofuscin pigments accumulate in the retina, FAF signal intensity also increases. In this case, these materials in the photoreceptor outer segments are inadequately phagocytosed.[15] Decreased or absent FAF signal intensity indicates RPE cell death.[16]

The visual field is assessed using a Humphrey 10-2 standard perimeter, which measures the central 10° temporally and nasally at 68 points separated by 2°. The earliest sign of HCQ retinopathy in the 10-2 visual field is reduced sensitivity in the paracentral area. Late toxicity can present as a complete ring defect with full bull's-eye scotoma, sparing the fovea relatively.[17]

SD-OCT provides detailed cross-sectional views of the retina and can identify characteristic changes before HCQ retinopathy becomes clinically evident.[18] In HCQ retinopathy, changes are observed in the outer nuclear layer, outer limiting membrane, inner-outer segment junction, and RPE in the parafoveal region on SD-OCT. The subfoveal retina is generally preserved, central vision is preserved despite advanced perifoveal HCQ retinopathy.[17]

This study aimed to investigate retinal toxicity associated with the duration of drug use before visual symptoms appear in patients using HCQ.

MATERIALS and METHODS

This study included individuals aged 18 to 55 who were taking 200 mg of HCQ per day between December 2022 and April 2023. The 70 eyes of 35 patients who had been using the medication for five years or less were classified as group I, and the 70 eyes of 35 patients who had been using the medication for more than five years were classified as group II.

It was ensured that the participants enrolled in the study had a corrected vision of at least 0.1 logMAR and had undergone a detailed ophthalmological examination. Patients who had undergone any eye surgery, had congenital eye diseases, glaucoma, cataracts, keratoconus, macular diseases, myopia over -4 diopters, hypermetropia over +3 diopters, a history of using medications that could affect the macula (such as tamoxifen), those who did not regularly use HCQ, those with unreliable visual field tests, and those with renal impairment were excluded from the study.

Patient records were extracted from the hospital database. Patients attending our clinic were assessed following the standard protocol based on the recommendations of the American Academy of Ophthalmology, revised in 2011 and 2016. The routine SD-OCT, FAF, and 10-2 visual field tests conducted on patients using HCQ were reviewed.

For the visual field test (Zeiss Humphrey 850), it was ensured that patients over 45 years of age were tested with their reading glasses, and those who routinely used glasses were tested with their own glasses. To increase the reliability of the visual field, the mean deviation (md) value and pattern standart deviation value (psd) from the second test were considered. If the reliability of test was low, the patient was excluded from the study.

Every patients were evaluated using the automatic calculation software system available on SD-OCT (Heidelberg Spectralis OCT version 1.10.4.0, Heidelberg Engineering, Heidelberg, Germany) for automated segmentation of the macula. The retinal layers were evaluated through automatic segmentation as shown in Figure.

The evaluation of FAF was conducted by two separate individuals, and the study reflected the consensus view.

The study was conducted in accordance with the principles of the Helsinki Declaration and received approval from the Ethics Committee of our hospital (approval number 23.05.2023/843).

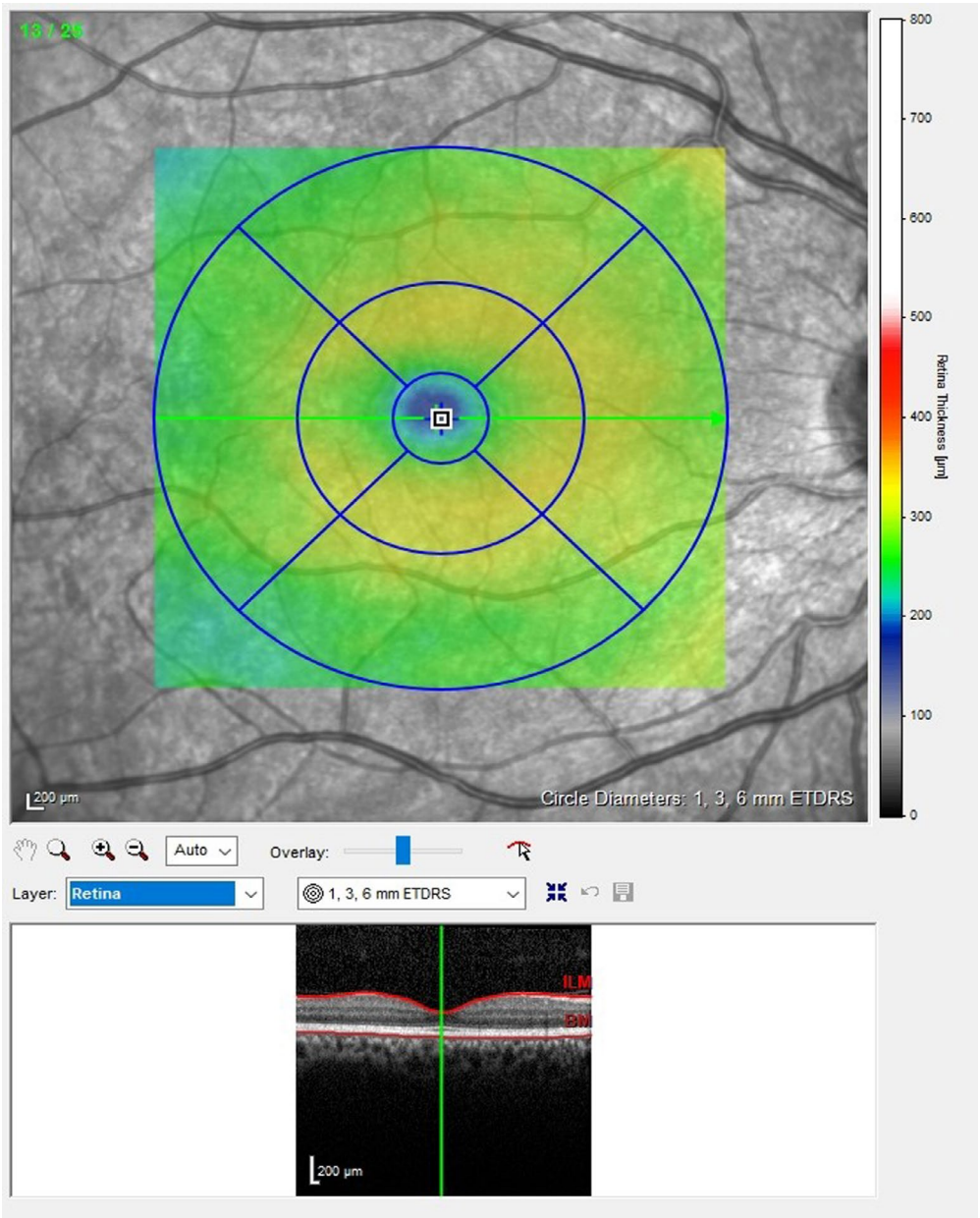

Figure: *The automatic segmentation of retinal layers.*

STATİSTİCAL ANALYSİS

The data analysis was performed with SPSS 25.0 software package. Categorical variables were summarized using counts and percentages, whereas quantitative variables were described by their mean, median, minimum, and maximum values. The Kolmogorov-Smirnov test statistic was used to test for normality. Cross tables were used for categorical data, and the Pearson Chi-Square test was employed to evaluate the relationship between the groups For continuous variables that adhered to a normal distribution, the Student's t-test was utilized for comparisons between the two groups, while the Mann-Whitney U test was applied for those with a non-normal distribution. For continuous variables with a normal distribution, the ANOVA test was used to compare more than two groups, while the Kruskal-Wallis test and Dunnett's multiple comparison test were used for more than two groups with a non-normal distribution. Spearman's rho correlation analysis was conducted to investigate the associations between variables that were not normally distributed. In the analysis, a p-value of less than 0.05 was considered statistically significant.

RESULTS

Patients who took part in the study, 63 were female (90%) and 7 were male (10%), with a mean age of 45.19 ± 8.50 years. No statistically meaningful difference was found between the two groups regarding mean age and gender ($p > 0.05$). In Group I, the average duration of drug use was 19.94 ± 18.61 months, while in Group II, it was 138 ± 55.58 months. In Group I, 2 patients (5.7%) had SLE, 24 (68.6%) had RA, and 9 (25.7%) had SS, whereas in Group II, 5 patients (14.3%) had SLE, 21 (60.0%) had RA, and 9 (25.7%) had SS. No statistically meaningful difference was observed between the two groups ($p > 0.05$). This is shown in Table 1.

Although periferic visual field pattern standard deviation (pvf-psd) and the periferic visual field mean deviation (pvf-md) values in Group II are higher compared to Group I, the difference is not considered statistically significant ($p > 0.05$). The full retina thickness (FRT), nerve fiber layer (NFL), inner plexiform layer (IPL), outer nuclear layer (ONL) and inner retinal layer (IRL) values in Group II are lower compared to those in Group I, the observed difference lacks statistical significance ($p > 0.05$). Although the inner nuclear layer (INL) and outer plexiform layer (OPL) values are higher in Group II, the difference is not meaningful ($p > 0.05$). The ganglion cell layer (GCL), retina pigment epithelium (RPE) and outer retinal layer (ORL) values are statistically lower in group II ($p < 0.05$). Comparison of measurement values with the duration of medication use is summarized in Table 2.

Group II and Group I were compared within each disease group. In SLE patients, a statistically significant variation exists in the mean pvf-md measurements between Group I and Group II ($p < 0.05$). The mean pvf-md, FRT, IPL and IRL measurements in SLE patients in Group II are significantly higher than that of those in Group I ($p < 0.05$). No statistically meaningful differences were observed in pvf-psd, NFL, GCL, INL, OPL, ONL, RPE and ORL values between Group I and Group II in SLE patients ($p > 0.05$) .

Table 1. *Demographic characteristics. SLE: Systemic Lupus Erythematosus, RA: Rheumatoid Arthritis, SS: Sjogren Syndrome.*

	Group I (n=35)	Group II (n=35)	Total (n=70)	p-value
Age	43.46±8.82 (27-55 years)	46.91±7.93 (28-55 years)	45.19±8.50 (27-55 years)	0.082*
Gender Female Male	31 (88.6 %) 4 (11.4 %)	32 (91.4 %) 3 (8.6 %)	63 (90.0 %) 7 (10.0 %)	0.690**
Duration of HCQ use	19.94±18.61 (3-60 months)	138±55.58 (72-300 months)	78.97±72.30 (3-300 months)	<0.000*
Type of disease	2 (5.7 %)SLE 24 (68.6 %)RA 9 (25.7 %)SS	5 (14.3 %) SLE 21 (60.0 %)RA 9 (25.7 %)SS	7 (10.0 %) SLE 45 (64.3 %)RA 18 (25.7 %)SS	0.466**

Table 2. *Comparison of measurement values with the duration of medication use. Pvf-md: periferic visual field mean deviation, pvf-psd: periferic visual field pattern standart deviation, FRT: full retinal thickness, NFL:nerve fiber layer, GCL: ganglion cell layer, IPLinner plexiform layer, INL:inner nuclear layer, OPL:outer plexiform layer, ONL: outer nuclear layer, RPE: retina pigment epitelium, IRL:inner retinal layers, ORL:outer retinal layers.*

	Total (n=140)		Group I (n=70)		Group II (n=70)		
	(Min.-Max.) Median	mean±sd	(Min.-Max.) Median	mean±sd	(Min.Max.) Median	mean±sd	p-value
Pvf-md	(0.07-5.34)1.41	1.63±1.14	(0.07-4.35) 1.66	1.61±1.00	(0.14-5.34)1.22	1.65±1.26	0.709*
Pvf-psd	(0.88-5.42)1.53	1.75±0.83	(0.92-3.78) 1.57	1.68±0.54	(0.88-5.42)1.49	1.82±1.04	0.490*
FRT	(217-303) 268	265.35±18.1	(228-301) 271	268.27±19.02	(217-303) 264	262.43±16.82	0.056**
NFL	(7-19) 12	12.19±2.18	(8-19) 12	12.49±2.25	(7-18) 12	11.89±2.08	0.163*
GCL	(8-40) 14	14.52±4.13	(9-40) 15	15.33±4.73	(8-27) 13	13.71±3.27	0.028*
IPL	(14-32) 19	19.58±2.98	(14-32) 19	20.06±3.27	(15-27) 19	19.10±2.60	0.072*
INL	(10-36) 19	18.98±4.64	(10-34) 18	18.40±4.47	(12-36) 19	19.56±4.77	0.196*
OPL	(14-89) 24	25.46±8.06	(14-40) 24	24.89±5.84	(17-89) 24	26.03±9.80	0.943*
ONL	(56-115) 89	88.25±10.35	(67-105) 89	88.59±9.62	(56-115) 89	87.91±11.09	0.703**
RPE	(12-24) 17	16.79±1.91	(13-23) 17	17.10±1.88	(13-24) 16	16.47±1.90	0.011*
IRL	(136-260) 180	178.50±18.7	(143-260) 183	180.80±20.83	(136-208) 176	176.20±16.28	0.297*
ORL	(76-99) 88	87.31±4.52	(76-95) 89	88.41±4.09	(77-99) 86	86.21±4.69	0.004**

Although Group II had higher mean values for pvf-md and pvf-psd compared to Group I among RA patients there is no significant statistical difference ($p>0.05$). Although the FRT, NFL, GCL, IPL, OPL, ONL, RPE, and IRL values in Group II are lower than those in Group I, but the differences are not statistically meaningful ($p > 0.05$). The INL value is higher in Group I, but no notable difference exists between the groups ($p > 0.05$). The average measurement of ORL in Group I is markedly above the average ORL measurement in Group II ($p < 0.05$).

Despite lower values of pvf-md, pvf-psd, ONL, IRL, and ORL among SS patients in Group II showed differences compared to Group I, these differences were not significant. ($p > 0.05$). The FRT, NFL, GCL, IPL, and RPE values were significantly lower in Group II ($p < 0.05$). Although the INL value was higher in Group I, no meaningful difference was found between the two groups ($p > 0.05$). The retinal layer changes in SLE, RA and SS based on the duration of medication use is shown in table 3.

DISCUSION

Hydroxychloroquine dosage (recommended dose 5 mg/kg/day), duration of drug use, renal dysfunction, and concomitant use of tamoxifen are major risk factors for retinopathy toxicity. The primary risk factor is an high daily dose given relative to body weight and the duration of drug use. When patients treated with HCQ at doses ranging from 800 to 1000 mg/day for non-rheumatic disorders, a 25% to 40% incidence of retinopathy and signs of damage was seen after 1 to 2 years.[18,19] In a different study, patients who developed retinal toxicity had been on HCQ for periods ranging from 6.7 to 21.9 years, with daily doses between 4.9 and 9.1 mg/kg.[20] In a study conducted by Melles and colleagues[21], retinopathy was detected in 81 out of 3,325 patients who had used HCQ for 5 years or more. They observed that the risk of retinopathy increased significantly as the dosage and duration of use increased. In our study, all participants were using 200 mg/day of HCQ. The duration of drug use was 19.94 ± 18.61 months on average in Group I, whereas it was 138 ± 55.58 months in Group II. Although the pvf-md and pvf-psd values in Group II are higher and FRT, NLF, GCL, IPL, ONL, RPE, IRL, and ORL values in Group II are lower compared to those in Group I, no meaningful differences was found. Longer durations of drug use can lead to thinning in the retinal layers. In the parafoveal region there is localized thinning of the photoreceptor layers and it can be showed by SD- OCT . Early damage can sometimes be identified as a focal disruption of the photoreceptor outer segment.[22,23] In a study comparing 14 eyes of 14 patients

Table 3. *Retinal layer changes in SLE, RA and SS based on the duration of medication use. Pvf-md: periferic visual field mean deviation, pvf-psd: periferic visual field pattern standart deviation, FRT: full retinal thickness, NFL:nerve fiber layer, GCL: ganglion cell layer, IPLinner plexiform layer, INL:inner nuclear layer, OPL:outer plexiform layer, ONL: outer nuclear layer, RPE: retina pigment epitelium, IRL:inner retinal layers, ORL:outer retinal layers.*

	SLE (n=14)			RA (n=90)			SS (n=36)		
	Group I	Group II		Group I	Group II		Group I	Group II	
	mean±sd	mean±sd	p	mean±sd	mean±sd	p	mean±sd	mean±sd	p-value
Pvf-md	2.35±0.19	1.17±0.81	0.024**	1.55±1.00	2.00±1.40	0.196**	1.59±1.08	1.11±0.79	0.214**
Pvf-psd	1.55±0.51	2.36±1.62	0.539**	1.68±0.48	1.88±1.03	0.891**	1.73±0.71	1.39±0.36	0.161**
FRT	249.75±5.56	271.50±9.77	0.001*	266.58±18.52	259.48±19.01	0.076*	276.89±18.66	264.28±12.34	0.022*
NLF	10.25±0.95	12.10±1.79	0.076**	12.15±1.98	11.76±2.32	0.368**	13.89±2.42	12.06±1.69	0.027**
GCL	12.75±3.50	15.20±2.74	0.188**	14.71±5.01	13.26±3.64	0.103**	17.56±3.32	13.94±2.38	0.001**
IPL	17.00±1.82	20.30±2.40	0.036**	19.67±3.28	18.74±2.80	0.141**	21.78±2.73	19.28±2.05	0.006**
INL	15.75±2.50	17.30±3.02	0.374**	18.35±4.73	19.74±5.54	0.324**	19.11±4.01	20.39±3.10	0.293**
OPL	26.75±10.43	27.30±7.90	0.945**	24.35±5.68	23.83±5.66	0.498**	25.89±5.22	30.44±15.67	0.406**
ONL	84.75±14.97	90.90±7.21	0.308*	88.54±8.99	87.26±12.98	0.584*	89.56±10.39	87.78±7.72	0.564*
RPE	16.00±2.70	16.20±1.22	0.374**	17.23±1.90	16.93±2.10	0.246**	17.00±1.64	15.56±1.33	0.005**
IRL	164.00±6.21	184.20±11.03	0.008**	177.35±16.53	172.83±18.58	0.220**	193.72±26.86	179.61±10.02	0.181**
ORL	85.25±3.77	87.40±2.27	0.207*	89.02±3.98	86.17±5.25	0.004*	87.50±4.14	85.67±4.36	0.205*

with HCQ toxicity with healthy individuals, thinning of the outer retina layers was detected.[24] In the study of 144 eyes using HCQ; FRT, IRL, and GCL decreased. There were no observed variations in either INL or ORL.[25] In an other study comparing patients using HCQ with healthy individuals, the parafoveal retinal thickness was found to be significantly thinner in HCQ users compared to the control group.[26] With prolonged use, the overall amount of the drug administered gradually rises as well. Consistent with reports found in the literature, our study found that as the dosage and duration of HCQ use increased, thinning in the retinal layers became more pronounced. Despite this thinning, none of our patients reported any complaints of vision loss. Regular monitoring of patients using HCQ can detect thinning in the retinal layers, changes in FAF, and alterations in the visual field before any vision complaints arise. This enables more attentive monitoring of the patient, and if needed, the treatment can be stopped before irreversible vision impairment develops.

Hydroxychloroquine (HCQ) is crucial in managing SS, SLE, and RA, due to its unique immune-modulating effect and fewer side effect. In Sjögren's syndrome, HCQ has been shown to enhance tear quality and lead to improvements in both objective and subjective inflammatory indicators.[27] In patients with SS in our study, individuals who took the medication for over 5 years exhibited a statistically significant decrease in FRT, NLF, GCL, IPL, and RPE values compared to those who used the medication for 5 years or less.

In a study, early retinal toxicity was observed in 3% of 345 SLE patients using HCQ having a mean treatment duration of 3.3 years.[28] In our SLE patients, while no meaningful difference was observed between Group I and Group II in pvf-psd, NLF, GCL, INL, OPL, ONL, RPE, and ORL values as the duration of drug use increased, there was a meaningful increase in FRT, IPL, and IRL values ($p < 0.05$). This could be associated with disease activity. Because ischemia, hemorrhage and edema can occur in the retina secondary to retinal vasculitis. On OCT, it manifests itself as a thickening of the retinal nerve fiber layer. Petri et al.[29] examined 537 SLE patients using HCQ and found retinopathy in 4.3%. In a study comparing 42 SLE and 36 primary SS patients without visual impairment to 76 healthy individuals, no difference in retinal thickness was found between the SLE and control groups, while a meaningful decrease was observed in SS patients compared to both the SLE and control groups. In individuals with SLE and SS, standard automated perimetry revealed that both the

pvf-md and pvf-psd were greater than those observed in the control group. Additionally, the visual field index was found to be reduced in both SLE and SS patients compared to the controls. Fundus perimetry abnormalities were more frequently detected among patients who did not take steroid among SLE participants and SS patients who had received a cumulative hydroxychloroquine dose more than 1,000 grams, no differences were noted.[30]

In our RA patients, all measured retinal layers, except for pvd-md, pvd-psd, and ORL, were observed to be lower in those who had been using the medication for more than 5 years compared to those who had been using it for 5 years or less. ORL was statistically significantly lower in Group II. When evaluating the retinal layers in RA patients using HCQ, ORL values may be more significant. In a research study conducted with 199 RA patients and 161 SLE patients, ocular complications were observed in 58 RA patients (29.4%) and 36 SLE patients (22.5%). Ophthalmic complications from HCQ in all patients were significantly influenced by the duration of drug use, disease duration, and cumulative doses ($p < 0.05$).[31]

FAF changes were detected in only one patient across both groups. This was a patient who had been using HCQ for 15 years and had no comorbidities other than RA. There was no meaningful change in vision.

The constraints of this study include its retrospective nature, the absence of a control group, and the lack of dosage adjustments based on the actual body weight of all patients.

The preservation of foveal outer segment structure integrity is crucial for sustaining visual acuity and should be regularly monitored through retinal imaging. In patients using HCQ, the thinning in the GCL, RPE and ORL layers is more significant. Thinning of the retinal layers does not cause any change in visual field or FAF measurements. If HCQ retinopathy is confirmed, it is advisable to discontinue the medication in consultation with the rheumatologist. It is important to inform patients that HCQ retinopathy may progress even after the medication has been discontinued. Extended follow-up of these borderline cases is necessary to assess whether retinal layer thinning prior to symptom onset might result in visual impairment over time. The affordability and accessibility of HCQ, along with its established safety profile, high patient adherence, and the option to monitor serum levels as a marker for potential long-term toxicity, all facilitate its practical use.

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