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Original Research Article

Comparitive study on short term and long term ocular side effects of hydroxychloroquine in rheumatoid arthritis and systemic lupus erythematosus

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Abstract

Background: Hydroxychloroquine (HCQ), a derivative of chloroquine, is widely used to treat autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Despite its therapeutic benefits, HCQ can cause ocular toxicity, particularly retinal damage, which can lead to irreversible vision loss.

Aim and Objectives: This prospective comparative study aimed to investigate the short- and long-term ocular side effects of HCQ in RA and SLE patients.

Materials and Methods: This study included 160 patients who received HCQ doses > 6.5 mg/kg per day or had a cumulative dose exceeding 1000 g. The patients underwent comprehensive ocular examinations, including best-corrected visual acuity, slit-lamp examination, color vision testing, dilated fundus examination, optical coherence tomography, automated perimetry, Amsler grid testing, and fundus autofluorescence imaging.

Results: Among 160 patients, 65.6% were aged ≥50 years and 69.4% were female. Premaculopathy was the most common ocular manifestation (13.1%), followed by posterior subcapsular cataract (PSC) (9.4%) and bull's eye maculopathy (2.5%). A higher incidence of ocular side effects was noted in patients taking a daily dose of 400 mg, with PSC in 12.6% and premaculopathy in 15.2%. Kidney problems were 8.8%, with a higher prevalence in those using HCQ for ≤7 years (11.4%) compared to >7 years (5.6%). Visual acuity assessments revealed that patients receiving HCQ for ≤7 years had better outcomes, with 35.2% achieving 6/9 vision in the right eye, whereas those receiving treatment for >7 years showed a decline in visual acuity.

Conclusions: The increased recognition of HCQ-induced ocular toxicity is attributable to advances in imaging modalities, heightened clinical awareness, and the implementation of standardized screening guidelines. Asymptomatic patients can exhibit toxicity, which necessitates objective testing methods for early identification.

Keywords: Hydroxychloroquine, Rheumatoid arthritis, Systemic lupus erythematosus, Retinal toxicity, Ocular side effects, Optical coherence tomography.

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1. Introduction

Hydroxychloroquine (HCQ) is derived from chloroquine, which is a member of the quinolone family. Since ancient times, it has been used in antimalarial medicine.[1] Chloroquine is administered for malaria therapy and prophylaxis and has since been used by rheumatologists and dermatologists to treat rheumatoid arthritis (RA) and lupus erythematosus.[2,3] Treatment durations and daily doses are longer than those in antimalarial therapy because of the increased usage of these drugs for conditions other than malaria.[4]

HCQ, also known as Plaquenil sulphate, is an antimalarial drug used to treat a wide range of autoimmune diseases. Some of these conditions include "systemic lupus erythematosus (SLE), RA, juvenile chronic arthritis, seronegative polyarthritis, discoid lupus erythematosus, and psoriatic arthropathy" Most patients who have been diagnosed with RA and SLE are treated with medication. Patients with RA and SLE have benefited from recent developments in the treatment of these conditions. However, HCQ, which is a derivative of chloroquine, continues to be

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the most essential component of treatment for both ailments.[1,3]

HCQ is the most well-tolerated medication for rheumatological and dermatological conditions. However, retinal toxicity remains a major concern. The occurrence of HCQ-related toxicity is uncommon.[5] However, if it occurs, the resulting vision loss is frequently irreversible even if the drug is discontinued. When high-risk factors were present, patients were more susceptible. In the eye, it affects the cornea, lens, ciliary body, and retina.[6]

Physicians who prescribe medications need to be aware of the potential ocular adverse effects before recommending the medication, and a preliminary ophthalmic assessment is required to determine whether maculopathy is present. Therefore, screening is still the most important part of management.[3,7] The choice of administering HCQ should be based on several factors, including the toxicity risk, the reversibility and severity of toxicity, and the accessibility of more advanced monitoring tools.[2] Longer duration course of HCQ associated with macular pathology and threat to vision.[8] Early identification of ocular side effects will help in the identification of high-risk patients by screening and following them.[9]

This study aimed to investigate the short- and long-term ocular side effects of HCQ in RA and SLE.

2. Materials and Methods

This prospective comparative study included 160 patients who visited the Ophthalmology OPD of SRM Medical College, Hospital and Research Centre, Kattankulathur, Chennai, from January 2023 to June 2024. The study had been cleared by the Institutional Ethics Committee before commencement and informed consent obtained from all the patients.

2.1. Inclusion criteria

All patients diagnosed with RA and SLE who received HCQ dose > 6.5 mg/kg per day or whose cumulative dose exceeded 1000 g were included.

2.2. Exclusion criteria

Patients with other causes of retinopathy (diabetes mellitus/systemic hypertension), age-related macular degeneration, RA patients who were on treatment with HCQ taking < 6.5 mg/kg, and patients who were on irregular medication were excluded.

2.3. Methods

A comprehensive clinical history and detailed ocular examination were performed, incorporating several key parameters. Best-corrected visual acuity was assessed using the Snellen chart to determine the sharpest vision achievable with corrective lenses. The slit-lamp examination provided a detailed evaluation of the anterior segment, aiding in the identification of structural abnormalities. Color vision testing was performed to detect deficits or disturbances. Dilated fundus examination, facilitated by 0.8% tropicamide and 5% phenylephrine, was performed using both 90D and 20D lenses for a thorough evaluation of the posterior segment.

High-resolution optical coherence tomography offers detailed cross-sectional imaging of the retinal layers. Automated perimetry was used to assess the visual field to identify functional deficits, while Amsler's grid testing was employed to screen for macular disorders. Fundus autofluorescence imaging was used to detect and evaluate retinal pigment epithelium changes and other abnormalities.

Premaculopathy refers to subtle retinal changes detected by Optical Coherence Tomography (OCT) before classical signs of maculopathy appear, such as disruption of the parafoveal outer retinal layers. For analysis, ocular changes observed within ≤7 years of HCQ use were categorized as short-term effects, whereas those appearing after >7 years were defined as long-term effects.

2.4. Statistical analysis

Data are presented as mean, standard deviation, frequency, and percentage. Continuous variables were compared using an independent-sample t-test. Categorical variables were compared using Pearson’s chi-square test. Significance was defined as p-values < 0.05 using a two-tailed test. Data analysis was performed using IBM-SPSS version 21.0.

3. Results

Our study predominantly comprised patients aged ≥ 50 years (65.6%) and females (69.4%). SLE (51.9%) was slightly more common than RA (48.1%). Among ocular manifestations, premaculopathy was the most frequent (13.1%), followed by posterior subcapsular cataract (PSC) (9.4%) and macular oedema was the least observed (0.6%). Among the patients, 55% had taken HCQ for ≤ 7 years, whereas 45% had used it for >7 years. Premaculopathy was diagnosed in 13.1% of patients after a follow-up period of 9 months (**Table 1**).

Patients taking a daily HCQ dose of 400 mg exhibited higher rates of ocular side effects than those receiving 200 mg, including PSC (12.6% vs. 6.2%), macular oedema (1.3% vs. 0%), and premaculopathy (15.2% vs. 11.1%), whereas corneal verticillata (CV) (3.7% vs. 1.3%) and bull’s eye maculopathy (BEM) (3.7% vs. 1.3%) were more prevalent in the 200 mg group. The number of patients consuming 200 mg and 400 mg was nearly equal (50.6% vs. 49.4%, respectively). The differences in HCQ dosage between patients aged ≤7 years (47.7% vs. 52.3%) and >7 years (54.2% vs. 45.8%) were not statistically significant (p=0.418) (**Table 2**).

Among patients, kidney problems were reported in 8.8% overall, with a higher prevalence in those using HCQ for ≤ 7

years (11.4%) compared to > 7 years (5.6%). Among those with kidney problems, the most common ocular manifestation was PSC (35.7%), whereas BEM and macular oedema were the least common (7.1% each). Liver problems were noted in 8.1% of patients overall, slightly higher in the HCQ ≤ 7 years group (9.1%) than in the > 7 years group (6.9%), with CV being the only associated manifestation (7.7%). Regarding visual acuity, the highest proportion of patients with 6/9 vision in the right eye (35.2%) and left eye (45.5%) were observed in the HCQ ≤ 7 years group. In contrast, the lowest proportion of 6/60 vision cases was found in the HCQ > 7 years group, with 4.2% in the right eye and 5.6% in the left eye (**Table 3**).

Among patients aged ≥ 50 years, PSC was the most prevalent (12.4%), whereas no cases of BEM or macular oedema were observed in patients aged < 50 years. Females exhibited higher rates of premaculopathy (14.4%) than males (10.2%). Patients on HCQ for > 7 years had significantly higher occurrences of PSC (16.7%) and BEM (5.5%) than those with ≤ 7 years of intake, where PSC was 3.4% and no cases of BEM were recorded. Among the dosage groups, PSC was more frequent with a dose of 400 mg (12.6%) than with 200 mg (6.2%), whereas premaculopathy was the highest among those taking 400 mg (15.2%). The lowest rates of ocular manifestations were consistently observed in patients receiving lower doses (200 mg) or shorter HCQ durations (≤ 7 years) (**Table 4**).

Table 1: Demographics, clinical characteristics, and ocular manifestations

		Frequency (%)
Age in years	< 50	55 (34.4%)
	≥ 50	105 (65.6%)
Gender	Female	69.40%
	Male	30.60%
Disease (n=160)	RA	77 (48.1%)
	SLE	83 (51.9%)
Ocular manifestation	CV	4 (2.5%)
	PSC	15 (9.4%)
	BEM	4 (2.5%)
	Macular oedema	1 (0.6%)
	Premaculopathy	21 (13.1%)
Duration of HCQ intake in years	≤ 7	88 (55%)
	> 7	72 (45%)
Follow-up premaculopathy	Diagnosed after 9 months	27 (13.1%)

Corneal verticillate (CV); Posterior subcapsular cataract (PSC); Bull's eye maculopathy (BEM); Hydroxychloroquine (HCQ)

Table 2: HCQ dosage and ocular manifestations

		Dosage (in mg)		**p-value**
		200mg (n=81)	400mg (n=79)	
Duration of HCQ intake in years	≤ 7	42 (47.7%)	46 (52.3%)	0.418
	> 7	39 (54.2%)	33 (45.8%)	
Ocular manifestation	CV	3 (3.70%)	1 (1.30%)	0.323
	PSC	5 (6.20%)	10 (12.60%)	0.159
	BEM	3 (3.70%)	1 (1.30%)	0.323
	Macular oedema	0%	1 (1.30%)	0.310
	Premaculopathy	9 (11.15%)	12 (15.20%)	0.445
HCQ dose		41 (50.60%)	39 (49.40%)	0.874

Corneal verticillate (CV); Posterior subcapsular cataract (PSC); Bull's eye maculopathy (BEM); Hydroxychloroquine (HCQ)

Table 3: Impact of HCQ duration on kidney, liver, and ocular manifestations

			Frequency (%)
Kidney problems		Overall	14 (8.8%)
		≤ 7 years	18.24 (11.4%)
		> 7 years	9 (5.6%)
		CV	34 (21.4%)
		PSC	57 (35.7%)
		BEM	11 (7.1%)
		Macular oedema	11 (7.1%)
		Premaculopathy	23 (14.3%)
Liver problems		Overall	13 (8.1%)
		≤ 7 years	15 (9.1%)
		> 7 years	11 (6.9%)
		CV	12 (7.7%)
		Others	0%
Right eye	Visual acuity	6/9	42 (26.3%)
		6/12	40 (25%)
	HCQ ≤ 7 years	6/9	56 (35.2%)
		6/12	53 (33%)
		6/36	0%
		6/60	0%
	HCQ > 7 years	6/24	29 (18.1%)
		6/36	22 (13.9%)
		6/60	7 (4.2%)
Left eye	Visual acuity	6/9	61 (38.1%)
		6/12	31 (19.4%)
	HCQ ≤ 7 years	6/9	73 (45.5%)
		6/12	44 (27.3%)
		6/60	0%
	HCQ > 7 years	6/9	46 (29.2%)
		6/24	33 (20.8%)
		6/60	9 (5.6%)

Corneal verticillate (CV); Posterior subcapsular cataract (PSC); Bull's eye maculopathy (BEM); Hydroxychloroquine (HCQ)

Table 4: Distribution of ocular manifestations by age, sex, duration of HCQ intake, and dosage

		Ocular manifestation				
		CV	**PSC**	**BEM**	**Macular oedema**	**Premaculopathy**
Age in years	< 50	1 (1.8%)	2 (3.6%)	-	-	3 (5.5%)
	≥ 50	3 (2.9%)	13 (12.4%)	4 (3.8%)	0.01%	18 (17.1%)
Sex	Male (n=49)	1 (2.1%)	5 (10.2%)	2 (4.1%)	0 (0%)	5 (10.2%)
	Female (n=111)	3 (2.7%)	10 (9.1%)	2 (1.8%)	1 (0.09%)	16 (14.4%)
Duration of HCQ intake in years	≤ 7 (n=88)	1 (1.1%)	3 (3.4%)	0 (0%)	0 (0%)	10 (11.4%)
	>7 (n=72)	3 (4.2%)	12 (16.7%)	4 (5.5%)	1 (1.4%)	11 (15.3%)
Dose (mg)	200	3 (3.7%)	5 (6.2%)	3 (3.7%)	-	9 (11.1%)
	400	1 (1.3%)	10 (12.6%)	1 (1.3%)	1 (1.3%)	12 (15.2%)

Corneal verticillate (CV); Posterior subcapsular cataract (PSC); Bull's eye maculopathy (BEM); Hydroxychloroquine (HCQ)

Among patients aged ≥ 50 years, PSC was the most prevalent (12.4%), whereas no cases of BEM or macular oedema were observed in patients aged < 50 years. Females exhibited higher rates of premaculopathy (14.4%) than males (10.2%). Patients on HCQ for > 7 years had significantly higher occurrences of PSC (16.7%) and BEM (5.5%) than those with ≤ 7 years of intake, where PSC was 3.4% and no cases of BEM were recorded. Among the dosage groups, PSC was more frequent with a dose of 400 mg (12.6%) than with 200 mg (6.2%), whereas premaculopathy was the highest among those taking 400 mg (15.2%). The lowest rates of ocular manifestations were consistently observed in patients receiving lower doses (200 mg) or shorter HCQ durations (≤ 7 years) (**Table 4**).

4. Discussion

In our study, the incidence of ocular toxicity was 15% on clinical examination; the total ocular manifestations diagnosed on clinical examination were Cornea verticellata (CV) (**Figure 1**), Posterior subcapsular cataract (PSC) (**Figure 2**), macular oedema (**Figure 3**), Premaculopathy and Bulls eye maculopathy (BEM) (**Figure 4**) . Wolfe et al. observed that 6.5% of HCQ lifetime users discontinued treatment because of an eye ailment, with 1.8% reporting retinal issues.[10] Melles et al. found that daily use (odds ratio, 5.67; 95% CI, 4.14-7.79 for >5.0 mg/kg) and length of use (odds ratio, 3.22; 95% CI, 2.20-4.70 for >10 years) were significantly linked with the overall prevalence of HCQ retinopathy (9.5%). The frequency of retinal toxicity was < 2% during the first ten years of administration for daily intakes of 4.0 to 5.0 mg/kg, but it rose to about 20% after twenty years.[11]

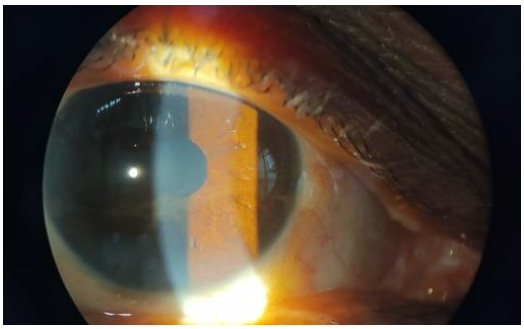

Figure 1: Showing cornea verticellata

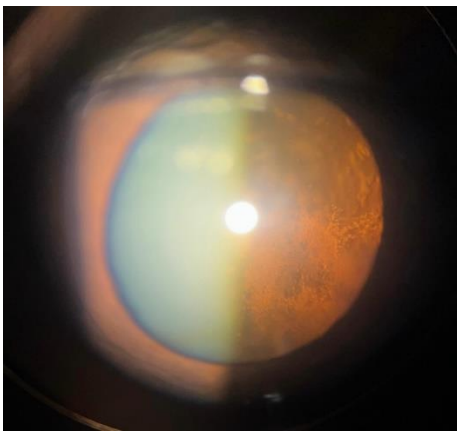

Figure 2: Showing posterior subcapsular cataract

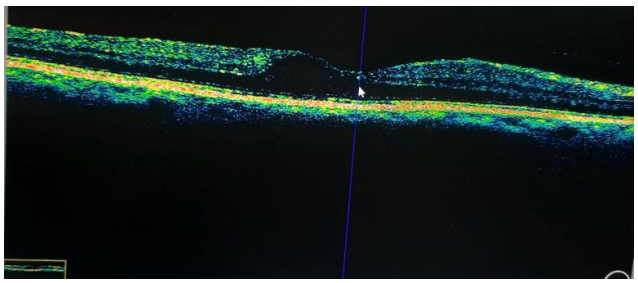

Figure 3: Showing Macular edema

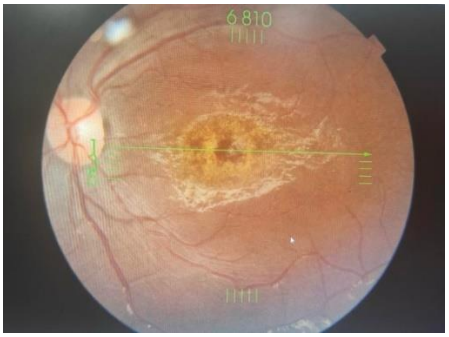

Figure 4: Showing bulls eye maculopathy in fundus photo

In our study, the HCQ premaculopathy rate was 13.1%, which is an high-definition optical coherence tomography (HD-OCT) finding that helps in the early detection of HCQ toxicity at the preclinical stage. Regarding the incidence of HCQ BEM, ≤7 years group had no BEM, but >7 years group had an incidence of 5.5% after using HCQ for > 7 years. Due to the limited sample size, this study's percentage results were higher than those of other studies.

Melles and Marmor's study found that the incidence of HCQ BEM, ≤7 years group had no BEM, but >7 years group had an incidence of 6% after using HCQ for > 10 years.[12] Several papers highlight the importance of OCT in detecting early signs of HCQ toxicity. Garrity et al. reports a novel finding of early OCT abnormalities in patients with normal Humphrey Visual Field (HVF) testing, suggesting that structural changes may precede functional impairment in some cases of early HCQ toxicity.[13] The varying findings across studies highlight the importance of using multiple screening modalities, including OCT, visual field testing, and other imaging techniques, to ensure comprehensive evaluation and early detection of HCQ-induced retinal changes.

In our study, the incidence of CV was 1.1% in the ≤7 years group and 4.2% in the >7 years group. Similarly, the incidence of PSC was 3.4% in the ≤7 years group and 16.7% in the >7 years group. These findings are comparable to those reported by Yam et al., who observed a 4% incidence of CV and a 20% incidence of PSC in patients with ≤7 years of HCQ use. True HCQ retinopathy remains rare, with fewer than 50 documented cases to date. Although its etiology is not well established, the risk factors include daily dosing of HCQ, total dose, treatment duration, existing renal or hepatic disease, patient's age, and simultaneous retinal disease.[6] A review of HCQ myopathy cases found that the mean duration of treatment was 37 months before symptoms appeared, suggesting that adverse effects may be more likely with prolonged use.[14]

In our study, patient age was one of the risk factors, in the < 50 years of age group 10.9% had ocular manifestations and > 50 years of age group 37% had ocular manifestations. This high incidence was due to the small sample size. Mavrikakis et al. have reported that of the first 58 long term

(>6 years) treated patients no HCQ retinal toxicity was noted. Two patients (3.4%) with HCQ associated maculopathy were identified 8 and 6.5 years after start of treatment" despite regular follow-up ophthalmologic evaluation.[15] Interestingly, in neuroblastoma cases, younger age at diagnosis (before 12 months) was associated with a more favorable prognosis.[16] This contrasts with the general trend of increased ocular manifestations in older patients seen in other conditions.

Our study demonstrated a higher proportion due to a small sample size, and it also includes premaculopathy, which was not accounted for in other studies. In all study groups, toxicity increased with increasing duration, and our study results showed toxicity in the ≤ 7 years group (15.9%) and the > 7 years group (31%). The major risk factors include the dosage of the drug, and the increased daily dose is also at a high risk since it causes rapid increase in the cumulative dose that leads to rapid tissue damage. This was found to be 31.6%. Our study demonstrates a higher proportion due to the small sample size, and it also includes pre-macular degeneration. A multi-center study identified several risk factors for HCQ toxicity, including daily dosage, cumulative dose, renal or liver disease, age, and prior retinal conditions.[17]

The association of kidney disease represents a greater risk factor for the occurrence of OCULAR findings in both studies, which are comparable, since both lie within a 95% confidence interval. There are no other notable studies in this association and liver disease is a lesser risk factor these data indicate that HCQ retinopathy has become more prevalent than previously recognized at daily higher dose intake and longer duration of therapy.

5. Conclusion

The increased recognition of HCQ-induced ocular toxicity is attributable to advances in imaging modalities, heightened clinical awareness, and the implementation of standardized screening guidelines. Clinical findings indicated a significant incidence of ocular toxicity, including conditions such as BEM, highlighting the importance of early identification. Asymptomatic patients have been found to exhibit ocular toxicity, emphasizing the need for objective testing methods such as HVF and HD-OCT, which are more effective than traditional subjective assessments. This study indicates that females are more susceptible to toxicity, with increased risks associated with higher daily doses and certain pre-existing conditions. Regular monitoring and adherence to updated screening protocols are crucial to mitigate potential vision loss from HCQ-induced retinal toxicity, particularly given that toxicity can progress even after discontinuation of medication.

6. Source of Funding

None.

7. Conflict of Interest

None.

8. Ethical Approval

Ethical No.: 2406/IEC/2021.

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