OCULAR TOXICITY OF HYDROXYCHLOROQUINE IN AUTOIMMUNE RHEUMATOLOGICAL DISEASES; A TERTIARY CARE EXPERIENCE IN PAKISTAN

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ABSTRACT

Objective: To determine the frequency of Hydroxychloroquine (HCQ) toxicity in patients suffering from autoimmune rheumatological diseases.

Methodology: It was a cross sectional study conducted in Fatima Memorial Hospital from May, 2019 to July, 2019. A total of 155 patients who were taking HCQ for autoimmune diseases for more than 5 years were included. Patients with maculopathy due to other causes were excluded. Patients having renal or liver dysfunction were also excluded. Ethical clearance was obtained from institutional review board and patients fulfilling inclusion criteria were enrolled in the study after getting informed consent. Optical Coherence Topography (OCT) was performed and interpreted by consultant ophthalmologist of the hospital.

Results: Mean age was 40.70 + 12.36 years ranging from 15 to 70 years. Majority, 136 (87.7%) were females. Most common disease was rheumatoid arthritis (RA) having 70 (45.2%) patients, followed by systemic lupus erythematosus (SLE) with 60 (38.7%) patients. Bulls eye maculopathy was present in 3 (1.9%) and pre-maculopathy in 24 (15.5%) patients. Blurring of vision was reported by 28 (18.16%) patients. Mean duration of HCQ therapy was 88.26 + 40.52 months. There was no association between retinal toxicity on OCT findings and age, gender, duration of the disease, HCQ dosage and cumulative HCQ dosage (p-value 0.797, 0.808, 0.494, 0.483 and 0.749 respectively). However, duration of HCQ therapy was significantly associated with maculopathy on OCT (p-value 0.025).

Conclusion: There is higher prevalence of retinal toxicity due to HCQ therapy in Pakistani population. There is a positive correlation between duration of HCQ therapy and retinal toxicity.

Key Words: Autoimmune diseases, Hydroxychloroquine, Optical coherence tomography. Retinal toxicity.

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INTRODUCTION

HCQ has been used in the management of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) for decades[1]. Its efficacy in preventing SLE flares has been proven with concrete evidence[2] and its other benefits include protection against the occurrence of diabetes and dyslipidemia, and is having survival benefit in SLE patients[3]. It has also been reported to effectively control the symptoms of Sjogren's syndrome and prevents thrombosis in antiphospholipid antibody syndrome[4]. Proposed modes of action of HCQ in these arthritides include accumulation of phagocytic cells in lysosomes and auto phagosomes, decreased production of pro-inflammatory cytokines e.g. interleukin-1, tumor necrosis factor-α and protection against cytokine-mediated cartilage resorption[4].

HCQ is generally well tolerated and the side effects profile comprise of gastrointestinal intolerance and skin pigmentation both of which usually disappear with dose reduction and rarely require treatment withdrawal. Retinal toxicity, although rare, but potentially vision threatening, presents as progressive spectrum of retinal damage starting from loss of retinal pigment epithelial cell layers to more advanced maculopathy leading to vision

loss[5]. HCQ can also cause blurring of vision due to corneal deposition but this is rare, reversible and improves even with continuation of drug[6].

The prevalence of hydroxychloroquine retinopathy ranges from 0.38% to 4% and it is related to the daily dose, the duration of treatment, the presence of other retinal disease as well as the kidney and liver function[7,8]. Melles et al. reported the overall incidence near 7.5 % in patients taking the drugs beyond 5 years[9]. The risk of HCQ-induced toxicity is very low at doses of 6.5 mg/kg/day (200–400 mg/day) and a cumulative dose of 1000g or less[7,10].

Older studies labelled advanced disease as toxicity, evident as Bull's eye maculopathy lesion, the hall mark of HCQ toxicity. Later studies included toxicity to retinal pigment epithelial cells as a feature of toxicity[10]. Rationale of this extension of toxicity spectrum was observed by studies of Moschos et al. and Marmor et al. that the drug cessation before damage to retinal pigment epithelium layer lead to improvement of visual acuity. However, patients with involvement of the retinal pigment epithelium demonstrated progressive damage on OCT even after drug cessation[11,12]. Early recognition of HCQ toxic effects before any fundus changes are visible, using visual fields and OCT (along with fundus auto fluorescence) greatly minimizes late progression and the risk of visual loss[12].

American Association of Ophthalmology (AAO) recommends an initial examination to be performed when initiating treatment to eliminate pre-existing maculopathy. Screening is then annual and starts from the 5th year of treatment. The two recommended tests for screening are the automated visual field and OCT[13]. Screening should look beyond the central macula in Asian patients, as they involve more peripheral involvement of retina away from usual parafoveal involvement[14].

Currently there is no treatment for this rare, devastating toxicity. Although effectivity of nutrients lutein and zeaxanthin, which deposit within the central retina to absorb short wavelength light and reduce oxidative damage, has been reported[14,15] but is still anecdotal. cessation of the drug, avoiding oxidative stress, control of other possible stresses and early diagnosis of toxicity in pre-maculopathy stage is corner stone of management[16].

Ahmed NM et al. have reported 9% chloroquine toxicity in Pakistani patients receiving chloroquine, and the toxicity reported was only maculopathy on fundoscopy[1]. Our study was aimed to determine HCQ toxicity using OCT as a screening tool, which is now a standard of care. It will help in establishing local data on the effects of HCQ on patients receiving drugs for extended periods, and will be the first local study on HCQ toxicity to the best of our knowledge.

METHODOLOGY

It was a cross sectional study conducted in Fatima Memorial Hospital, Lahore over a period of 3 months from May, 2019 to July, 2019. A sample of size 155 patients was selected using 3% level of significance, 97% confidence interval and 5% margin of error with 9% chloroquine toxicity in Pakistani patients. Patients were enrolled using purposive sampling. All patients of either gender, with no age limit, using HCQ for autoimmune diseases for more than 5 years were included. Patients with maculopathy of other causes like diabetes mellitus, infections and vascular insult were excluded from the study. The patients having renal or liver dysfunction were also excluded. Ethical clearance was obtained from institutional review board and patients fulfilling inclusion were enrolled in the study after getting informed consent. Data obtained included demographic data, dosage and duration of therapy and OCT reports findings. HCQ toxicity was defined as any degree of maculopathy evident on OCT scans.

Data was entered and analyzed in SPSS version 20. Descriptive analysis was performed on all the variables. Categorical variables were presented in form of frequency and percentages whereas quantitative variables were presented in the form of mean (SD). Pie charts were constructed for categorical variables. Maculopathy was stratified according to age and gender. Chi square test was applied to OCT findings and age, gender, cumulative dosage, duration of HCQ therapy, HCQ dosage and duration of the disease. P-value equal or less than 0.05 was considered significant.

RESULTS

The characteristics of the study population are summarized in table 1. Mean age was 40.70 + 12.36 years ranging from 15 to 70 years. Majority , i.e. 136 (87.7%) patients were female. Most common disease was RA with 70 (45.2%) patients followed by SLE having 60 (38.7%) patients as shown in table 1. Bulls eye maculopathy was present in 3 (1.9%) and pre-maculopathy in 24 (15.5%) patients. Out of total, 127 (81.9%) had no eye symptoms while blurring of vision was present in 28 (18.16%) as shown in table 1 and 2.

Mean HCQ dosage was 277.10 + 83.79 mg while mean duration of HCQ therapy was 88.26 + 40.52 (Table 2). There was no association between retinal toxicity and age, gender, duration of disease, HCQ dosage and cumulative HCQ dosage (p-value 0.797, 0.808, 0.494, 0.483 and 0.749 respectively). However, duration of HCQ therapy was significantly associated with maculopathy on OCT findings (p-value 0.025) (Table 3).

Table 1: descriptive statistics of study population

Parameter	Values
Age (years)	
Mean + SD	40.70 + 12.36
Minimum	15
Maximum	70
Gender	
Male	19 (12.3%)
Female	136 (87.7%)
Diagnosis	
Rheumatoid Arthritis	70 (45.2%)
Seronegative Polyarthritis	6 (3.9%)
Juvenile Idiopathic Arthritis	6 (3.9%)
Systemic lupus erythematosus	60 (38.7%)
Overlap syndrome	2 (1.3%)
Mixed connective tissue disease	5 (3.2%)
Undifferentiated arthritis	1 (0.6%)
Antiphospholipid syndrome	1 (0.6%)
Undifferentiated connective tissue disease	3 (1.9%)
Sjogren's syndrome	1 (0.6%)
Eye symptoms	
No symptoms	127 (81.9%
Blurring of vision	28 (18.1%)

Table 2: Frequency of HCQ toxicity

Normal	128 (82.6%)
Bulls eye maculopathy	3 (1.9%)
Pre maculopathy	24 (15.5%)

Table 3: Association of retinal toxicity on OCT findings in different groups

OCT findings					Total	P-Value
Normal	Bulls eye maculopathy		Pre maculopathy			
Age (years)						
	<40	61	2	12	75	0.797
	>40	67	1	12	80	
Total	128		3	24	155	
Gender						
	Male	1624	0	3	19	0.808
	Female	112	3	21	136	
Total	128		3	24	155	
Duration of the disease (Months)						
	<120	89	3	16	108	0.494
	>120	39	0	8	47	
Total	128		3	24	155	

HCQ dosage (mg)						
	<200	3	0	0	3	0.483
	200-299	56	1	15	72	
	300 or more	69	2	9	80	
Total	128		11	24	155	
Duration of HCQ therapy						
	<70	46	3	13	62	0.025
	>70	82	0	11	93	
Total	128		3	24	155	
Cumulative HCQ dosage (gm)						
	<1000	117	11	27	155	0.749
	>1000	108	3	20	131	
Total	128		3	24	155	

DISCUSSION

Female patients were more frequent in this study showing predominance of immune mediated diseases in female gender. It is in accordance with the past studies showing that women had more prevalence of immune mediated diseases; up to 85%[17].

Our study showed that 17.4% of patients taking HCQ developed retinal toxicity on OCT findings. Most of these patients had pre maculopathy while a small percentage developed bulls' eye maculopathy. Its prevalence is high in our study as compared to studies conducted in past. The retinal toxicity has been reported in 0-4% of patients using HCQ depending upon dose and duration of HCQ therapy in previous studies[18]. In a study by Wolfe F et al., retinal toxicity was found to be present in 1.8% patients using HCQ but definite evidence of retinal toxicity on OCT findings was present only in 0.5% of patients. This study also stands in contrast to the results of our study with retinal toxicity of up to 17.4% which is very high[19]. The exact reason, why retinal toxicity is so high in our population, is not known and is a subject for debate and possibly we need further studies to find out the reason.

In our study, duration of HCQ therapy was significantly associated with maculopathy on OCT findings (p-value 0.025). This was previously demonstrated in a study by Espander et al. in which the duration of HCQ therapy was significantly associated with retinal toxicity on OCT findings (p-value <0.001)[20].

While there was no association between retinal toxicity on OCT findings and age, gender, duration of disease, HCQ dosage and cumulative dosage (p-value 0.797, 0.808, 0.494, and 0.483 and 0.749 respectively), few previous studies have shown definite association between cumulative HCQ dosage and retinal toxicity[9]. The small sample and ethnic differences may be responsible for higher incidence and pattern of retinal toxicity in our population but the reason is yet to be determined.

This was a single center, small-scale study and there is a need to conduct large scale, multi center studies. The question that retinal toxicity due to HCQ therapy is reversible or irreversible in our population is still unanswered and there is a need of longitudinal studies on these patients.

CONCLUSION

It is concluded that there is higher incidence of retinal toxicity due to HCQ therapy in Pakistani population. There is a positive correlation between duration of HCQ treatment and retinal toxicity.

RECOMMENDATIONS

It is recommended that OCT should be done at least once in 5 years to detect retinal toxicity earlier in order to prevent retinal toxicity and withdraw the drug before permanent damage sets in. Patient education in this regard is essential for better understanding of the disease process and development of HCQ toxicity.

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CONTRIBUTORS

MF conceived the idea, wrote initial manuscript, carried out literature search and organized bibliography. MH, MSAA and AUK executed the project, helped acquisition and interpretation of data, revised initial manuscript and wrote references. MAS and MZA went through the manuscript, did corrections, interpreted the data in the light of objectives and wrote final manuscript. All authors contributed significantly to the submitted manuscript.