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Original Research Article

Evaluation of hydroxychloroquine induced retinal toxicity in systemic lupus erythematosus patients

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder, which affects the major organs in the human body. Pathophysiology of SLE is unknown. It mainly affects the joints, and restricts their movement. Hydroxychloroquine (HCQ) an anti-malarial drug is used as the first line of drugs used to treat SLE. The major adverse effect of this drug is irreversible retinopathy. The aim of the study was to evaluate the incidence and prevalence of retinopathy in patients with long-term usage of hydroxychloroquine (for more than 1 year).
Methods: In patients with SLE, we recorded a review on HCQ induced toxicity among those taking it for longer period (>1 year). All the patients were above 18 years of age. A total data of 210 patients suffering from SLE and taking HCQ for more than one year was collected. Patients were categorized according to gender and dose pattern. Out of 210 patients, 0 patients were found to be retinal toxic induced by HCQ.
Results: Suitable statistical tools were used and data was analysed which showed the incidence and prevalence of HCQ induced toxicity. With the results of our study we can understand that incidence and prevalence rates were very low among the subjects.
Conclusions: HCQ is said to reduce the risk of disease remission, improves survival, minimizes the risks of vital organ damage, reduces the frequency of flares and has a protective effect on cardiovascular health. HCQ medication is usually well tolerated. But irreversible retinopathy is the major effect on long term use of HCQ. The present study concludes that in the nominal daily dose of 200mg did not reveal any signs of retinal toxicity in 100% of the population tested within 5 years of HCQ treatment suggesting that the toxicity is rare and can be prevented by reducing the dose of the drug.

Keywords: Systemic lupus erythematosus, Hydroxy chloroquine's, Retinal toxicity

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder identified by the production of autoantibodies and deposition of immune complexes. Signs and symptoms are different and vary among the people affected by SLE. Pathogenesis is complex and remains unknown, whereas damage to the range of organs like joints, kidneys, hemopoietic system, CNS and skin is considered to be the major symptoms of SLE.[1]

Anti-malarial drugs especially hydroxychloroquine is the first line of choice of drugs in SLE. Unless the drug is contraindicated antimalarial drugs are prescribed for most of the patients of SLE.[2] In a few conditions, chloroquine is used as an alternate for HCQs.[3] Comparatively the safety

and efficacy of HCQ are better and can be used during pregnancy and in breastfeeding women.[4]

Hydroxychloroquine

Originally hydroxychloroquine is developed to treat malaria, later is used to treat autoimmune disorders like Rheumatoid arthritis and systemic lupus erythematosus. The dose is calculated based on body weight and dose adjustment is very crucial in patients suffering from renal failure. For the patient with ideal body weight, the daily dose is calculated and given at the dose of 6.5 mg/kg.[5] Retinal toxicity is the major side effect of HCQs which is irreversible and is observed in the patients with long term treatment (more than five years) and the patients taking higher doses (daily dose of 200 mg to 400 mg). Even though this type of toxicity is rare but is considered as a major side effect as this leads to complete loss of vision.[6] Hydroxychloroquine toxicity may be explained by the mechanism in which the HCQs alter the metabolism of cells in the retina and also attaches to the melanin. The site of toxicity is the photoreceptor layer with secondary degeneration of retinal pigment epithelium.[7] Few studies indicate that HCQs inhibit the uptake of all-trans-retinol in retinal pigment cells and probability of accumulation of drugs are also high after cessation of the drug indicating the progressive of toxicity.[8] To test the extent of HCQ retinopathy guidelines laid by the American Academy of Ophthalmology (AAO) screening techniques that are to be carried out are dilated fundus examination, special domain optical coherence tomography (SD-OCT), fundus auto fluorescence (FAF) test.[9]

According to AAO guidelines the patients who need to be screened at regular intervals are patients who are receiving HCQs for more than five years, patients who are above 60 years, patients taking more than 6.5 mg/kg dose of HCQs/day, patients with other disease conditions.[10] Dose adjustment and reduction is mainly considered as a major factor responsible to prevent retinal toxicity.[11] Initial stages of HCQ induced retinopathy could be asymptomatic. Earliest symptoms appear as trouble with reading, fine visual alteration, reduced colour vision. Retinal examination indicates the toxicity in the form of a bull's eye (Figure 1). The early stage is asymptomatic and the physician needs to advise the patient for a total eye screening before recommending HCQs.

Aim

The aim of the study was to evaluate the retinal toxicity in systemic lupus erythematosus patients with regular term hydroxychloroquine's treatment.

Objectives

The objectives of this study were (a) to identify the incidence of retinal toxicity in systemic lupus erythematosus patients with hydroxychloroquine usage; (b) to assess the frequency of testing for retinopathy in patients with HCQ'S usage and verify how many patients are symptomatic and asymptomatic having changes in the retina; (c) to evaluate all the retinal changes that occurred in the patients during the treatment hydroxychloroquine; and (d) to identify all possible risk factors that lead to retinopathy and to assess the probable dose adjustment need to be done to prevent the progressive retinopathy.

METHODS

A prospective observational study was designed. This study was conducted in the department of rheumatology, Krishna institute of medical sciences (KIMS) hospital. This study was conducted for 8 months (August 2019-March 2020).

Sample size

The sample size was 210.

Inclusion criteria

Patients of either sex with systemic lupus erythematosus aged ≥18 years undergoing hydroxychloroquine treatment for more than 1 year.

Exclusion criteria

Patients already having a history of retinopathy (other causes), patients newly diagnosed with systemic lupus erythematosus and paediatrics.

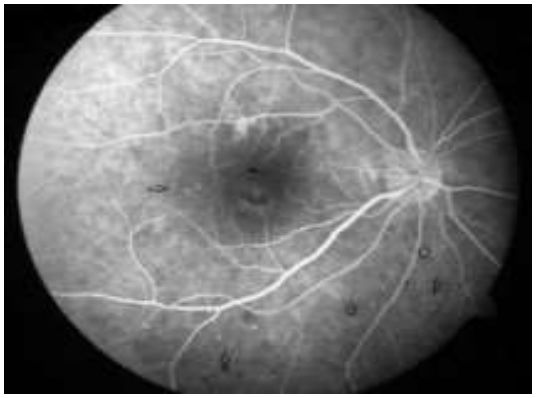

Figure 1: Bull's eye like finding in the retina of the person taking HCQs for a long period.

All the subjects attending rheumatology department in Krishna institute of medical sciences- Secunderabad, who were diagnosed with SLE, and taking HCQ for more than one year, and willing to give consent were included in the study. Subjects according to inclusion and exclusion criteria were selected and demographic details were collected from case sheets and by interacting with the subjects and by other relevant sources. The study was conducted for six months, and the collected was analyzed for results.

All the data was collected in a structured performa and collected data were analyzed according to statistical tool and results are concluded

Source of data

The source data of the study was- (a) patients diagnosed with systemic lupus erythematosus and having a medication history of using hydroxychloroquine's for more than one year; (b) laboratory test data; (c) case sheets of systemic lupus erythematosus patients; and (d) interacting with the patients and physicians

Screening tests for retinal toxicity

Screening tests for renal toxicity were- (a) automated visual field test; (b) fundoscopy; and (c) ocular CT (if necessary).

Institutional human ethics committee approval was obtained. Written consent was obtained from all the study participants, and only those participants willing to sign the informed consent were included in the study. The confidentiality of study participants will be maintained.

Statistical analysis

All the data collected was tabulated in a Microsoft excel spreadsheet in a master chart and analysed using suitable statistical tools.

RESULTS

In the present study, a total of 210 subjects were enrolled based on inclusion and exclusion criteria from the department of rheumatology, Krishna institute of medical sciences (KIMS) in which all were taking HCQs for more than one year (>1 year).

The subjects were distributed based on the demographic details females were 194 (92%) and males 16 (8%).

Distribution according to the age group of patients

Patients were divided based on their age. Among the total number of 210 patents, 61 (29%) members were from 18-30 years of age. 76 (36%) members were from 31-40 years, 45 (22%) members were from 41-50, 21 (10%) members were from 51-60 years. People of age above 61 years were 7 (3%) members.

Table 1: Distribution of subjects based on gender.

Gender	No. of patients (%)
Total	210
Females	194 (92)
Males	16 (8)

Table 2: Distribution according to the age group of patients.

Age groups (year)	No. of patients (%)
18-30	61 (29)
31-40	76 (36)
41-50	45 (22)
51-60	21 (10)
Above 61 years	7 (3)

Distribution according to the gender group of patients

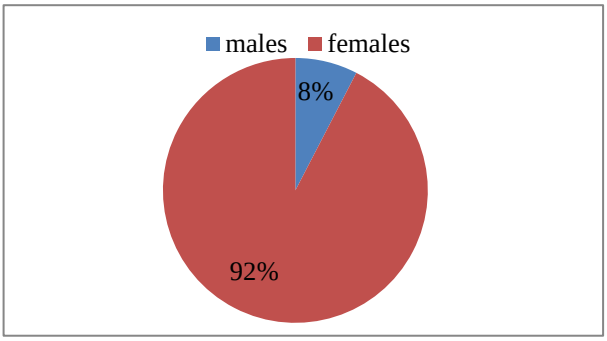

Figure 2: Distribution of population-based on gender.

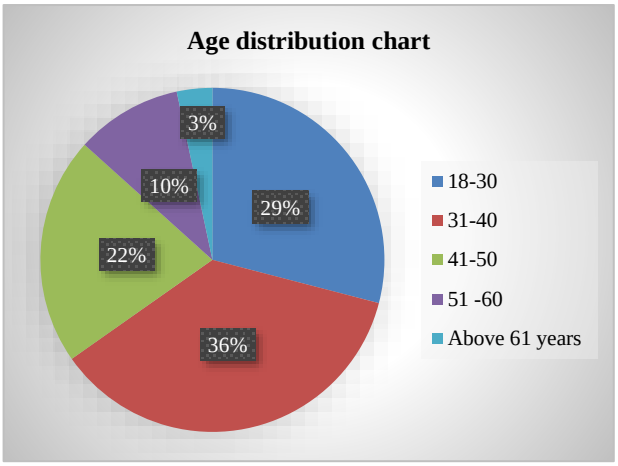

Figure 3: Age distribution chart of subjects.

Distribution based on the dose of the subjects

Total subjects were distributed based on the doses and 192 (91%) were found to be taking the HCQs at a regular dose (200 mg daily dose) and 18 (9%) were taking at irregular doses (200 mg alternate day).

Table 3: Characterization of subjects based on dose.

The dose of the patient	No. of patients (%)
Regular (200 mg daily dose)	192 (91)
Irregular (200 mg alternate day)	18 (9)

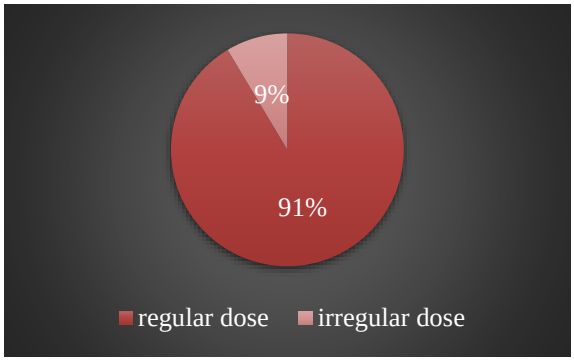

Figure 4: Distribution of subjects based on doses.

Analysis

All the collected data were analysed and the total incidence rate of retinal toxicity was evaluated. The incidence rate was calculated by dividing the subjects who were having retinopathy with the total population included in the study.

After a complete analysis of the subjects by the end of the study, a total of 0 subjects were found to be affected with hydroxychloroquine induced retinopathy. The incident rate was found to be 0% of the total population. This indicates the incidence rate is very low in the people taking HCQs at 200 mg of dose as far as this study was concerned.

Table 4: Distribution of subjects based on retinopathy.

Distribution	Total no. of subjects (%)
Included in the study	210
Taking HCQs for more than one year	210
Subjects with retinal toxicity	0 (0)

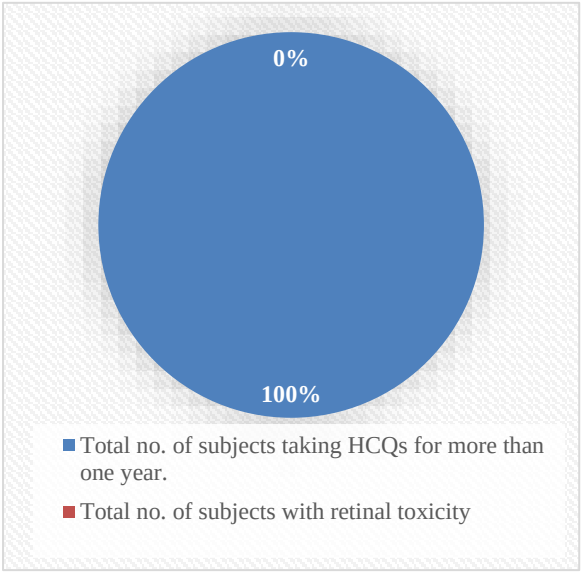

Figure 5: Distribution of subjects based on retinopathy.

DISCUSSION

Hydroxychloroquine, though used as anti-malarial drug has shown positive response in treating auto-immune disorders like SLE. One of the major side effects that was to be looked for was irreversible retinal toxicity. HCQ is available in 200-400 mg doses.

Yusuf et al reported prevalence of HCQ retinopathy in 7.5% in 2361 patients who received HCQs for more than 5 years and 20-50% in patients who took HCQs for more than 20 years.[12]

Mavrikakis et al reported conducted a retrospective and continuing review. A study was conducted in 360 Greek patients treated for rheumatoid arthritis and SLE, 58 of whom received long-term (more than six years) treatment. Two young women (3.5%), one treated for rheumatoid arthritis the other treated for SLE, developed typical toxic retinal lesions.[13]

Grierson et al conducted a study on 758 patients. The study stated that regular ophthalmic screening is not required if the daily dose is less than 6.5 mg/kg and cumulative doses are 200 g. 12 patients were reported to have visual disturbances and 7 patients showed corneal drug deposits which were cleared on reducing the dose and by stopping HCQ's.[14]

Ronald et al in their study reported that the prevalence of HCQ retinal toxicity is very high and it depends on various risk factors like a daily dose of the drug, duration of administration and use and underlying kidney disease. Their results suggested the importance of revising the dose to reduce retinopathy.[15] We assumed that the major contributing factors for this retinal toxicity were- (a) dose of the drug; and (b) duration of usage of hydroxychloroquine. However, the limitation of the study was, patients with other retinal problems and with other underlying diseases were excluded.

CONCLUSION

HCQ is said to reduce the risk of disease remission, improves survival, minimizes the risks of vital organ damage, reduces the frequency of flares and has a protective effect on cardiovascular health. HCQ medication is usually well tolerated. But irreversible retinopathy is the major effect on long term use of HCQ. The present study concluded that in the nominal daily dose of 200 mg did not reveal any signs of retinal toxicity in 100% of the population tested within 5 years of HCQ treatment suggesting that the toxicity is rare and can be prevented by reducing the dose of the drug.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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