

Screening the adequacy of hydroxychloroquine prescription and monitoring of ocular toxicity in patients with rheumatic disease

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ABSTRACT

Background: Hydroxychloroquine (HCQ) an anti-inflammatory drug used in treatment of rheumatic diseases causes retinal toxicity in a minority of patients which are both time and dose dependent. The aim of this study was to assess the compliance with guidelines of American Association of Ophthalmology for screening and dosage of this drug.

Patients and methods: In this cross-sectional analysis, the medical records of patients who were on HCQ, attending Rheumatology Outpatient Department of Fatima Memorial Hospital Shadman, Lahore from 25-05-2019 to 30-05-2019 were reviewed. The dosage and, duration of HCQ were collected, files were reviewed for physician recommendation of screening tests for retinal toxicity. HCQ dose of 5mg/kg/day was labeled as adequate dose; dose below 4.5mg/kg/day under dosed, while dose of 6mg/kg/day and above was considered overdose.

Results: Data was collected from 81 patients during the study period, 74 (91.4%) of them being female, with mean age 35.15 ± 12.6 years. Based on total body weight, 23 patients (28.4%) were receiving the correct dosage of the drug around 5mg/kg/day whereas 39 (48.1%) patients were under-dosed below 4.5mg/kg/day, and 19 patients (23.5%) were over dosed, out of which 5 (6.17%) were receiving doses above 6.5mg/kg. Baseline eye screening examination by ophthalmologist was performed within 1 year of commencing treatment in 54 (66%) patients. Of the 27 patients receiving HCQ more than 5 years, 6 patients underwent Spectral coherence Ocular CT scan (SD-OCT) evaluation at 5 years. There was minimal compliance (less than 70% of Patients) to optimum drug dosage, partial compliance (70-89% patients) to preventing over-dosage of the drug, and full compliance (more than 90% patients) was achieved in baseline screening exam recommendation. Follow-up screening documentation and 5-years screening examination had minimal compliance.

Conclusion: A significant proportion of patients are underdosed, especially the obese population where the recommended dosage is not prescribed.

Keywords:

Hydroxychloroquine; OCT; Toxicity; Screening; Optimal dosage

INTRODUCTION

Antimalarial hydroxychloroquine (HCQ) has been used in management of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) for decades now.¹ Its efficacy in preventing SLE flares has proven evidence and its other benefits, along with being inexpensive, include protection against the occurrence of diabetes, dyslipidemia, and survival benefit in SLE patients.^{2,3} It has also been reported to effectively control the symptoms of Sjogren's syndrome, and preventing thrombosis in antiphospholipid antibody syndrome.⁴ Proposed modes of action of HCQ and chloroquine (CQ) in these arthritides include:

accumulation in lysosomes and autophagosomes of phagocytic cells; decreased production of pro-inflammatory cytokines e.g. interleukin-1, tumor necrosis factor- α ; protection against cytokine-mediated cartilage resorption.⁵ HCQ is generally well tolerated. Side effects profile comprise of gastrointestinal intolerance, and skin pigmentation both of which usually disappear with dose reduction and rarely require treatment withdrawal; and retinal toxicity, although rare but potentially vision threatening, presenting as progressive spectrum of retinal damage starting from loss of retinal pigment epithelial cell layers to more advanced maculopathy leading to vision loss.⁶ HCQ can also cause blurring of vision due to corneal deposition, but this is rare, reversible and improves even with continuation of drug.⁷ The prevalence of hydroxychloroquine retinopathy ranges from 0.38% to 4% and it is related to daily dose, duration of treatment, the presence of other retinal disease, as well as the kidney and liver function.^{8,9} Melles et al published the

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overall incidence near 7.5 % in patients taking the drugs beyond 5 years.¹⁰ The risk of hydroxychloroquine-induced toxicity is very low at doses 6.5 mg/kg/ day (200–400 mg/day) and a cumulative dose 1000g.^{11,12} Early recognition of hydroxychloroquine toxic effects before any fundus changes are visible, using visual fields and optical coherence tomography (along with fundus autofluorescence) greatly minimizes late progression and the risk of visual loss.¹³ American association of Ophthalmology (AAO) recent recommendation consists of: an initial examination to be performed when initiating treatment to eliminate pre-existing maculopathy. Screening is then annual and started from the 5th year of treatment. The two recommended tests for screening are the automated visual field and the Optical coherence tomography (OCT).¹⁴ Aim of this study was to assess the compliance with international guidelines recommended by AAO on prescription of hydroxychloroquine dosage and screening for ocular toxicity.

PATIENTS AND METHODS

It was a cross sectional analysis (Audit) of outpatient department conducted at the Rheumatology Department of Fatima Memorial Hospital Lahore from 18th of May to 25th of May 2019. Fatima Memorial Hospital is a tertiary care teaching hospital in Central Lahore and is a referral center for rheumatic diseases. Total 81 patients, diagnosed cases of rheumatic diseases who were on HCQ were selected for file review. Demographic details, duration of illness, HCQ dosage both per day and weight-based, and retinopathy screening documentation and assessment both at baseline and at 5 years follow-up were evaluated. Data was entered and analyzed in SPSS version 23. Quantitative variables were presented as mean \pm SD or Median (IQR) depending upon their distribution. Categorical variables were presented as frequency and percentage. The compliance to recommended dosages were documented as adequate dose (5mg/kg/day), under-dosage (4.5mg or less/kg/day) and over dosage (6mg or above/kg/day); retinopathy screening documentation was assessed by fulfilling the baseline eye examination by ophthalmologist, and Spectral coherence Ocular CT scan (SD-OCT) evaluation at 5 years. Compliance was scaled as full compliance (if was fulfilled in over \geq 90% patients); partial compliance (between 70% and 89%patients) and minimal compliance (if fulfilled in less than 70% patients).

RESULTS

Data was collected from 81 patients, 74 (91.4%) of them being females. Mean age of the patients was 35.15 \pm 12.6 years. Rheumatoid arthritis (RA) was the predominant diagnosis in 43 (53%) patients, followed by systemic lupus erythematosus (SLE) in 34 (42%) patients. The remaining (4.9%) patients had various other underlying rheumatic diseases. Based on total body weight, 23 patients (28.4%) were receiving the correct dosage of the drug 5mg/kg. Thirty-two (39.5 %) were receiving doses below 4mg/kg. Total 19 patients (23.5%) were over-dosed, out of which 5 (6.17%) were receiving doses above 6.5mg/kg. Only 6 patients had received a cumulative dose greater than 1000g. Twenty-seven (33.3%) patients were on treatment for 5 years or more. Risk factors other than age (hepatic/renal impairment, retinal toxicity, hypertension and co-administration of other retinal toxic drugs) for toxicity were present in 16 (19.7%) patients. Nine of 13 (69%) obese patients were under dosed below 4.3 mg/kg/day.

Baseline eye screening examination was advised by treating physician with written documentation in 76 (94%) patients. However, it was performed within 1 year of commencing treatment in 54 (66%) patients. Documentation was missing in 5 patients. The screening included slit lamp examination of the macula, checking for color vision and visual acuity, however automated threshold visual field testing with a white 10-2 pattern was not carried out in any patient. Objective eye examinations like, Spectral Domain-Optical Coherence Tomography (SD-OCT), Fundus Auto fluorescence (FAF), Multifocal Electroretinogram (mf-ERG) were not carried out at baseline. Patients were followed 3 to 6 monthly in Rheumatology department depending on disease activity, And yearly Ophthalmology Examination was standard of care. Follow-up eye examination was advised yearly in all patients. Screening was done in 48 (59%) patients on last follow-up. Out of the 27 patients receiving HCQ for more than 5 years, 6 (22%) patients underwent SD-OCT evaluation at 5 years. However, recommendation of OCT was advised to 10 (37%) patients only. Five-year screening examination documentation also missed automated threshold visual field testing with a white 10-2 pattern which is recommended by AAO. This shows minimal compliance (<70%) to optimum drug dosage, partial compliance (70-89%) to preventing over-dosage of the drug. Full compliance (>89%) was achieved in baseline screening exam recommendation. However,

follow-up screening documentation and 5- year screening examination had minimal compliance (<70%).

DISCUSSION

Total of 81 patients were evaluated for dosages of HCQ and for documentation of screening examination for retinopathy. Results of this study showed full compliance in documentation of screening examination (94%), while minimal compliance in both recommended dose of HCQ and follow up screening examination documentation. Reasons of these minimal compliances are multifactorial, including overestimated retina toxicity, non-uniformity of results of toxic dose, to lack of literature on geographical and ethnic differences. Current study showed 24% of patients being over dosed, in comparison to the findings of Braslow and coauthors, where almost half of patients were over-dosed.¹⁵ In addition, 39% of patients in this study were under dosed (<4 mg/kg/day). The possible reasons of such under-dose treatment in this study seems to be a fear of retinopathy, plus fix dose 200 mg strength of HCQ, which leads to under dosage when calculated for weight based. Moreover, the toxic dose of HCQ was reported to be equal to 6.5 mg/kg body weight, which further lead to reduction in dose prescribed.¹⁶ Baseline screening examination recommendation recently has been changed from more subjective ones to objective tests.¹⁷ The rationale of early detection of retinopathy in pre maculopathy and reversible stage resulted in widespread recommendation of OCT and Automated visual field testing as baseline. In this study more subjective tests were still followed in routine as screening tool. Possible cause other than non-adherence to recommendations include high expense of the OCT, which is a major hurdle in this part of the World and lack of coordinated clinics between ophthalmology and rheumatology which should be improved. However, currently subjective examination like color vision, funduscopy, etc. are no more recommended and have been replaced by SD-OCT and automated visual field testing with more peripheral testing in the Asian population.¹⁸

CONCLUSIONS

While prescribing HCQ or Chloroquine, adequate dosage based on total body weight should be instituted. This will avoid unnecessary under or over-dosing. Risk factors for further Retinal toxicity should be identified and such patients should have more frequent screening. Screening methods should include automated threshold visual field testing and SD-OCT. Furthermore,

documentation should be more accurate and on each follow-up.

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