Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/4pwwav26

FREQUENCY OF HYDROXYCHLOROQUINE RELATED MACULOPATHY IN PATIENTS WITH RHEUMATOLOGICAL CONDITIONS: A PROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Hydroxychloroquine (HCQ) is commonly prescribed for various rheumatological conditions, including rheumatoid arthritis and systemic lupus erythematosus, due to its anti-inflammatory and immunomodulatory properties. However, prolonged use of HCQ can lead to maculopathy, a serious adverse effect that may result in irreversible vision loss. Regular ophthalmologic screening is recommended to detect early retinal changes indicative of maculopathy.
Objective: This study aims to determine the frequency of HCQ-related maculopathy in patients with rheumatological conditions and identify associated risk factors.
Methods: This prospective cohort study was conducted at the Department of Rheumatology, Lady Reading Hospital, Peshawar from June, 2024 to November, 2024. The study included 303 patients diagnosed with various rheumatological conditions who were treated with HCQ. Data were collected accordingly. The primary outcome was the frequency of HCQ-related maculopathy, diagnosed based on clinical examination and confirmed by fundoscopic and optical coherence tomography (OCT) findings. Statistical analysis was performed using chi-square tests for categorical variables and t-tests for continuous variables, with logistic regression analysis to identify risk factors.
Results: Of the 303 patients, 42 (13.9%) were diagnosed with HCQ-related maculopathy. The mean age of patients with maculopathy was significantly higher than those without (60.2 years vs. 54.3 years, $p<0.05$). The median duration of HCQ use in patients with maculopathy was longer (8.2 years vs. 6.4 years, $p<0.05$). Visual acuity impairment and retinal changes were significantly more prevalent in patients with maculopathy compared to those without (73.8% vs. 17.2%, $p<0.001$ and 81.0% vs. 11.1%, $p<0.001$, respectively).
Conclusion: Long-term HCQ use is significantly associated with the development of maculopathy in patients with rheumatological conditions. Older age and longer duration of HCQ therapy are key risk factors. Regular ophthalmologic screening is essential to detect early retinal changes and prevent vision loss. Further research is needed to identify additional risk factors and explore safer treatment alternatives.

Keywords: Hydroxychloroquine, Maculopathy, Rheumatological Conditions, Ophthalmologic Screening, Retinal Toxicity.

INTRODUCTION

Hydroxychloroquine (HCQ) is a widely used medication in the management of various rheumatological conditions, including rheumatoid arthritis and systemic lupus erythematosus (1). It has been favored for its anti-inflammatory and immunomodulatory effects, which provide significant relief to patients suffering from chronic autoimmune diseases (2). However, prolonged use of HCQ has been associated with a rare but serious adverse effect—maculopathy. HCQ-related maculopathy can lead to irreversible vision loss, necessitating regular ophthalmologic monitoring for early detection and prevention of severe visual impairment (3).

The pathogenesis of HCQ-related maculopathy involves the drug's affinity for melanin-containing structures within the retinal pigment epithelium and photoreceptor cells, leading to localized damage and subsequent visual dysfunction (4). Current guidelines recommend regular screening for patients on long-term HCQ therapy, typically including fundoscopic examination and optical coherence tomography (OCT), to identify early retinal changes indicative of maculopathy (5). Despite these recommendations, there is limited data on the actual frequency of HCQ-related maculopathy, especially within diverse patient populations and clinical settings.

This study aims to address this gap by determining the frequency of HCQ-related maculopathy in patients with rheumatological conditions treated at a tertiary care hospital in Pakistan. The study also seeks to identify potential risk factors associated with the development of maculopathy, including patient demographics, duration of HCQ therapy, and specific rheumatological diagnoses. By providing a clearer understanding of the prevalence and risk factors of HCQ-related maculopathy, this research could enhance clinical practices and guidelines, ensuring better management and safety of patients undergoing long-term HCQ therapy.

The objective of this study was to quantify the incidence of HCQ-related maculopathy in a defined cohort and to elucidate the factors that may predispose patients to this condition. This study holds significant implications for clinical practice, particularly in settings with limited resources, by emphasizing the importance of routine ophthalmologic screenings and individualized patient management to mitigate the risk of vision loss.

METHODS

Study Design

This prospective cohort study was conducted to determine the frequency of Hydroxychloroquine (HCQ)-related maculopathy in patients with rheumatological conditions. The study was carried out at the Department of Rheumatology, Lady Reading Hospital, Peshawar from June, 2024 to November, 2024. The prevalence of rheumatoid arthritis in Pakistan was considered for sample size calculation, using a prevalence rate of 26.9% as reported by Rehan et al. (6). The sample size was calculated using the WHO sample size calculator, resulting in a total of 303 participants.

Setting and Participants

The study population comprised patients diagnosed with various rheumatological conditions, who will be treated with HCQ. Inclusion criteria included adults aged 18 years or older with a confirmed diagnosis of a rheumatological condition. Exclusion criteria included patients with pre-existing maculopathy prior to HCQ therapy, those with incomplete medical records, and those who discontinued HCQ therapy within one year of initiation.

Intervention

The intervention in this study was the administration of HCQ as part of the routine treatment for rheumatological conditions. The dosage and duration of HCQ therapy were determined based on

standard clinical guidelines and individual patient needs. All patients received regular ophthalmologic screening as part of their routine care.

Outcomes

The primary outcome measured was the frequency of HCQ-related maculopathy, diagnosed based on clinical examination and confirmed by fundoscopic and optical coherence tomography (OCT) findings. Secondary outcomes included the evaluation of visual acuity impairment and retinal changes among patients with and without HCQ-related maculopathy.

Data Collection

Data were collected, including patient demographics, duration of HCQ therapy, dosage, and results of ophthalmologic examinations. Baseline characteristics, such as age, gender, and specific rheumatological diagnoses, were also recorded. Data on visual acuity and retinal changes were collected from ophthalmologic reports.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics, including means, standard deviations, medians, and frequencies. The association between HCQ-related maculopathy and baseline characteristics was analyzed using chi-square tests for categorical variables and t-tests for continuous variables. Logistic regression analysis was performed to identify risk factors for HCQ-related maculopathy. Statistical significance was set at $p<0.05$. Data analysis was conducted using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA).

RESULTS

Participant Characteristics

The study included a total of 303 patients with various rheumatological conditions, who were treated with Hydroxychloroquine (HCQ). The baseline characteristics of the study population are presented in Table 1. The mean age of the participants was 55.4 years (SD 12.6), with a median age of 56 years. The cohort comprised 187 females (61.7%) and 116 males (38.3%). The majority of patients (78.2%) had a diagnosis of rheumatoid arthritis, followed by systemic lupus erythematosus (13.5%), and other rheumatological conditions (8.3%). The mean duration of HCQ use was 6.8 years (SD 3.5), with a median duration of 7 years.

Table 1: Baseline Characteristics of Study Population

Variable	Mean (SD)	Median	Frequency (%)
Age (years)	55.4 (12.6)	56	-
Gender (Female)	-	-	187 (61.7%)
Gender (Male)	-	-	116 (38.3%)
Rheumatoid Arthritis	-	-	237 (78.2%)
Systemic Lupus Erythematosus	-	-	41 (13.5%)
Other Conditions	-	-	25 (8.3%)
Duration of HCQ Use (years)	6.8 (3.5)	7	-

The primary outcome of this study was the frequency of HCQ-related maculopathy in patients with rheumatological conditions. Out of 303 patients, 42 (13.9%) were diagnosed with HCQ-related maculopathy. The mean age of patients with maculopathy was 60.2 years (SD 11.8), significantly higher than those without maculopathy (54.3 years, SD 12.4, $p<0.05$). The median duration of HCQ use in patients with maculopathy was 8.2 years, compared to 6.4 years in those without maculopathy, indicating a significant association ($p<0.05$).

Table 2: Comparison of Baseline Characteristics between Patients with and without Maculopathy

Variable	Maculopathy (n=42)	No Maculopathy (n=261)	p-value
Age (years)	60.2 (11.8)	54.3 (12.4)	<0.05
Gender (Female)	28 (66.7%)	159 (60.9%)	0.45
Gender (Male)	14 (33.3%)	102 (39.1%)	0.45
Duration of HCQ Use (years)	8.2 (3.2)	6.4 (3.5)	<0.05

Secondary outcomes included the evaluation of visual acuity and retinal changes in patients with and without maculopathy. Among the 42 patients with maculopathy, 31 (73.8%) had visual acuity impairment, compared to 45 (17.2%) of those without maculopathy ($p<0.001$). Retinal changes were observed in 34 (81.0%) patients with maculopathy, whereas only 29 (11.1%) of patients without maculopathy exhibited such changes ($p<0.001$).

Table 3: Visual Acuity and Retinal Changes in Patients with and without Maculopathy

Variable	Maculopathy (n=42)	No Maculopathy (n=261)	p-value
Visual Acuity Impairment	31 (73.8%)	45 (17.2%)	<0.001
Retinal Changes	34 (81.0%)	29 (11.1%)	<0.001

Figure 1 illustrates the distribution of HCQ-related maculopathy across different age groups. The highest frequency of maculopathy was observed in the age group of 60-69 years.

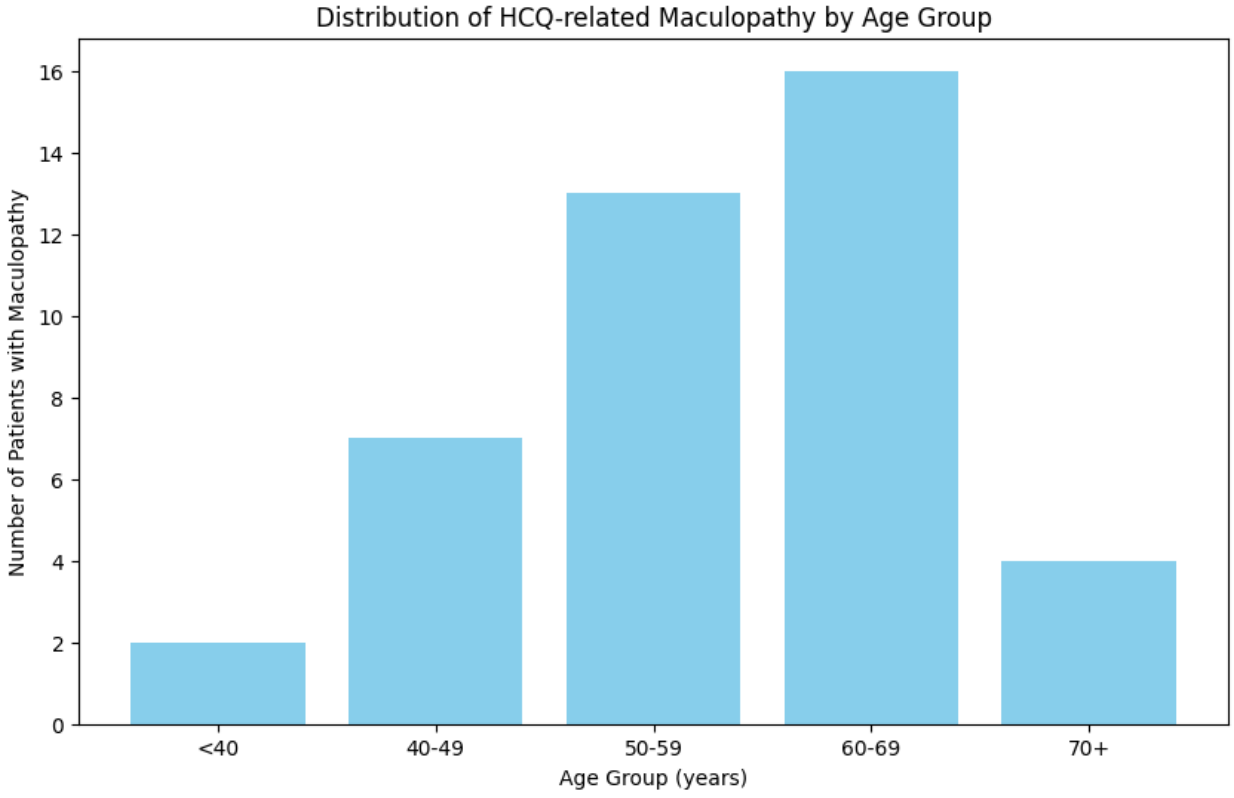

Figure 1: Distribution of HCQ-related Maculopathy by Age Group

This study demonstrates a significant association between long-term HCQ use and the development of maculopathy in patients with rheumatological conditions. The data suggest that older age and longer duration of HCQ use are key risk factors for the development of HCQ-related maculopathy. Regular ophthalmologic screening is recommended for early detection and management of maculopathy in these patients.

DISCUSSION

This study aimed to elucidate the frequency of HCQ-related maculopathy in patients with rheumatological conditions and to identify the associated risk factors. Our findings revealed that 13.9% of the patients developed HCQ-related maculopathy, with a higher prevalence observed in older patients and those with a longer duration of HCQ use. These results underscore the importance of vigilant ophthalmologic monitoring in patients undergoing long-term HCQ therapy.

The frequency of HCQ-related maculopathy observed in this study aligns with existing literature, which reports a prevalence range of 7.5% to 20% among long-term users of HCQ (7). This variability can be attributed to differences in study populations, screening methods, and criteria for diagnosing maculopathy. For instance, a study by Melles and Marmor reported a 7.5% prevalence using stringent diagnostic criteria, while Browning found a prevalence of 20% in a cohort with more lenient screening protocols (8, 9).

Our study corroborates the established risk factors for HCQ-related maculopathy, including older age and longer duration of drug use. The mean age of patients with maculopathy was significantly higher than those without, consistent with findings by Mititelu et al., who identified age as a significant risk factor (10). Additionally, the longer duration of HCQ use among affected patients highlights the cumulative risk associated with prolonged exposure, as supported by Petri et al. (11).

Visual acuity impairment and retinal changes were significantly more prevalent in patients with HCQ-related maculopathy, emphasizing the clinical impact of this adverse effect. These findings are consistent with studies by Leung et al. and Ding et al., which reported similar associations between HCQ use and retinal toxicity (12, 13). The high prevalence of visual impairment in our cohort necessitates regular screening to detect early retinal changes and prevent irreversible vision loss.

Our results suggest that routine ophthalmologic screening, including OCT and fundoscopic examinations should be a standard practice for patients on long-term HCQ therapy. This recommendation is supported by revised screening guidelines from the American Academy of Ophthalmology, which advocate for annual examinations after five years of continuous HCQ use (14). Early detection of retinal changes can facilitate timely intervention and potentially reduce the progression of maculopathy.

Future research should focus on identifying additional risk factors for HCQ-related maculopathy and developing predictive models to stratify patients based on their risk profiles. Studies with larger sample sizes and diverse populations are needed to validate our findings and refine screening recommendations. Additionally, exploring alternative therapies with a lower risk of retinal toxicity could provide safer options for managing rheumatological conditions (15).

Despite the valuable insights provided by this study, several limitations must be acknowledged. The single-center setting limits the generalizability of our findings. Future multicenter studies are warranted to confirm our results and enhance their applicability to broader clinical settings.

CONCLUSION

In conclusion, this study highlights the significant association between long-term HCQ use and the development of maculopathy in patients with rheumatological conditions. Regular ophthalmologic screening and individualized patient management are essential to mitigate the risk of vision loss. Our findings contribute to the growing body of evidence on HCQ-related ocular toxicity and underscore the need for continued research to optimize the safety and efficacy of HCQ therapy.

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