

Adherence of Ophthalmologists and Rheumatologist to the Latest Recommendations of HCQ Retinopathy Screening in Saudi Arabia

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Abstract

Purpose: To assess how well ophthalmologists and rheumatologists followed the latest HCQ retinal toxicity detection recommendations. **Methods:** A cross-sectional study was carried out on a purposive sample of 149 ophthalmologists and rheumatologists in Saudi Arabia. A purposive sample was used to target physicians with experience in HCQ prescribing and monitoring. An online questionnaire was used to collect data on participants' demographics, practice level, the number of patients treated with HCQ, the dosage recommended to reduce the risk of retinopathy (optimal dose defined as ≤ 5 mg/kg/day actual body weight), the recommended screening tests, including baseline and annual retinal evaluation using OCT and visual field testing, the timing of follow-up screening for patients with and without risk (patients "at risk" defined as those with renal or liver dysfunction, high cumulative dose, prolonged treatment duration, or concurrent medications such as tamoxifen), and actions to be taken if screening tests were abnormal. However, since purposive sampling is a non-random method, the findings may not be fully generalizable to all ophthalmologists and rheumatologists in Saudi Arabia. **Results:** 149 participants, 57.7% were ophthalmologists, 57.5% were female, and 53% were consultants. Overall, 53.7% reported the optimal HCQ dose to reduce retinopathy risk as ≤ 5 mg/kg/day actual body weight, and 56.4% performed screening before initiating HCQ. In cases of abnormal screening results, 59.7% reported stopping HCQ therapy. The most reported risk factor

for retinal toxicity was cumulative HCQ dose (30.9%). Comparative analysis showed that ophthalmologists had a significantly higher percentage of performing screening tests and were more likely to stop treatment when SD-OCT findings were abnormal ($p < 0.05$). They also reported significantly higher recognition of key risk factors, including age > 70 years, impaired liver and renal function, HCQ dose, cumulative HCQ dose and use, prior ocular pathology and treatment duration ($p < 0.05$). **Conclusion:** There is a need for better compliance with established recommendations among rheumatologists.

Keywords

Ophthalmologists, Rheumatologist, Recommendations, HCQ, Retinopathy

1. Introduction

The antimalarial medication hydroxychloroquine, also known by its commercial name Plaquenil, is well-known for treating dermatological and rheumatological conditions. Lately, it has also been shown to be useful in the treatment of pediatric inflammatory disorders [1]. Rheumatoid arthritis (RA), Sjögren's syndrome (SS), and systemic lupus erythematosus (SLE) are examples of rheumatic disorders. Those given HCQ treatment, which is proven to lower morbidity and death [2]. There isn't a perfect medication, though. It is known that HCQ has a wide range of negative consequences. One is that it produces dose- and time-dependent retinal damage [3].

Although one study found that hydroxychloroquine (HCQ) strongly inhibits the uptake activity of organic anion transporting polypeptide 1A2 (OATP1A2), which is present in human retinal pigment epithelium (RPE) cells, the precise mechanism by which HCQ causes retinopathy remains unknown [3]-[5]. This polypeptide has a role in all-trans-retinol recycling, suggesting that HCQ may have an effect on the visual cycle. Furthermore, in primary human RPE cells and human embryonic kidney cells (HEK293), HCQ significantly inhibited all-trans-retinol uptake. Major risk factors for HCQ retinopathy include length of therapy, high weight-based dose (>5 mg/kg/day), concurrent use of tamoxifen, established retinal or macular illness, and renal impairment [6] [7].

Previous data indicated that the prevalence of HCQ retinopathy was 7.5% overall. However, after 20 years of use, the prevalence rises to around 20% for users taking 4.0 - 5.0 mg/kg (actual body weight; ABW)/day and may exceed 50% for users using more than 5.0 mg/kg ABW/day [1]. According to recent reports, the frequency of HCQ retinopathy is higher than the 7.5% previously estimated [8]. New research suggests that HCQ retinopathy is more common than previously thought [9]. Therefore, it is imperative to diagnose and evaluate HCQ retinopathy early to potentially prevent vision loss and stop its progression [8] [9]. Annual and baseline retinal screenings are advised for patients on HCQ. An ophthalmologist will do a baseline screening using optical coherence tomography (OCT) to exam-

ine the macula during the first 12 months of beginning the medication. After five years of treatment, in addition to yearly screening [9].

It is difficult to follow established guidelines for screening for HCQ/CQ retinopathy; in US research, only 54.8% of patients received a proper examination. 25.7% of patients underwent fewer tests than what was reported; fundus autofluorescence (AF) and multifocal ERG (mfERG) were routinely disregarded while SD-OCT and 10-2 visual field tests were regularly performed [1]. More administrative support and regional coordination may be required to include quality control into the HCQ retinopathy screening procedure [1].

The care physician (either a rheumatologist or a general practitioner) and patients on HCQ need to be made aware of the screening schedule to guarantee that patients who need screening get it. In addition, as part of quality control, ensure that patients are assessed and called back as necessary [1]. Insufficient awareness of the requirements for screening for HCQ toxicity was found in a recent study, including rheumatologists and ophthalmologists, to assess compliance with recommendations about HCQ retinopathy [8].

As far as we can tell, ophthalmologists and rheumatologists don't use these suggestions much. Thus, the purpose of this study was to assess ophthalmologists and rheumatologists' adherence to the latest recommendations of HCQ retinal toxicity detection in Saudi Arabia.

2. Subjects and Methods

Study design, setting and time: A cross-sectional study was carried out to on ophthalmologists and rheumatologists in Saudi Arabia in the time from July to September 2024.

Study population and sample: A purposive sample of 149 ophthalmologists and rheumatologists, of both genders, was chosen. The exclusion criteria were residents and ophthalmologists and rheumatologists from outside Saudi Arabia.

Data collection: A self-administrated questionnaire was used to collect data about the participants' demographics and work experience (gender, practice level, how many patients take care of by HCQ and the dosage recommended to reduce the risk of retinopathy), the recommended screening tests for patients and how to preform it time of follow up screening for patients with and without risk and risk factors for abnormal retinal toxicity and action that would be taking if screening tests was abnormal.

Ethical considerations: An ethical approval for the study was obtained from the research ethics committee of Qassim University, Saudi Arabia. Informed consent was obtained from the targeted population, combined with the survey, before participating in the study.

Data analysis: Data were statistically analyzed using the (SPSS) application version 26. To investigate the association between the variables, the Chi-squared test (χ^2) was applied to qualitative data that was expressed as numbers and percentages. A p-value of less than 0.05. was considered statistically significant.

3. Results

The study included 149 physicians of them 86 (57.7%) were Ophthalmologists and 63 (42.3%) were rheumatologists. Of the participants, 57.5% were females and 53% were consultants. The majority (79.2%) reported receiving patients taking HCQ and more than one-third (35.6%) screened 1 - 3 patients who were treated with HCQ in the past year. A non-significant difference was found between ophthalmologists and rheumatologists according to their demographics ($p \Rightarrow 0.05$). Ophthalmologists received a higher rate of patients on HCQ compared to rheumatologists (81.4% vs. 76.2%), and rheumatologist had a higher rate of screening patients on HCQ (30.2% vs. 20.9%), however this difference was non-significant ($p \Rightarrow 0.05$) (**Table 1**).

Table 1. Comparison between ophthalmologists and rheumatologists according to their demographics practice level, receiving patient on hydroxychloroquine (HCQ) and number of patients screened (No.: 149).

| Variable | Total | Specialty | | χ^2 | p-value |
|--|------------|-----------------------------|---------------------------|----------|---------|
| | No. (%) | Ophthalmologists No. (%) | Rheumatologist No. (%) | | |
| Gender | | | | | |
| Female | 63 (42.3) | 31 (36) | 32 (50.8) | 3.24 | 0.072 |
| Male | 86 (57.7) | 55 (64) | 31 (49.2) | | |
| Practice level | | | | | |
| Consultant | 79 (53) | 50 (58.1) | 29 (46) | 2.14 | 0.143 |
| Specialist | 70 (47) | 36 (41.9) | 34 (54) | | |
| Did you receive patient taking HCQ? | | | | | |
| No | 31 (20.8) | 16 (18.6) | 15 (23.8) | 0.59 | 0.439 |
| Yes | 118 (79.2) | 70 (81.4) | 48 (76.2) | | |
| In the past year, how many patients did you screen, who were treated with HCQ? | | | | | |
| 1 - 3 | 53 (35.6) | 34 (39.5) | 19 (30.2) | 2.76 | 0.43 |
| 4 - 6 | 41 (27.5) | 25 (29.1) | 16 (25.4) | | |
| 7 - 10 | 18 (12.1) | 9 (10.5) | 9 (14.3) | | |
| >10 | 37 (24.8) | 18 (20.9) | 19 (30.2) | | |

Table 2 demonstrates that more than half of the participants (53.7%) reported that the optimal dose for HCQ to reduce the risk of retinopathy was Equal to or less than 5 mg/kg of the actual body weight or 400 mg/day. About 56% (56.4%) reported that they perform the screening test before initiating HCQ treatment, with Ocular examination (47.9%), Visual field testing (47.7%) and Spectral domain optical coherence tomography (42.3%) the most performed tests. More than half of the studied physicians (58.4%) reported that the optimal time of follow-up screening tests for patients without risk is yearly, after 5 years of treatment. While for patients at risk, 54.4% reported that the optimal time of follow-up is yearly, after started the treatment. About 59% 59.7% reported that they stopped HCQ

therapy because of an abnormal screening test, of them 48.3% reported that the abnormal test was the visual field testing and 44.9% reported that it was the Spectral domain optical coherence tomography. The most reported risk factors for retinal toxicity were cumulative HCQ dose (30.9%), treatment duration (28.2%) and concomitant tamoxifen use (24.8%). When ophthalmologists were compared to rheumatologist, a non-significant difference was found according to performing the screening test ($p = > 0.05$). On the other hand, ophthalmologists had a significant higher percent of those performing Color testing, Spectral domain optical coherence tomography, Fundus photography, Fundus autofluorescence, Ocular examination or Visual field testing ($p = < 0.05$). While rheumatologist had a significant higher percent of referring the case to the ophthalmologist ($p = < 0.05$). A non-significant difference was found between the two studied specialties, according to previous stops in HCQ therapy because of an abnormal screening test ($p = > 0.05$). But ophthalmologists had a significantly higher percentage of stopping treatment when the Spectral domain optical coherence tomography was abnormal ($p = < 0.05$). As for major risk factors for retinal toxicity, ophthalmologists had a significant higher percent of reporting age > 70 years, liver function, renal function, HCQ dose, cumulative HCQ dose, cumulative HCQ use, previous ocular pathology, genetic factors and treatment duration as risk factors ($p = < 0.05$).

Table 2. Comparison between ophthalmologists and rheumatologists according to their knowledge about HCQ optimal dose to reduce retinopathy risk, timing and types of screening tests, optimal time of follow-up screening tests for patients with and without risk, if stopped HCQ therapy because of an abnormal screening tests and major risks factors for retinal toxicity (No.: 149).

| Variable | Total | Specialty | | χ^2 | p-value |
|---|-----------|-----------------------------|---------------------------|----------|---------|
| | No. (%) | Ophthalmologists No. (%) | Rheumatologist No. (%) | | |
| What is the optimal dose for HCQ to reduce the risk of retinopathy? | | | | | |
| 200 mg once daily | 49 (32.9) | 23 (26.7) | 26 (41.3) | 3.56 | 0.168 |
| 200 mg twice daily | 20 (13.4) | 12 (14) | 8 (12.7) | | |
| Equal to or less than 5 mg/kg of the actual body weight or 400 mg per day | 80 (53.7) | 51 (59.3) | 29 (46) | | |
| When do you perform the screening test? | | | | | |
| Before initiating HCQ treatment | 84 (56.4) | 43 (50) | 41 (65.1) | 7.81 | 0.05 |
| During first year of HCQ treatment | 26 (17.4) | 17 (19.8) | 9 (14.3) | | |
| During the first 5 years of HCQ treatment | 27 (18.1) | 21 (24.4) | 6 (9.5) | | |
| Only in patients at risk | 12 (8.1) | 5 (5.8) | 7 (11.1) | | |
| Which tests should be performed for screening? | | | | | |
| Color testing | 44 (29.5) | 32 (37.2) | 12 (19) | 5.76 | 0.016 |
| Spectral domain optical coherence tomography | 63 (42.3) | 46 (53.5) | 17 (27) | 10.46 | 0.001 |
| Fundus photography | 52 (34.9) | 40 (46.5) | 12 (19) | 12.07 | 0.001 |
| Fundus autofluorescence | 35 (23.5) | 25 (29.1) | 10 (15.9) | 3.52 | 0.061 |
| Ocular examination | 74 (49.7) | 53 (61.6) | 21 (33.3) | 11.64 | 0.001 |

Continued

| | | | | | |
|--|-----------|-----------|-----------|-------|--------|
| Visual field testing | 71 (47.7) | 52 (60.5) | 19 (30.2) | 13.38 | <0.001 |
| Up to the ophthalmologist | 21 (14.1) | 0 (0.0) | 21 (33.3) | 33.37 | <0.001 |
| What is the optimal time of follow-up screening tests for patients without risk? | | | | | |
| Yearly, after started the treatment | 31 (20.8) | 19 (22.1) | 12 (19) | 1.41 | 0.492 |
| Yearly, after 3 years of treatment | 31 (20.8) | 15 (17.4) | 16 (25.4) | | |
| Yearly, after 5 years of treatment | 87 (58.4) | 52 (60.5) | 35 (55.6) | | |
| What is the optimal time of follow-up screening tests for patients at risk? | | | | | |
| Yearly, after started the treatment | 81 (54.4) | 46 (53.5) | 35 (55.6) | 0.16 | 0.921 |
| Yearly, after 3 years of treatment | 30 (20.1) | 17 (19.8) | 13 (20.6) | | |
| Yearly, after 5 years of treatment | 38 (25.5) | 23 (26.7) | 15 (23.8) | | |
| Have you ever stopped HCQ therapy because of an abnormal screening test? | | | | | |
| No | 60 (40.3) | 36 (41.9) | 24 (38.1) | 0.21 | 0.643 |
| Yes | 89 (59.7) | 50 (58.1) | 39 (61.9) | | |
| If yes, which test was abnormal? (No.: 89) | | | | | |
| Color testing | 22 (24.7) | 14 (28) | 8 (20.5) | 0.66 | 0.417 |
| Spectral domain optical coherence tomography | 40 (44.9) | 28 (56) | 12 (30.8) | 5.63 | 0.018 |
| Fundus photography | 17 (19.1) | 9 (18) | 8 (20.5) | 0.09 | 0.765 |
| Fundus autofluorescence | 8 (8.9) | 6 (12) | 2 (5.1) | 1.26 | 0.261 |
| Ocular examination | 28 (31.4) | 13 (26) | 15 (38.5) | 1.57 | 0.209 |
| Visual field testing | 43 (48.3) | 28 (56) | 15 (38.5) | 2.69 | 0.1 |
| What are the major risk factors for retinal toxicity? | | | | | |
| Age > 70 Years | 24 (16.1) | 24 (27.9) | 0 (0.0) | 20.95 | <0.001 |
| Liver function | 27 (18.1) | 27 (31.4) | 0 (0.0) | 24.15 | <0.001 |
| Renal function | 42 (28.2) | 42 (48.8) | 0 (0.0) | 42.84 | <0.001 |
| HCQ dose | 42 (28.2) | 42 (48.8) | 0 (0.0) | 42.84 | <0.001 |
| Cumulative HCQ dose | 46 (30.9) | 46 (53.5) | 0 (0.0) | 48.74 | <0.001 |
| Cumulative HCQ use | 15 (10.1) | 15 (17.4) | 0 (0.0) | 12.21 | <0.001 |
| Concomitant tamoxifen use | 37 (24.8) | 24 (27.9) | 13 (20.6) | 1.03 | 0.31 |
| Previous ocular pathology | 20 (13.4) | 20 (23.3) | 0 (0.0) | 16.92 | <0.001 |
| Genetic factors | 14 (9.4) | 14 (16.3) | 0 (0.0) | 11.31 | 0.001 |
| Treatment duration | 42 (28.2) | 42 (48.8) | 0 (0.0) | 42.84 | <0.001 |

For rheumatologists, the most common diseases that HCQ was prescribed for were Rheumatoid arthritis (71.4%) and Systemic lupus erythematosus (69.8%). And most of them (42.9%) were prescribing HCQ at a dose of 200 Mg OD. Almost one third of the rheumatologists (31.7%) reported that the patients are currently treated with HCQ for less than one year, while 23.8% reported more than 5 years of treatment. Almost half of the rheumatologists (50.8%) will follow an ophthalmologist recommendation if one of the screening tests is abnormal (**Table 3**).

Table 3. Distribution of rheumatologists according to disease they prescribe HCQ for and its dose, duration, patients currently treated with HCQ, and action done if one of the screening tests is abnormal (No. 63).

| Variable | No. (%) |
|---|-----------|
| For what disease you are prescribing? | |
| Rheumatoid arthritis | 45 (71.4) |
| Systemic lupus erythematosus | 44 (69.8) |
| Sjogren's syndrome | 16 (25.4) |
| OA hands | 1 (1.6) |
| What dose of HCQ do you usually prescribe? | |
| 100 Mg OD | 3 (4.8) |
| 200 Mg BID | 12 (19) |
| 200 Mg OD | 27 (42.9) |
| 5 Mg/Kg | 15 (23.8) |
| 6.5 Mg/Kg | 6 (9.5) |
| What is the average time period your patients are currently treated with HCQ? | |
| <1 year | 20 (31.7) |
| 1 - 2 years | 11 (17.5) |
| 3 - 4 years | 8 (12.7) |
| 4 - 5 years | 9 (14.3) |
| >5 years | 15 (23.8) |
| If one of the screening tests is abnormal, what would be your next step? | |
| Decrease the dose | 17 (27) |
| Stop the medication | 22 (34.9) |
| Follow ophthalmologist recommendation | 32 (50.8) |

4. Discussion

This study sought to assess ophthalmologists' and rheumatologists' adherence to the most recent HCQ retinal toxicity detection recommendations in Saudi Arabia. Based on the findings, rheumatologists have considerable knowledge gaps regarding HCQ dosing and retinopathy screening protocols. This finding is consistent with a previous study, which revealed that most rheumatologists did not follow the most recent AAO screening criteria for HCQ retinopathy [10].

To limit the risk of retinopathy, the American Academy of Ophthalmology (AAO) recommends that the daily dose of HCQ not exceed 5 mg/kg of actual body weight [11]. In our study, 59.3% of ophthalmologists and 46% of rheumatologists correctly identified this dose. Similarly, a previous Saudi study found that only 45.4% of respondents adhered to this recommendation, with many continuing to use non-weight-based dosing [10]. Notably, 41.3% of rheumatologists in our study incorrectly selected 200 mg once daily, highlighting a persistent knowledge gap that may increase the risk of HCQ-induced retinopathy [10].

According to retinal screening, baseline screening should be done within the first year of treatment (which implies that HCQ can be begun before baseline

screening). Annual ocular toxicity screening should commence after 5 years of usage, unless patients are deemed high-risk or have ophthalmologic symptoms [12]. Our findings revealed that rheumatologists (9.5%) have low adherence to screening within the first five years, which may indicate a lack of awareness of the progressive nature of HCQ retinopathy and the essential window for early identification. Following abnormal screening results, both ophthalmologists and rheumatologists were equally likely to terminate HCQ therapy, with 59.7% of physicians reporting doing so. It was observed that HCQ retinopathy is irreversible.

In this study, there were some significant disparities between ophthalmologists and rheumatologists' approaches to HCQ retinopathy screening. Ophthalmologists were more likely to do the essential tests and had a better grasp of the relevant risk factors. To improve patient outcomes, better cooperation between these two specialties is required, with rheumatologists taking a more active role in ensuring early and consistent screening while ophthalmologists continue to provide expert evaluation. Standardized protocols and interdisciplinary communication can help bridge the gaps and guarantee that HCQ patients receive the necessary care to avoid retinopathy.

In terms of risk factor recognition, ophthalmologists demonstrated greater awareness than rheumatologists regarding key factors such as age, HCQ dose, renal and hepatic function, cumulative dose and duration, prior ocular disease, genetic factors, and treatment duration. Both specialties recognized tamoxifen use as a significant risk factor. In our study, 30.9% of respondents identified cumulative HCQ exposure as a major contributor to toxicity. These findings align with established evidence that daily dose, cumulative dose, renal or liver dysfunction, treatment duration exceeding five years, pre-existing retinal disease, and older age significantly increase the risk of HCQ-induced retinopathy [13].

5. Limitations

The current study's limitation was the use of a cross-sectional study design, which indicated correlations but not causal relationships between studied variables. Additionally, reliance on self-reported data may introduce recall and response biases.

6. Conclusion

This study found considerable knowledge gaps among rheumatologists about hydroxychloroquine (HCQ) dose and retinopathy screening protocols. Only 46% of rheumatologists correctly identified the recommended HCQ dose, compared to 59.3% of ophthalmologists. Furthermore, adherence to baseline screening within the first year of starting HCQ medication was very poor among rheumatologists (9.5%). In contrast, ophthalmologists showed a better awareness of the risk variables linked with HCQ retinopathy. These findings underscore the urgent need for better education and communication between rheumatologists and ophthalmologists to improve patient outcomes and assure compliance with established recommendations.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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