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Current screening practice in patients under long-term hydroxychloroquine medication in Taiwan

A nationwide population-based cohort study

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Abstract

Hydroxychloroquine (HCQ), an analog of chloroquine, is widely used in various rheumatologic and dermatologic disorders. However, it may cause severe retinopathy with long-term use. The guidelines proposed by the American Academy of Ophthalmology suggested a baseline fundus examination and an annual screening after 5 years by using automated visual fields (VF) plus spectral-domain optical coherence tomography (SD-OCT). Both multifocal electroretinogram (mfERG) and fundus autofluorescence (FAF) can also be used to improve the accuracy of diagnosis. The purpose of this study was to examine if the current HCQ screening practice in Taiwan was sufficient according to the guidelines to prevent severe macular complications.

This study could remind every doctor to explain visual side effects thoroughly to every patient using HCQ, and refer patients for the ophthalmologic survey to eliminate potential visual impairment caused by this medicine.

This nationwide population-based cohort study included all patients who started taking HCQ (n = 5826) from January 1, 1997, to December 31, 2007, in the Longitudinal Health Insurance Database 2000. The ICD codes used for HCQ retinopathy were 362.10, 362.55, 362.89, and 362.9. Patients previously diagnosed these retinal disorders were excluded. Demographic data including sex, age, diagnostic tools used, and the date of the initial diagnosis of the subsequent HCQ-related retinal disorder were collected. Patients were divided into 2 groups. The patients taking HCQ <5 years were defined as group 1, and >5 years as group 2. The risk of developing retinal diseases between these 2 groups was compared with a 2-sample *t*-test for continuous variables, and Fisher's exact test for discrete variables. Multiple logistic regressions were used for odds ratio calculation.

The baseline examination ratio of the automated VF, SD-OCT scans, and multifocal electroretinograms (mfERGs) in the first 3 months were only 0.2% in both groups. The screening ratio of the 3 examination tools after 5 years were 1.1% in group 1 and 1.2% in group 2. 2.5% and 3.9% of patients developed a retinal disorder after HCQ use in group 1 and 2, respectively. The risk of developing retinal disorder was significantly higher in group 2 (relative risk = 1.53, $P = .006$). The odds ratio (OR) was also significantly higher in group 2 (1.67 with 95% *cumulative* incidence 1.20–2.30)

The examination ratio according to the guidelines was very low in Taiwan. Thus, it is very important for doctors who prescribe HCQ to schedule both baseline and annual ophthalmology screening tests and inform patients of possible severe ocular complications, even in the patient taking HCQ <5 years. It is also important for ophthalmologists to review medical history carefully to find out the causes of retinotoxicity. Medications should be stopped, if possible when toxicity is recognized or strongly suspected.

Abbreviations: CI = *cumulative* incidence, HCQ = hydroxychloroquine, LHID2000 = Longitudinal Health Insurance Database 2000, mfERGs = multifocal electroretinograms, OR = odds ratio, RA = rheumatoid arthritis, RPE = retinal-pigmented epithelium, RR = relative risk, SD-OCT = spectral-domain optical coherence tomography, SLE = systemic lupus erythematosus, VF = visual fields.

Keywords: automated visual fields, hydroxychloroquine, hydroxychloroquine retinopathy, multifocal electroretinogram (mfERG), screening practice, spectral-domain optical coherence tomography (SD-OCT)

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Prevalence of Retinal Toxicity during Current Hydroxychloroquine Current Screening Practice in Patients under Long-Term Hydroxychloroquine Medication in Taiwan: A Nationwide population-based cohort study

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1. Introduction

Hydroxychloroquine (HCQ), an analog of chloroquine, is widely used in various rheumatologic and dermatologic disorders.[1–3] However, it could bind to melanin in the retinal-pigmented epithelium (RPE) and cause retinal toxicity in long-term use.[4] The most troubling aspect of the toxicity is its irreversibility and continuity of vision loss, despite that its incidence was low.[5] The initial presentations of HCQ retinopathy include a paracentral scotoma with corresponding external limiting membrane loss, disruption of the ellipsoid zone, parafoveal thinning of the outer nuclear layer, and RPE damage.[6,7] One research study also indicated that there was both decreased thickness of the inner segment/outer segment, and ganglion cell-inner plexiform layer, in addition to the increased thickness of RPE/Bruch's membrane in patients using HCQ.[8] These subtle functional and anatomical changes can be detected by an automated threshold visual field test with a white pattern and SD-OCT, respectively.[9] According to the guidelines in the 2016 Clinical Statement from the American Academy of Ophthalmology, the risk of developing retinal toxicity was less than 1% in patients taking HCQ less than 5 mg/kg/day in the first 5 years of therapy.[10] Other research also revealed that a dosage of 5 mg/kg/day, based on the patient's real body weight, might be a safer alternative to avoid retinal toxicity. However, some cases still developed retinopathy even though the dose was taken at the so-called "safety" dose.[11] Thus, it is appropriate to screen every individual using HCQ, both at baseline and annually after treatment. Previous literature suggested a baseline fundus examination and an annual screening after 5 years by using automated visual fields plus SD-OCT. Both multifocal electroretinogram (mfERG) and fundus autofluorescence (FAF) can also be used to improve the accuracy of diagnosis.[10] Jaumouillé et al[12] had collected 184 long-term HCQ users to compare different screening procedures for HCQ retinopathy, and found significant correlation between cumulative HCQ dose and positive results on SD-OCT and 10.2 visual field, but not in fundus examination, autofluorescence, or multifocal ERG. Despite the clear screening suggestions, relevant data are insufficient in Asian countries.

In this study, we used the National Health Insurance Database in Taiwan to evaluate the ratio, timing, and methods of ophthalmic screening, in every HCQ user. This study could remind every doctor to explain visual side effects thoroughly to every patient using HCQ, and refer patients for the ophthalmologic survey to eliminate potential visual impairment caused by this medicine.

2. Materials and methods

In Taiwan, the government launched national health insurance as a mandate on March 1, 1995, and the coverage rate is around 99%. A longitudinal, nationwide, population-based, case-controlled cohort study was conducted to evaluate the examination ratio of patients using HCQ. The Longitudinal Health Insurance Database 2000 (LHID2000) is a sub-dataset of the National Health Insurance Research Database and includes all claims data (from 1997 to 2013) of one million randomly selected beneficiaries. LHID2000 is limited to medical research only and only for researchers who fulfilled the requirements of conducting projects were able to use. Computer-Processed Personal Data Protection Law and related regulations of National Health Insurance Administration and National Health Research Institutes were also be followed by all applicants. There was no significant difference in age, sex, or average payroll-related insurance premiums between the sample group and those of all enrolees.

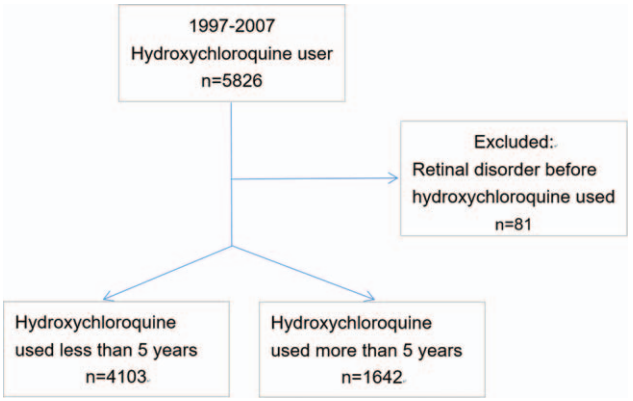

Figure 1. Flowchart of the selected patients.

This nationwide population-based cohort study included all patients who started taking HCQ (n = 5826) from January 1, 1997, to December 31, 2007, in the LHID2000. The ICD codes used for HCQ retinopathy mostly were 362.10 and 362.55 in the previous literature.[13] However, in the early stage of HCQ retinal toxicity, the macular degeneration was relatively unspecific, thus 362.89 and 362.9 were also included in our study to detect potential HCQ retinopathy. We ruled out patients who were previously diagnosed these retinal disorders, and 5745 patients remained for analysis. The patients taking HCQ <5 years were defined as group 1, and >5 years as group 2 (Fig. 1).

We collected demographic data including sex, age, the diagnostic tools used, and the date of the initial diagnosis of subsequent HCQ-related retinal disorder. Adequate examination of patients using HCQ was defined as using automated visual field testing, SD-OCT, or mfERG in the first 3 months of long-term HCQ use and repeated annually after 5 years. Patients were divided into 2 groups based on that whether they had followed retinal conditions after 5 years annually. The risk of developing retinal diseases between these 2 groups was compared with a 2-sample *t*-test for continuous variables, and Fisher's exact test for discrete variables. Multiple logistic regressions were used for odds ratio calculation. SAS for Windows 9.3 was used for the analyses.

This study was approved by the Research Ethics Committee of Taipei City Hospital, Taiwan (TCHIRB-10702106-W). Since this study analyzed de-identified data, the review board waived the requirement for written informed consent from the patients involved.

3. Results

The demographics of HCQ users are listed in Table 1 based on whether these patients taking HCQ >5 years or not. The median age was 50.0 ± 18.6 and 45.5 ± 15.9 years in group 1 and 2, respectively. The sex ratio was male/female 29.4%/70.6%, respectively. The initial baseline examination ratio of any one of the 3 examination tools in the first 3 months were only 0.2% in both the groups. The examination ratio of any one of the 3 examination tools in patients taking HCQ >5 years annually were 1.1% and 1.2%, respectively. In our study, 2.5% in group 1 and 3.9% in group 2 developed retinal disorder after HCQ use,

Table 1

Demographies of hydroxychloroquine user.

	Hydroxychloroquine used <5 years		Hydroxychloroquine used >5 years	
Variable	**n = 4103**	**%**	**n = 1642**	**%**
Gender				
Male	1208	29.4	275	16.7
Female	2895	70.6	1367	83.3
Age (mean ± SD)	50.0 ± 18.6		45.3 ± 15.9	
Baseline examinations within 3 months				
Spectral domain OCT	3	0.1	1	0.1
Multifocal ERG	0	0.0	0	0.0
Automated visual field	6	0.1	4	0.2
Either one	9	0.2	4	0.2
Annual screening after 5 years				
Spectral domain OCT	12	0.3	13	0.8
Multifocal ERG	0	0.0	1	0.1
Automated visual field	35	0.9	14	0.9
Either one	44	1.1	20	1.2
Retinal disorder				
Yes	104	2.5	64	3.9
No	3999	97.5	1578	96.1
Observation time (days, median)	3377		3603	

ERG = electroretinograms, OCT = optical coherence tomography, SD = standard deviation.
Either one means that patients received either spectral domain OCT, multifocal ERG or automated visual field.

respectively. The median observation time of our study was about 9 years in both groups. The risk of developing retinal disorder was revealed in Table 2 and showed significantly higher in group 2 (relative risk = 1.53, $P = .006$). There was no significant difference in gender distribution, age, and baseline examination in first 3 months. Multiple logistic regression for risk of retinal disorder also revealed that the adjust odds ratio was significantly higher in group 2 (1.67 with 95% cumulative incidence 1.20–2.30, Table 3)

Table 2

Risk of retinal disorder.

	No retinal disorder		Retinal disorder		
Variable	**n = 5577**	**%**	**n = 168**	**%**	***P* value**
Gender					.435
Male	1444	97.4	39	2.6	
Female	4133	97.0	129	3.0	
Age (mean ± SD)	48.5 ± 18.0	5.29 ± 16.7	0.002		
Baseline examinations within 3 months				0.320	
Yes	12	92.3	1	7.7	
No	5565	97.1	167	2.9	
Hydroxychloroquine used*					.006
<5 year	3999	97.5	104	2.5	
≥5 year	1578	96.1	64	3.9	

* Relative risk = 0.0389/0.0253 = 1.54.
SD = standard deviation.

Table 3

Multiple logistic regression for risk of retinal disorder.

	crude OR		adjusted OR	
Variable	**OR**	**95%CI**	**OR**	**95%CI**
Gender				
Male	0.87	0.60–1.24	0.90	0.62–1.30
Female	1.00		1.00	
Age (mean ± SD)	1.01	1.01–1.02	1.01	1.01–1.02
Baseline examinations within 3 months				
Yes	2.78	0.36–21.48	2.48	0.32–19.35
No	1.00		1.00	
Hydroxychloroquine used				
<5 year	1.00		1.00	
≥5 year	1.56	1.14–2.14	1.67	1.20–2.30

CI = cumulative incidence, OR = odds ratio, SD = standard deviation.

4. Discussion

Retinal toxicity is a rare but devastating complication in long-term HCQ users. Previous literature revealed the prevalence of HCQ retinopathy was 0.65%.[14] However, as sensitive diagnostic tools are now more available, previously undetectable retinal changes can be found. Kim et al. surveyed the risk of retinal toxicity in long-term users of HCQ by using SD-OCT, FAF, mfERG, and automated visual field testing, and reported the prevalence to be as high as 13.8%. Browning and Lee had evaluated the sensitivities and specificities of 10-2 VF, mfERG, and SD-OCT in detecting HCQ retinopathy. The sensitivities in detecting HCQ retinopathy were 85.7%, 92.9%, and 78.6%, respectively, and the specificities were 92.5%, 86.9%, and 98.1%, respectively The combinations of 10-2 VF and mfERG or SD-OCT and mfERG were more sensitive (100%) than either test alone.[15] However, most of the cases were found based on SD-OCT and automated VF in our study. It may be due to the popularity of these 2 screening tools in comparison to mfERG in Taiwan. It may be necessary to add mfERG as routine screening tools to rule out potential undetected HCQ retinopathy. In addition, HCQ use of longer duration is directly related to HCQ retinal toxicity, which correlated with our study.[16]

The most common diseases which require long-term HCQ treatments are systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[17] The females had a higher incidence of SLE compared with males. The sex ratio ranged from 2:1 to 15:1.[18] The same condition also occurred in RA, in which the ratio was 3:1 to 4:1.[19] These data could explain the proportion of female and male patients were provided as 83.3% and 16.7%, respectively.

Although some studies mentioned the importance of routine monitoring the HCQ retinopathy, few discussed the actual ratio of standard survey tools and timing. Melisa et al[20] analyzed 1409 patients who used HCQ for >4 years and found 27.9% of these patients lacked regular eye care visits, and 34.5% had no diagnostic testing for maculopathy in 5 years. Tucker et al[21] estimated if the US guidelines were used in United Kingdom, it would result in up to 100,000 patients needing annual screening by 2020. This would cause a huge burden to the National Health Service. In our study, patients who received standard annual screening after 5 years were only 1.2% in Taiwan. Most of the cases were found based on SD-OCT and automated VF in our study. It may be due to the popularity of these 2 screening tools in comparison to mfERG in Taiwan. It may be necessary to add mfERG as routine screening tools to rule out potential undetected HCQ retinopathy.

A previous study revealed that the risk of HCQ retinal toxicity was <1% in patients using HCQ for <5 years, and <2% at 10 years.[21] The prevalence of HCQ retinopathy was 1.8% if using HCQ for <5 years, and it increases to 3.9% if using HCQ for >5 years. One research study found dose-related retinal toxicity in 20% of patients after 20 years of intake.[22] This result might be indicative of whether we should annually screen patients taking HCQ continuously to prevent further tissue damage. We found that the risk of developing retinal disorder was significantly higher in patients taking HCQ >5 years, which was similar to the previous studies. However, there were still 2.5% of the patients taking HCQ for <5 years developed retinal disorders. It may remind us the importance for earlier screening to find out potential retinal disorder in patients taking HCQ.

The reason that we chose the National Health Insurance Database is that the prevalence of HCQ retinopathy in the normal population was very low. It is difficult to collect enough data even in a medical center. Most importantly, it could eliminate selection bias to some extent. However, there are still several limitations in our study. First, there may have been several diagnostic discrepancies among individuals since HCQ retinopathy was diagnosed by different ophthalmologists, and some borderline values may occasionally be excluded. Second, since there is no specific code for the diagnosis of HCQ retinopathy, the diagnosis based on ICD-9 in our study may be overestimated. Finally, although retinal toxicity could be detected under the SD-OCT, mfERG, and automated VF in patients using HCQ, the exact cause was technically challenging to ascertain in our study. In other words, it may be difficult to categorize unspecific retinal degenerations if detected early. Iftikhar et al assessed both the sensitivity and specificity of different diagnostic tools and found microperimetry had better specificity in diagnosing HCQ retinopathy.[23] Thus, it may be appropriate to evaluate every potential patient with microperimetry. Adequate collection of these data may yield a more precise evaluation in the future.

5. Conclusion

Although HCQ retinopathy was well known, the examination ratio according to the guidelines was very low in Taiwan. It is essential for doctors who prescribe HCQ to schedule both baseline and annual ophthalmology screening tests and inform patients of possible severe ocular complications. Early referral for examination of advanced retinal conditions is crucial in clinical practice, even in the patient taking HCQ <5 years.

5.1. What was known

1. HCQ, an analog of chloroquine, is widely used in various diseases in dermatology and rheumatology.
2. Long-term usage of HCQ may cause retinal toxicity and lead to both irreversible and continuous vision loss. However, relevant data is insufficient in Asian countries.

5.2. What this paper adds

1. This research provides nationwide population-based data including screening rates and prevalence of HCQ retinopathy in Taiwan.
2. The very low screening rate of HCQ retinopathy may prompt us to place greater emphasis on interdisciplinary communication among different medical departments and long-term HCQ users.
3. The earlier screening to find out potential retinal disorder in patients taking HCQ may be still needed in patients taking HCQ <5 years, even the risk is relatively lower.

Author contributions

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Supervision: Ju-Chuan Yen, Chun-Chen Chen, Po-Chen Tseng.
Writing – Original Draft: Chu-Yu Yen.
Writing – Review & Editing: Po-Chen Tseng.

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