Eye (2021) 35:1171–1177
https://doi.org/10.1038/s41433-020-1028-4

The ROYAL COLLEGE of OPHTHALMOLOGISTS

ARTICLE

Two years' experience of screening for hydroxychloroquine retinopathy

Anne Gobbett[1] · Ajay Kotagiri[1] · Claire Bracewell[2] · Jonathan Smith[1]

Received: 2 January 2020 / Revised: 4 June 2020 / Accepted: 5 June 2020 / Published online: 7 July 2020

Abstract

Background The Royal College of Ophthalmologists (RCOphth) recently produced new guidelines for the screening of hydroxychloroquine (HCQ) retinopathy. New imaging techniques have suggested an increased prevalence of retinopathy (7.5%) compared with previous studies (0.5%).

Methods We collected prospective data from all patients referred to Sunderland Eye Infirmary, Sunderland for HCQ screening. Patients were screened according to RCOphth guidelines. In addition to retinal images, the data recorded included visual acuity, visual fields and multifocal electroretinography as appropriate, the patient's age, diagnosis, weight, renal function and use of tamoxifen.

Results Of the 678 patients screened, 333 were categorised to be at risk (251 patients had been on HCQ >5 years, 117 had an estimated glomerular function rate <60 ml/min/1.73 m^2, and 46 were on a dose >5 mg/kg/day). Eighty patients had multiple risk factors, 31 had been on doses of >5 mg/kg/day for >5 years. One hundred and sixty-eight of these patients have now been screened twice. The prevalence of HCQ retinopathy was 2/678 (0.3%) of all screened, 2/333 (0.6%) of patients at risk.

Conclusions Our results show a far lower rate of retinopathy compared to the widely reported figure taken as standard by the RCOphth. This may be multifactorial: this prospective analysis has fewer patients taking higher doses of HCQ and shorter follow up, the comparison of serial images may highlight more cases and in addition, there are significant numbers of patients yet to be referred. Finally, the RCOphth's diagnostic criteria is more exacting than that of the recent literature.

Introduction

The widespread use of anti-malarial drugs during World War II led to the discovery that they improved the condition of people with inflammatory joint disease. Subsequently, Hydroxychloroquine (HCQ) and Chloroquine have been used in the treatment of long-term inflammatory diseases since the early 1950s [1–3]. Following several reports of possible retinal toxicity in the late 1950s and early 60s, the use of these drugs declined [4–6]. The introduction of the idea of a safe dose and screening by Ophthalmologists by various methods including measuring visual acuity, fundoscopy, Amsler charts, visual field testing and electrodiagnostics allowed more cautious use of these beneficial drugs, increasing their use again [7–10]. Further studies showed that HCQ was thought to be safer than Chloroquine [11], with a rate of retinopathy of 0.5–2% [12–15], and in the 1990s routine screening for HCQ retinopathy became the remit of Optometrists rather than Ophthalmologists in the UK. In 1998, the Royal College of Ophthalmologists (RCOphth) produced revised guidelines [16] for rheumatologists and dermatologists: "Patients should be monitored yearly enquiring about visual symptomatology, rechecking acuity and assessing for blurred vision using the reading chart." Any impaired vision was to be referred to an optometrist before referral to Ophthalmology if necessary. More recently, the lifelong use of HCQ has been recommended for all patients with Systemic Lupus Erythematosus (SLE), increasing its use further [17]. It can be used as

Earlier data and some of the ideas in this paper were presented at RCOphth Annual Congress (Glasgow, May 2019) and at the National Consultants Meeting sponsored by Novartis (London, November 2019) for which the first author received a speaker's fee.

✉ Anne Gobbett
agobbett@doctors.org.uk

[1] Sunderland Eye Infirmary, Queen Alexandra Rd, Sunderland SR2 9HP, UK

[2] Sunderland Royal Hospital, Kayll Rd, Sunderland SR4 7TP, UK

monotherapy and does not need regular blood monitoring. HCQ is safe for the treatment of auto-immune diseases during pregnancy [18] and it is very well tolerated. National Institute for Health and Care Excellence (NICE) guidelines TA375 [19] also encourage the use of HCQ in combination therapy within rheumatology before biological therapies are tried.

New imaging techniques (spectral domain optical coherence tomography (SD-OCT) and auto-fluorescent (AF) retinal images) have however suggested an increased prevalence of retinopathy compared with previous studies. Melles and Marmor [20] performed a retrospective study of 2361 patients, diagnosing HCQ retinopathy in 177 patients. This diagnosis was based on one abnormal test: either SD-OCT or 10-2 Humphrey Visual Fields (HVF). For visual field testing, toxicity meant partial or full ring scotomata mainly involving the para-foveal region. For SD-OCT, this meant predominantly para-foveal thinning of the outer retina and loss of photoreceptor outer segment marker lines (ellipsoid zone and interdigitation zone). They investigated these patients further determining that higher doses, longer duration of use, renal failure and concurrent use of tamoxifen were causative factors. They published a graph demonstrating the variable risk of developing HCQ retinopathy according to the dose and duration of HCQ therapy. The prevalence varied from 1 to 53%, with an overall prevalence of 7.5%. Following the publication of this study [20] HCQ retinopathy was again considered to fit the criteria [21] for a formal screening programme. The American Academy of Ophthalmology in 2016 [22], the British Society of Rheumatology in 2017 [23] and the RCOphth in 2018 [24] produced new guidelines.

We report the results of HCQ retinopathy screening for all patients screened at Sunderland Eye Infirmary (SEI), Sunderland, United Kingdom (UK) from 01/11/17 to 31/10/19 and discuss our results in the light of the work of Melles and Marmor [20].

Method

We collected continuous prospective data from all patients referred to SEI for HCQ screening. An electronic referral pathway for use by our own Trust's Physicians was created. Referrals were also accepted from external sources including Choose and Book from General Practitioners (GP), Nurse Practitioners, Optometrists and other Physicians from outside the Trust. In order to obtain all the clinical information needed, the internal electronic referral form created requested all necessary clinical and demographic details. We also attempted to obtain similar data from external referrals by sending automated letters requesting the information needed, on receipt of a referral.

Patient and treatment details included:

- Age
- Gender
- Ethnicity
- Diagnosis
- Dose and duration of HCQ treatment
- Patient's weight and renal function (eGFR)
- Concurrent use of tamoxifen

Patients were screened according to RCOphth guidelines [24] in a virtual clinic. They were not reviewed face to face in a clinic unless HCQ retinopathy was suspected. All patients had colour fundus photos using a Kowa VX-20 retinal camera and SD-OCT of the macular using a Heidelberg Spectralis machine. Those at risk, requiring annual screening (duration > 5 years, dose > 5 mg/kg/day, estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or concurrent use of Tamoxifen) also had their visual acuity recorded, AF retinal images taken using the Heidelberg Spectralis machine and 10-2 HVF tests performed. Multifocal Electroretinography (mfERG) was performed either to confirm the diagnosis of HCQ retinopathy, or if there was reasonable suspicion based on the results from other tests. All imaging was performed in the SEI photography department. The department employs four qualified medical photographers who specialise in ophthalmic imaging. Specific clinic slots were established for the 10-2 HVF tests in the Glaucoma unit, so that those administering the test were experienced practitioners. All results were then reviewed by one single Ophthalmologist (AG) in charge of HCQ screening at SEI.

The test results recorded in the clinical notes, and results were conveyed to the referring clinician, the GP and the patient in a standardised letter. Patients who had been referred for baseline screening only were discharged leaving the onus for re-referral for annual screening at the appropriate time with the referring clinician. Those with risk factors (duration > 5 years, dose > 5 mg/kg/day, eGFR < 60 ml/min/1.73 m^2 or concurrent use of Tamoxifen) requiring annual follow up were given virtual imaging appointments for the following year. Due to capacity issues any patient who failed to attend their appointment was discharged despite the RCOphth guidelines suggesting resending appointments. The onus was on either the patient or referring clinician to seek a further appointment. All patients requiring further tests based on their results, who were found to be unsuitable for screening and those found to have features consistent with HCQ retinopathy were written to individually. All decisions regarding stopping HCQ treatment were left to the prescribing clinician to make.

Statistics

The chi-squared test was used to determine the significance of any difference between our cohort and that of Marmor and Melles [20].

Results

Of the 742 patients referred for HCQ retinopathy screening 64 (8.6%) patients failed to attend. A total of 114 appointments were missed with new appointments being requested by either the patient or physician which were then attended. Of the 678 patients screened 577 (85%) were women, 663 (98%) were Caucasian and 15 (2%) were of Asian origin and the average age was 59.5 years (range 21–88 years). Analysis of the diagnostic indication for HCQ treatment showed 279 (41%) had rheumatoid arthritis, 100 (14.7%) had SLE, and 94 (13.8%) had inflammatory arthritis, for further diagnostic analysis see (Fig. 1). Of those screened 345 patients had baseline screening and 333 patients with the risk factors detailed above had annual screening tests performed. Of these 333 patients who underwent annual screening 251 (37%) patients had been receiving HCQ for >5 years, (Fig. 2) 117 (17%) had impaired renal function (eGFR < 60 ml/min/1.73 m^2) and 46 (6.7%) were on a dose >5 mg/kg/day (Fig. 3). Eighty (12%) patients had multiple risk factors and 31 (4.6%) patients had been on HCQ for >5 years at a dose >5 mg/kg/day. Twenty-six (3.8%) patients were deemed unsuitable for screening because of co-existing pathology, only four (0.6%) of these had received HCQ for more than 5 years, 22 had been referred for baseline screening. Of those having annual screening 168 (50%) patients have now been screened twice (A total of 846 colour fundal photographs and SD-OCTs, and 501 10-2 HVF tests and AF images have been performed in the two years of running our screening service.).

Two patients so far have been diagnosed with HCQ retinopathy. Two further patients have possible pathological changes in their field test only and are being kept under regular review. The first patient was a 55-year-old woman with rheumatoid arthritis, who had taken a dose of 3 mg/kg/day for 10 years. She was asymptomatic with a vision of 6/6 in both eyes. Her eGFR was 72 ml/min/1.73 m^2. She had subtle changes on colour photography and AF images, but clear peri-foveal loss of the ellipsoid zone on SD-OCT. Her visual field test showed moderate bilateral ring scotomas. The second patient was a 52-year-old woman with SLE,

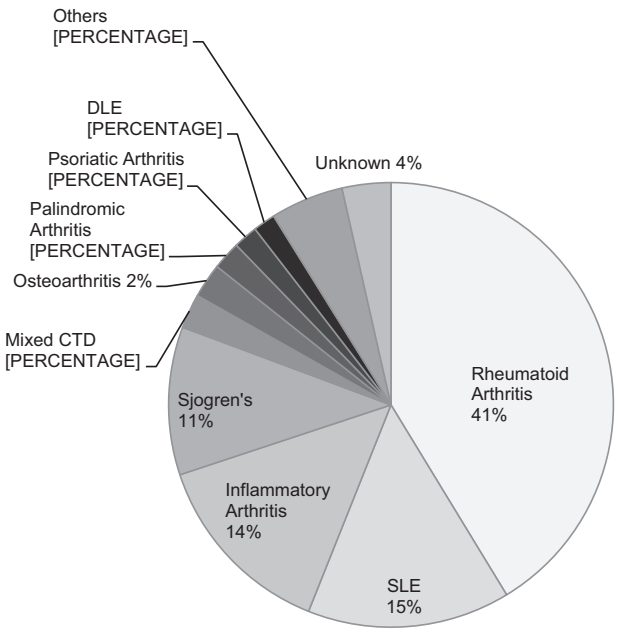

Fig. 1 Diagnostic breakdown of patients screened $n = 678$. Chart showing the analysis of the diagnostic indication for HCQ treatment in our cohort of patients $n = 678$.

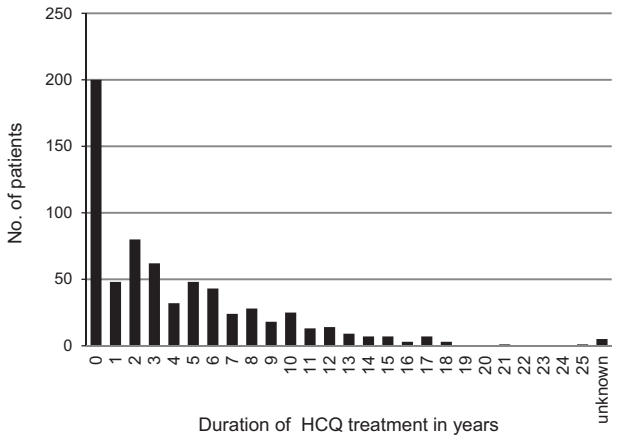

Fig. 2 Duration of HCQ treatment in patients screened $n = 678$. Chart showing the duration of treatment with HCQ in our cohort of patients $n = 678$.

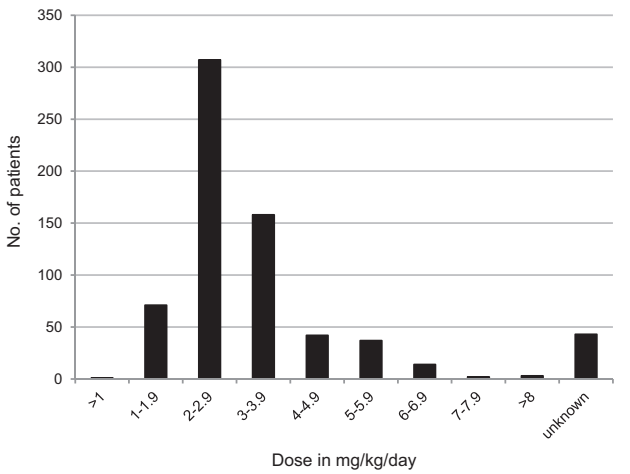

Fig. 3 Prescribed dose of HCQ of patients screened $n = 678$. Chart showing the dose of HCQ taken by our cohort of patients $n = 678$.

who had taken a dose of 8 mg/kg/day for 15 years. She was also asymptomatic with a visual acuity of 6/9 in both eyes. Her eGFR was 65 ml/min/1.73 m^2. She had significant changes on both colour photography and AF images, with peri-foveal loss of the ellipsoid zone and corresponding retinal pigment epithelium damage on SD-OCT. Her visual field test was unreliable, despite repeating it. Both patients had para-central loss of amplitude on mfERG by over 60% of the expected value. Both patients have since stopped taking HCQ following the advice of their treating clinicians.

The prevalence of HCQ retinopathy, using the RCOphth definition of retinopathy (two positive tests), for our entire cohort was 2/678 (0.3%), the prevalence for those defined to be at risk (RCOphth definition of risk) was 2/333 (0.6%) and the prevalence for those with duration of >5 years, (Melles and Marmor's definition of risk [20]), was 2/251 (0.8%). Using Melles and Marmor's definition of retinopathy (one positive test), the prevalence for the entire cohort would be 4/678 (0.6%), the prevalence for those at risk using the RCOphth definition of risk would be 4/333 (1.2%) and using Melles and Marmor's definition of risk, 4/251 (1.6%).

Discussion

Our two years' results for HCQ retinopathy screening suggest a lower prevalence compared with the recent literature [20] on which the RCOphth screening guidelines were based [24]. The lower prevalence of retinopathy within our data may be multifactorial.

a) Different demographics: our cohort has different demographics with far fewer patients being on higher doses of HCQ and for longer durations than those of the Melles and Marmor study [20]. All the 2361 patients in Melles and Marmor's study had taken HCQ for more than 5 years; our cohort had only 251/678 (37%) who had been on HCQ that long. Only 31/251 (12%) of those patients in our cohort were on a dose >5 mg/kg/day compared to 533/2361 (23%) of Melles and Marmor's cohort ($p = 0.0001$). Only 22/251 (8.8%) of patients whilst 716/2361(30%) of Melles and Marmor's cohort had taken HCQ > 15 years ($p < 0.0001$). Therefore, our prevalence of HCQ retinopathy would be expected to be lower.

Melles and Marmor in their pivotal paper [20] produced a graph of the percentage risk of developing retinopathy at different levels of daily and cumulative dose for patients who had taken HCQ for more than 5 years. The data from this graph can be transposed into a table (Table 1: shaded columns) each figure being the percentage risk of retinopathy for the different doses (mg/kg/day) and durations (years) of hydroxychloroquine treatment. Twenty different risk groups can be created. If any patient's dose and duration of HCQ treatment is known, their risk group and their percentage risk of developing HCQ retinopathy can be determined. Inserting the numbers of patients in each risk group from our own cohort of 251 patients who had taken HCQ for more than five years into the table, the expected number of cases and risk for our cohort was calculated (Table 1). This gave the expected number of cases to be 9.43 and a theoretical percentage risk of 3.75%. Our actual prevalence for the cohort was 0.8%. This is still significantly lower ($p = 0.0268$) than the expected calculation.

b) Diagnostic criteria: The RCOphth guidelines [24] state that to diagnose HCQ retinopathy a combination of reliable objective and subjective tests must be used. Melles and Marmor's study [20] relied on only one positive test either an abnormal SD-OCT or 10-2 HVF defect. If working with Melles and Marmor's criteria for diagnosis and risk, our expected prevalence of HCQ retinopathy would be 4/251 (1.6%) which would no longer be statistically significant ($p = 0.139$).

Are two tests better than one? Marmor and Melles [25] have suggested that there could be a disparity between SD-OCT findings and visual field testing, with 10% of patients having significant field loss before anatomical changes could be seen on SD-OCT. Garrity et al. [26] on the other hand have suggested that subtle SD-OCT changes may occur before visual field loss. Work by Browning and Lee [27] published in the same year as Melles and Marmor's work however estimated that if there was only one positive diagnostic test, then its positive predictive value was less than 30%, (the probability of having hydroxychloroquine retinopathy). They suggest that neither visual field testing nor electrodiagnostic tests are highly reproducible, making SD-OCT the most reliable one. Only by combining all three tests is it possible to achieve 100% sensitivity.

c) Reliability of visual field testing: like Browning and Lee [27] we found visual field testing could be unreliable, increasing the need for two positive tests to make an accurate diagnosis of HCQ retinopathy. Unreliable field tests were recorded in 56/333 (17%) of our cohort. Kinavisarut et al. [28] suggest that 30% of their patients undergoing screening for chloroquine retinopathy produced unreliable field test results. We did not have the resources (financial or time) to repeat every field test until we had reliable repeatable results. We were reticent to consider a diagnosis of HCQ retinopathy based on non-contiguous areas of loss of sensitivity alone. In the absence of corresponding SD-OCT changes, only if there was suggestion of a ring or partial ring (Melles and Marmor's definition of a positive field test [25]) was the field test repeated until a reliable repeatable result was obtained, an mfERG performed, and a medical retinal opinion sought. We may have missed some cases, but as

Table 1 Table taking figures (dark shaded area) from the graph published by Melles and Marmor [18] showing the percentage risk of developing HCQ retinopathy at different levels of daily and cumulative dose for patients who had taken HCQ for more than 5 years.

Dose and Duration of HCQ	% RISK (M&M)	No. of our patients	Expected no. of cases
5-9 years			
<3mg/kg/day	1	94	0.94
3-3.9mg/kg/day	1	46	0.46
4-4.9mg/kg/day	2	3	0.06
5-5.9mg/kg/day	8	11	0.88
>6mg/kg/day	20	7	1.4
10-14 years			
<3mg/kg/day	1	31	0.31
3-3.9mg/kg/day	3	19	0.57
4-4.9mg/kg/day	8	7	0.56
5-5.9mg/kg/day	20	10	2
>6mg/kg/day	28	1	0.28
15-19 years			
<3mg/kg/day	2	8	0.16
3-3.9mg/kg/day	6	7	0.42
4-4.9mg/kg/day	15	2	0.3
5-5.9mg/kg/day	21	1	0.21
>6mg/kg/day	40	2	0.8
>20 years			
<3mg/kg/day	4	2	0.08
3-3.9mg/kg/day	9	0	0
4-4.9mg/kg/day	15	0	0
5-5.9mg/kg/day	30	0	0
>6mg/kg/day	53	0	0
TOTAL		**251**	**9.43**

Inserting the numbers of our patients in each category allows the calculation of the expected number of cases and percentage risk of developing retinopathy in our cohort. 251 of our patients had a duration of >5 years. The expected number of cases of retinopathy is calculated as 9.43, giving a theoretical percentage risk of 3.75%.

field tests are subjective even when reliable, their combination with an objective test for diagnosis as required by the RCOphth guidelines [24] will be more accurate in diagnosing HCQ retinopathy. Stopping HCQ unnecessarily based on a false positive test may have a significant impact on a patient's medical condition. It is important to get the diagnosis correct.

d) Duration of study: we currently only have images for baseline screening and two-year follow-up. The comparison of serial images may highlight more cases of retinopathy. Melles and Marmor may have had up to 5 years of serial images to view depending on what tests had been performed on their patients [20].

e) Smaller numbers: our cohort has relatively small numbers though potentially there could be significant numbers of patients yet to be referred. The RCOphth has suggested that up to 320,000 patients taking HCQ nationwide [24]. Our trust serves a population of 278,000, assuming a UK population of 66.4 million [29], this suggests up to 1,300 patients may be prescribed HCQ in our catchment area. We have only seen half this number so far.

Cost

Screening has been expensive. The cost of internal referrals (574/678 (85%)) had to be absorbed by the block contract for the Ophthalmology directorate. External referrals (104/678 (15%)) by Choose and Book received funding. As well as all the testing, four hours of admin and secretarial time, and four hours of medical time at Specialty and Associate Specialist (SAS) doctor level have been given over to the work. Screening tests whether baseline or annual testing, were coded at the same price of £95 (average price as different financial years had different tariffs).

Screening tests	£95 × 846	£80,370
Admin/secretarial time	£2500/year	£5,000
Medical time	£7000/year	£14,000
Total		£99,370

Yates [30] from Kings College London estimated a cost of £45,680 for the first year's screening based on 887 patients having just an SD- OCT at £51 per test. This does not include the cost of other images or visual fields as needed, let alone medical or admin time. Our local rheumatologists commonly prescribe methotrexate, leflunomide, sulphasalazine and HCQ in various combinations for rheumatoid arthritis, often adding in HCQ to prevent changing to biological treatments. The average cost of a non-biological drugs used in auto-immune diseases is £82 pa (range £11–£161). The average cost of biological treatments is £9000 pa (range £350–£16,000) (data for costs are taken from our hospital pharmacy budget). The use of HCQ, even if used in combination with other non-biological drugs and including the cost of screening is however far cheaper than having to progress to treatment with biological therapies.

Screening may then be cost-effective, but we believe there could be changes to the current RCOphth screening

guidelines [24] to make it more cost and time effective. Baseline screening revealed only 22/345 (6.3%) of patients were unfit for screening due to co-existing pathology. Not every patient started on HCQ continues it for five years. Perhaps visual acuity testing and or optometry review would be an adequate baseline test before commencing treatment?

Many units in the UK have not started HCQ screening. Some have dropped baseline screening due to funding issues. Others are still negotiating for extra equipment or staff to carry it out. To the best of our knowledge no screening is happening at all in Scotland. (All information obtained from personal communication). The RCOphth workforce census in 2018 suggests that an extra 230 consultants and 204 SAS grade doctor are needed in Ophthalmology in the next two years to meet rising demands. Three quarters of units have consultant posts not filled by substantive posts [31]. It is not tenable to continue or start screening in its present form, when units are so hard pressed, unless external funding is procured.

Conclusion

Our present results show a prevalence of HCQ retinopathy more in keeping with the earlier studies [12–15] rather than the more recent studies [20]. In part this reflects the different prescribing practices in our area, but also the use of different diagnostic criteria. To determine an accurate prevalence, large prospective population-based studies with accurately collected data, using standardised diagnostic tests, with an agreed definition of the disease are needed. Hopefully, our data when combined with that of others who have followed the RCOphth HCQ screening guidelines [24] will go some way to achieving this.

As both financial and work force issues have had a significant impact on many units' ability to deliver standard ophthalmic care, the additional work of screening for HCQ retinopathy has been difficult if not impossible to achieve [31]. We feel these early results may point toward the possibility of modifying the existing RCOphth HCQ screening pathway [24], with the use of resources being targeted toward those patients at higher risk of developing sight-threatening HCQ retinopathy.

Summary

What was known before

- New advances in retinal imaging, SD-OCT and autofluorescence imaging have suggested the prevalence of HCQ retinopathy is higher (7.5%) (Melles and Marmor) than originally thought (0.5–2%). The AAO, BSR and RCOphth produced new guidelines for the screening for HCQ retinopathy.

What this study adds

- We present the figures from two years of HCQ retinopathy screening. Our results suggest a much lower prevalence than the work of Melles and Marmor. Different local prescribing practices and the tighter diagnostic criteria of the RCOphth than that used by Melles and Marmor may account for this.

Acknowledgements We acknowledge the work of the photography department, the nursing staff, and clerical and secretarial staff at SEI who took on this work with no extra funding, equipment, time or staffing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Shee JC. Lupus erythematosus treated with chloroquine. Lancet. 1953;265:201–2.
2. Rogers J, Finn OA. Synthetic antimalarial drugs in chronic discoid lupus erythematosus and light eruptions. AMA Arch Derm Syphilol. 1954;70:61–6.
3. Goldman L, Cole DP, Preston RH. Chloroquine diphosphate in treatment of discoid lupus erythematosus. JAMA. 1953;152:1428–9.
4. Hobbs HE, Sorsby A, Freedman A. Retinopathy following chloroquine therapy. Lancet. 1958;2:478–80.
5. Ellsworth RJ, Zeller RW. Chloroquine induced retinal damage. AMA Arch Ophth. 1961;2:269–72.
6. Grupper C, Bregeat P, Juge P. Severe retinopathy during treatment of lupus erythematosus by synthetic antimalarials (2 cases). Bull de la Soc francaise de dermatologie et de syphiligraphie. 1963;70:824–32.
7. Lloyd LA, Hiltz JW. Ocular complications of chloroquine therapy. Can Med Assoc J. 1965;92:508–13.
8. Mackenzie AH, Scherbel AL. A decade of chloroquine maintenance therapy: rate of administration governs incidence of retinopathy. Arthritis Rheum. 1968;11:496 (Abstract).
9. Carr RE, Gouras P, Gunkel RD. Chloroquine retinopathy early detection by retinal threshold test. Arch Ophthalmol. 1966;75:171–8.
10. Percival SPB, Meanock I. Chloroquine: ophthalmological safety and clinical assessment in rheumatoid arthritis. Br Med J. 1968;3:579–84.
11. Finbloom DS, Silver K, Newsome DA, Gunkel R. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. J Rheumatol. 1985;12:692–4.

12. Morsman CDG, Livesey SJ, Richards IM, Jessop JD, Mills PV. Screening for hydroxychloroquine retinal toxicity: is it necessary? Eye. 1990;4:572–6.
13. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2010;62:775–84.
14. Yam JC, Kwok AK. Ocular toxicity of hydroxychloroquine. Hong Kong Med J. 2006;12:294–304.
15. Spalton DJ, Verdon Roes GM, Hughes GRV. Hydroxychloroquine, dosage parameters and retinopathy. Lupus. 1993;2:355–8.
16. Fielder A, Graham E, Jones S, Silman A, Tullo A. Royal College of Ophthalmologists guidelines: ocular toxicity and hydroxychloroquine. Eye. 1998;12:907–9.
17. Tang C, Godfrey T, Stawell R, Nikpour M. Hydroxychloroquine in lupus: emerging evidence supporting multiple beneficial effects. Intern Med J. 2012;42:968–78.
18. Abarientos C, Sperber K, Shapiro DL, Aronow WS, Chao CP, Ash JY. Hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. Expert Opin Drug Saf. 2011;10:705–14.
19. National Institute for Health and Care Excellence (NICE) Adalimumab, etanercept, infliximab, certolizumab, pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed TA375 published 26th January 2016. https://www.nice.org.uk/guidance/ta375/chapter/3-The-technologies.
20. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol. 2014;132:1453–60.
21. Public Health England Guidance Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. Updated 23 October 2015. https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme.
22. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF, for the American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology. 2016;123:1386–94.
23. Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, on behalf of the BSR and BHPR Standards Guidelines and Audit Working Group, et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying antirheumatic drugs. Rheumatology. 2017;56:865–8.
24. Hydroxychloroquine and chloroquine retinopathy: recommendations on screening. RCO February 2018. https://www.rcophth.ac.uk/wpcontent/uploads/2018/07/Hydroxychloroquine-and-Chloroquine-Retinopathy-Screening-Guideline-Recommendations.pdf.
25. Marmor MF, Melles RB. Disparity between visual fields and optical coherence tomography in hydroxychloroquine retinopathy. Ophthalmology. 2014;121:1257–62.
26. Garrity ST, Jung JY, Zambrowski O, Pichi F, Su D, Arya M, et al. Early hydroxychloroquine retinopathy: optical coherence tomography abnormalities preceding Humphrey visual field defects. Br J Ophthalmol. 2019;103:1600–4.
27. Browning DJ, Lee C. Relative sensitivity and specificity of 10-2 visual fields, multifocal electroretinography, and spectral domain optical coherence tomography in detecting hydroxychloroquine and chloroquine retinopathy. Clin Ophthalmol (Auckl, NZ). 2014;8:1389–99.
28. Kunavisarut P, Chavengsaksongkram P, Rothova A, Pathanapitoon K. Screening for chloroquine maculopathy in populations with uncertain reliability in outcomes of automatic visual field testing. Indian J Ophthalmol. 2016;64:710–4.
29. "Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2018". Office for National Statistics. 2019.
30. Yates M, Bechman K, Subesinghe S, Rutherford A, Russell M, Malaiya R, et al. Hydroxychloroquine use, risk of retinal toxicity and potential impact of screening in a large tertiary centre. Rheumatology. 2018;57:key075.188 (Abstract).
31. Hingorani M, Harcourt J Workforce census 2018 RCOphth. https://www.rcophth.ac.uk/publications/workforce-census-2018/.