BMJ Open

RetINal Toxicity And HydroxyChloroquine Therapy (INTACT): protocol for a prospective population-based cohort study

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To cite: Daftarian N, Lima A, Marozoff S, *et al*. RetINal Toxicity And HydroxyChloroquine Therapy (INTACT): protocol for a prospective population-based cohort study. *BMJ Open* 2022;**12**:e053852. doi:10.1136/bmjopen-2021-053852

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-053852).

Received 27 May 2021
Accepted 03 February 2022

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ABSTRACT

Purpose Hydroxychloroquine (HCQ) is an important medication for patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other rheumatic diseases. Although it is well-tolerated and cost-effective, the risk of HCQ retinal toxicity is of increasing concern. The aim of this study is to re-examine the HCQ retinal toxicity incidence rate, risk factors and clinical course after discontinuation.

Methods We designed a prospective population-based cohort study in adult patients with SLE or RA, currently receiving HCQ for five or more years, who are residents of British Columbia (BC), Canada. Based on administrative data, we identified 5508 eligible participants (1346 SLE and 4162 RA). They will participate in annual or biannual retinal screening over 5 years in alignment with the recently revised American Academy of Ophthalmology guidelines. To standardise procedures for retinal screening, imaging, diagnostic criteria, severity staging and data transfer, a consensus meeting was convened in December 2019 with participation of BC retinal specialists and the research team. Agreement was attained on: use of spectral domain-optical coherence tomography as the primary objective screening modality; classification of images into categories of normal, equivocal or abnormal; and transferring the equivocal and abnormal images plus corresponding subjective test results via cloud-based server from each clinic to a reading centre. Confirmation of HCQ retinal toxicity diagnoses and severity staging will be performed by three independent and masked reviewers. The incidence of HCQ retinal toxicity will be calculated, accounting for the competing risk of death. Hazard ratios for each risk factor will be calculated for the risk of HCQ retinopathy, after adjusting for confounders. We will also estimate the risk of HCQ retinal toxicity progression over 5 years.

Ethics and dissemination This study has received approval from the University of British Columbia Clinical Research Ethics Board (H20-00736) and the Vancouver Coastal Health Research Institute.

Strengths and limitations of this study

- ► To the best of our knowledge, this is the first prospective, population-based cohort study designed to address the incidence rate, risk factors for and clinical course of hydroxychloroquine (HCQ)-induced retinal toxicity and progression.
- ► Access to British Columbia's (BC) administrative health data from the single-payer health care system allowed us to establish a large population-based cohort of all individuals with systemic lupus erythematosus or rheumatoid arthritis, exposed to HCQ for at least 5 years in BC.
- ► Linking participant self-report demographic and medical history, retinal imaging, and administrative health data will allow for calculation of an accurate risk of HCQ-induced retinal toxicity, which will provide vital safety information for patients, physicians and policy makers.
- ► A structured consensus meeting led to the development of a novel and pragmatic standard operational protocol for the screening and follow-up of patients on long-term HCQ medication for retinal toxicity.
- ► Five years of follow-up may be inadequate to capture long-term results for the cases with 5–10 years of HCQ medication.
- ► It is possible that non-adherence to the dosage of prescribed HCQ treatment may occur before or during the study. This issue can only be addressed through evaluation of serum levels of HCQ, which should be considered in future studies.

INTRODUCTION

The antimalarial medication hydroxychloroquine (HCQ) has been the cornerstone medication in the treatment of systemic lupus erythematosus (SLE), and often in

mild to moderate rheumatoid arthritis (RA), alone or in combination; both diseases are chronic with marked disability and premature death.[1–5] HCQ is inexpensive and has been shown to improve survival in patients with SLE and to reduce synovitis and physical disabilities in patients with RA.[6–10] HCQ is also considered to be one of the very well tolerated medications for rheumatic diseases (ie, better than non-steroidal anti-inflammatory drugs, like ibuprofen or naproxen),[11 12] and is considered sufficiently safe to be recommended for pregnant patients with SLE.[13 14]

A landmark trial led by Esdaile *et al*, showed that HCQ discontinuation after achieving disease control, led to 2.5 times higher risk of SLE flare up and 6.1 times higher risk of severe flare up in vital organs (eg, kidney involvement, vasculitis) within 6 months of HCQ withdrawal.[3] Moreover, a long-term study by the same group, on the effect of HCQ withdrawal in SLE, using an intent-to-treat analysis, showed a potential protective effect against a major flare for those randomised to continue HCQ (OR=0.43 (95% CI 0.17, 1.12)).[15] These findings had a significant impact on clinical practice, making HCQ a universal therapy in SLE regardless of disease activity and severity. Since then, many studies have confirmed wide-ranging benefits of HCQ, including improved survival, reduced disease activity; and lower risks of nephritis, pregnancy complications, venous thromboembolism, dyslipidaemia and insulin resistance in patients with SLE.[16–18] Recently, a retrospective population-based study by our group using the administrative health data of the residents of British Columbia (BC), Canada with incident SLE and incident HCQ use between 1997 and 2015 showed a 71% and 83% lower risk of death among patients with SLE, who adhered to HCQ in comparison to patients with SLE, who were non-adherent or discontinued the medication, respectively.[6 7]

Despite being considered relatively safe, it has been reported that with long-term use, HCQ can accumulate in the retinal pigment epithelial cells and may cause progressive outer retinal toxicity with retinal pigment epithelial and photoreceptor cell death and secondary vision loss. Based on the accumulating evidence of HCQ retinal toxicity, the American Academy of Ophthalmology (AAO) recommends annual screening for patients receiving HCQ for 5 years or more.[19] Retinal toxicity had a previously estimated occurrence of 0.5%–2% in long-term users.[19] However, a 2014 retrospective study using the US Kaiser Permanente Northern California (KPNC) database demonstrated that among users of HCQ with use ≤5 mg/kg of their real body weight, the risk was <2% for 5–10 years of therapy, but almost 20% after 20 years of use. Conversely, patients with a mean daily use >5 mg/kg had approximately a 10% risk of retinal toxicity for 5–10 years of HCQ use and almost a 40% risk after 20 years.[20] This is at least 10 times higher than previously published rates and caused alarm to patients and physicians.[21–23] Retinal toxicity secondary to HCQ is a major concern expressed by patients and clinicians. It is one of the main reasons for non-adherence to HCQ.[24–28] However, this study reported 32% missing data and did not adjust for the competing risk of death, thus results might have been susceptible to selection bias and overestimation of the true risk.[20 29]

A systematic review on the risk of HCQ retinopathy and its risk factors in patients with rheumatic diseases found that most previous studies have been case series or retrospective cohorts.[30] This included a few prospective studies, all of which were limited in size (58–225 patients) and duration of follow-up (1–3 years).[22 29 30] Recently a joint statement has been published by the American College of Rheumatology, the AAO, the American Academy of Dermatology and Rheumatologic Dermatology Society, on HCQ ocular safety. They indicated that there is a critical lack of data from a population-based prospective study on HCQ retinal toxicity.[31] A prospective study to better estimate the risk, risk factors and clinical course of HCQ retinal toxicity is therefore needed.

To address this, we established a prospective population-based cohort study to follow patients with RA and SLE with a minimum of 5 years of HCQ use, for potential retinal toxicity. To enable development of a standard operating protocol (SOP) for this study, a consensus meeting was convened among board certified practicing rheumatologists and retinal specialists from BC, including specialists from both urban and rural areas. The objective of the meeting was to identify and agree on an SOP for screening and follow-up for the retinal examinations and assessments. The SOP was to align with the most up to date principles of evidence-based screening protocols for HCQ retinal toxicity, feasible in a routine practice of retinal ophthalmologists to maximise patient and practitioner participation.

COHORT DESCRIPTION/METHODS

Design

A prospective population-based cohort study among patients diagnosed with RA or SLE, with five or more years HCQ use, between January 1990 and December 2020, in BC and who were alive. The patients will be followed for at least 5 years, from July 2021 to December 2026.

Goals

The main aims of our prospective and population-based study are to: (1) determine the incidence rate of retinopathy in HCQ users of ≥5 years duration of treatment, (2) determine the risk factors for HCQ retinopathy and (3) describe the clinical course of retinopathy following HCQ discontinuation, based on retinal examination, multimodal retinal imaging, visual fields (VFs) and patient-reported outcomes from the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25).[32]

Data source

We will use administrative data extracted from Population Data BC (PopData) which is an extensive data

resource for applied health services and population health research used by our group and others.[33–39] PopData covers the entire population of BC from 1990 onwards (5.1 million in 2021). Individuals can be traced over time and ultimately as the data expands longitudinally, over their lifespan. The main linkable databases include the following files: Medical Services Plan (physician visits and procedures data),[40] Hospital Separation (discharge summaries including up to 25 diagnostic codes),[41] PharmaNet (all medications dispensed for all BC residents),[42] Vital Statistics (date and cause of death)[43] and the BC Cancer registry.[44] We have previously developed a unique Laboratory Services link that provides laboratory results linked to the administrative data as well as survey data collected from consenting individuals.

Patient and public involvement

No patient was involved in the development of the research question and outcome measures, study design and conduct of the study.

Study population (SLE and RA cohorts)

Adults (aged ≥18 years) with RA or SLE were identified from outpatient physician billing files or from the hospital discharge database using International Classification of Diseases ninth (ICD-9) and tenth (ICD-10) revision diagnostic codes. SLE and RA cases are defined using at least two ICD codes for SLE and RA, at least 2 months apart within a 2-year window period from 1990 to 2020. The validity of this algorithm to identify patients with RA has been evaluated to have a positive predictive value (PPV) of 82%.[45] Similarly, for identifying patients with SLE, the validity of this algorithm when one ICD code is from hospitalisation and the other by a rheumatologist, has been evaluated to have a PPV of 97% in Swedish registry data.[46] In our previous studies, >80% of SLE cases had at least one code from hospitalisation or from a rheumatologist.[38 47 48]

Using these algorithms, we identified 4104 patients with SLE and 21 265 patients with RA who had started HCQ since 1 January 1997 in BC. Of those, 1346 patients with SLE and 4162 patients with RA (total N=5508) had taken HCQ for at least 5 years by December 2020. Only rare cases who had used chloroquine before commencing HCQ for SLE or RA will be excluded from this study. There will be no exclusion criteria for patients with any underlying systemic disease, ocular disease and/or ocular surgeries with macular involvement. These may include diabetic macular oedema, cystoid macular oedema, retinal vascular occlusive disease, age-related macular degeneration, inherited retinal dystrophy and uveitis. However, patients with advanced macular anatomical alterations due to comorbidities, which could interfere with an HCQ retinal toxicity diagnosis, may be excluded in data analysis (with provided explanation).

Recruitment

Eligible participants identified from our population-based RA and SLE database who fulfil the inclusion criteria will receive an invitation letter containing the study information as well as a consent form. After obtaining informed consent from patients, we will contact the rheumatologists or primary care physicians to inform them of their patient's participation in the study and send reminders for baseline screening and annual referrals, as per 2016 AAO guidelines and current standard of care, to the participating retina specialists' clinics who we will call the 'retina specialist network of the INTACT study'. Rheumatologists and primary care physicians throughout BC may also refer eligible patients based on the inclusion criteria to the retina specialist network of the RetINal Toxicity And HydroxyChloroquine Therapy (INTACT) study, after obtaining informed consent.

Self-report questionnaire

Participants will fill out a self-report questionnaire (see online supplemental file 1—Patient self-report questionnaire) to collect information on risk factors, confounders and patient-reported outcomes, at the time of their first retina examination as part of this study. This data will be updated at each annual visit. The survey questionnaire will collect information on potential risk factors such as chronic kidney disease, diabetes, hypertension, liver disease, retinal or macular disease as well as comorbidities, race, current HCQ dose, weight, height and disease duration.[19] Data on medications with a known risk of retinopathy (eg, tamoxifen, anastrozole) will be collected in the self-report questionnaire as well as obtained from PharmaNet.[49]

Patients with the confirmed diagnosis of HCQ-induced retinopathy will be asked to fill out the NEI VFQ-25, to provide a better understanding of the impact of this side effect on their daily lives.[32]

Consensus description/methods

On 14 December 2019, a consensus meeting was convened in Richmond, BC. Participants in the consensus meeting were project team members, including, three board-certified academic retinal specialists (DALM, KP-V, SDL), three board-certified academic rheumatologists (JAA-Z, JE, KS), one pharmaco-epidemiologist (ME) and one knowledge broker (AH). All practicing retinal specialists in BC were invited (n=27), of which 18 attended the consensus meeting and agreed to participate in the study (the retina specialist network of the INTACT study). In addition, research coordinators from ophthalmology clinics, research staff from Arthritis Research Canada and a guest speaker (Ronald B Melles, MD) attended the meeting.

The consensus meeting commenced with a presentation by the guest speaker who highlighted and discussed key findings from the KPNC study. Two academic retinal specialists (KP-V, SDL) then gave presentations, highlighting key points from the AAO 2016 revised

recommendations on HCQ retinal toxicity screening examinations by spectral domain-optical coherence tomography (SD-OCT) imaging and automated VF test.

After the presentations, two consensus sessions, led by the knowledge broker, were held to identify and address the main challenges that were highlighted in the presentations and were pertinent to developing the SOP:

1. To develop the process for annual HCQ retinal toxicity screening and follow-up examinations by the retina specialist network of the INTACT study for patients with an HCQ retinal toxicity diagnosis. These were to be based on the latest AAO 2016 revised recommendations[16] using at least one objective test of three potential options: SD-OCT, fundus auto-fluorescence (FAF) or multifocal electroretinography confirming the subjective standard automated VF assessment.
2. To define the standardised criteria for detecting normal versus abnormal SD-OCT imaging, define equivocal cases versus definite cases, and determine appropriate follow-up procedures for patients in each group.
3. To determine standardised severity stages of retinal toxicity in cases with abnormal diagnoses.

The consensus session began with individual reflection. Participants were asked to independently identify and record on post-it notes, potential concerns regarding the implementation of the standardised screening and operational protocols relevant to their routine office practice and the potential challenges with eye examination protocols, SD-OCT imaging and automated VF assessment. The knowledge broker then collected and categorised the responses. The categories were shared with participants who then voted to identify the following five main challenges:

I. Standardisation of SD-OCT image acquisition and automated VF assessment.
II. Criteria for diagnosis of HCQ retinal toxicity.
III. Classification of HCQ retinopathy into different severity stages of disease.
IV. Data collection training of medical office assistants (MOA) and research staff at the clinics.
V. Data storage and transfer to the Eye Care Centre at Vancouver General Hospital (VGH) and Arthritis Research Canada.

The second phase of the process was achieved through small group discussions of five participants. Each group was assigned one of the five main challenges and asked to brainstorm logical and feasible solutions for the challenge which could be included in the SOP.

Following the small group discussions, a representative from each group presented a summary of their discussion to the large group. This permitted further discussion to elucidate key points that had been most salient or missing from the small group discussions. The knowledge broker then summarised the options for each of the main challenges and all participants voted. If 100% agreement on the solution(s) for each of the challenges was not initially achieved, another cycle of discussion was undertaken enabling consensus to be reached on the solutions for all challenges.

Consensus results/proposed solutions

The group made the following consensus statements for the five categories mentioned earlier (figure 1).

I. Standardisation of SD-OCT image acquisition and automated VF examination assessment:
   - Only three types of SD-OCT machines are acceptable for this study: Spectralis OCT (Heidelberg Engineering), Cirrhus HD-OCT (Carl Zeiss Meditec) and Topcon 3D-OCT 2000 (Topcon Corporation). At least one of these three machines is available in every retinal clinic participating in this study. Additionally, the same machine(s) must be used for a patient at all of their visits.
   - To completely demonstrate pathologies of the macular area including, foveal, para-foveal and peri-foveal zones, macular SD-OCT scan should cover a minimum of 20°×20° for non-Asian patients and 30°×30° for Asian patients. This difference in macular SD-OCT scanning is based on the AAO guidelines for HCQ retinopathy screening recommendations, according to the findings on racial differences for HCQ retinopathy involvement of macula.[19 50] Block size and raster technique will be machine-specific. For Heidelberg SD-OCT machines, a 12 mm×9 mm cube scan was recommended.
   - Each scan must be able to clearly delineate both inner and outer retinal bands. Specifically, the outer retinal bands at the para-foveal and peri-foveal zones should be in focus and clearly visible. The presence of vessel shadowing will ensure a high-quality scan.
   - SD-OCT imaging must be done for all patients as the main screening exam.
   - If a patient's SD-OCT scan is normal, that patient will be scheduled for their next appointment in a year. However, if the scan is considered equivocal or abnormal, the patient must be evaluated with standard automated 10–2 VF (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, California, USA) assessment. If the 10–2 scan is also considered equivocal or abnormal, then a standard automated 24–2 or 30–2 VF assessment must be done. For Asian participants, both the standard automated 10–2 and 24–2 or 30–2 VF must be performed in all cases with equivocal or abnormal SD-OCT scans.
   - FAF imaging was defined as complementary (to the SD-OCT and automated VF) objective screening examination. Its performance will be left to the discretion of the retina specialist network of the INTACT study, based on their clinical judgement (not mandatory).
II. Criteria for diagnosis of HCQ retinal toxicity:

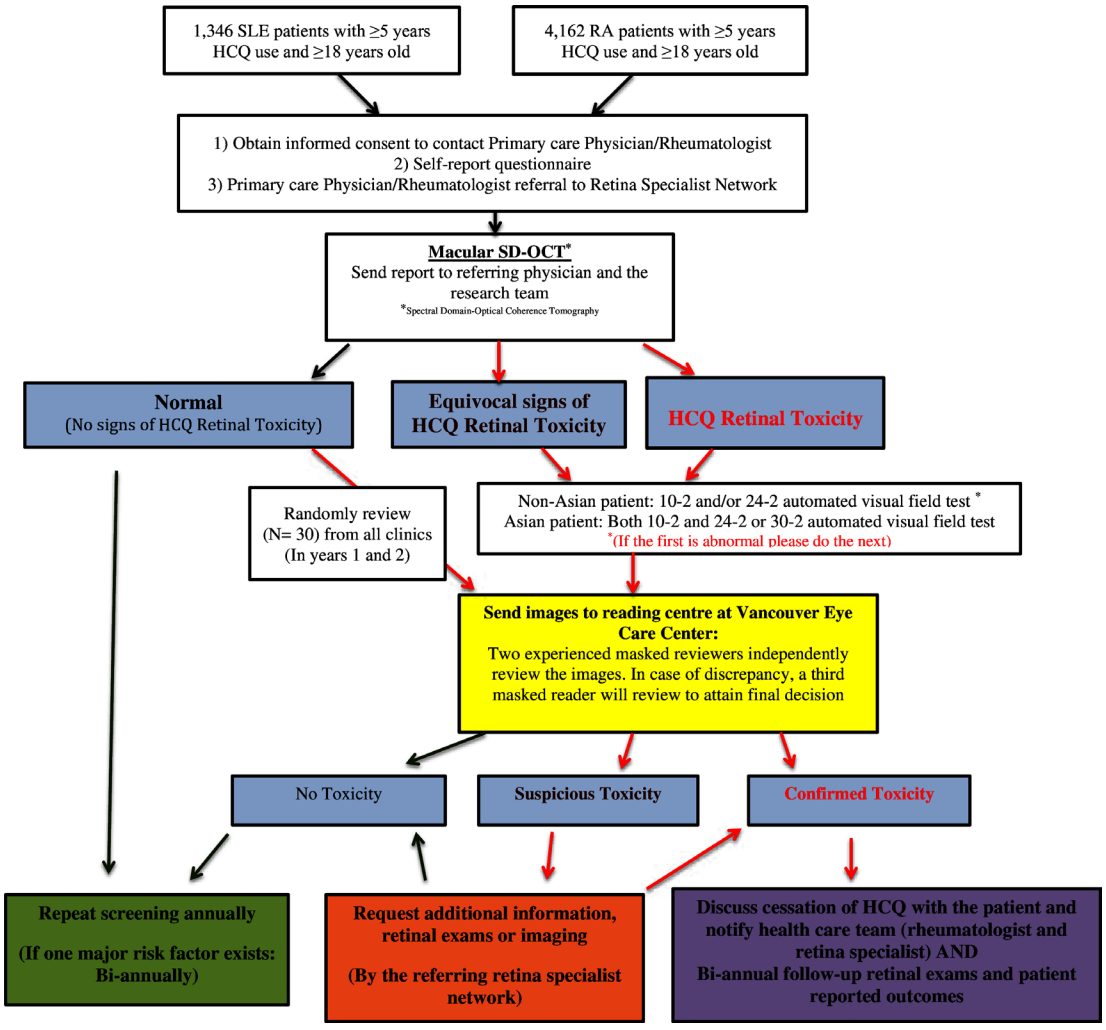

Figure 1 HCQ retinal toxicity screening protocol flowchart for RetINal Toxicity And HydroxyChloroquine Therapy (INTACT) study: the consensus results. HCQ, hydroxychloroquine; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

- All patients on HCQ must be examined according to the standard of care and current guidelines regardless of any comorbidities. However, diagnosis of HCQ retinopathy will be determined by the clinician's (retina specialist network of INTACT study) interpretation of results based on standard images that will be sent to them as guidance packages which are in accordance with the peer-reviewed publications, of macular SD-OCT and standard automated VF findings in HCQ retinal toxicity.[19 51] The standard images will be prepared by the INTACT study team's experienced academic retinal specialists (DALM, KP-V and SDL).
- All scans must only be classified as no signs of HCQ retinal toxicity (normal), suspicious signs of HCQ retinal toxicity (equivocal) or typical signs of HCQ retinal toxicity (abnormal) by the retinal specialist and recorded by checking the box that applies in a reporting form that will be sent to researchers at the VGH Eye Care Centre (see online supplemental file 2—Retina specialist reporting form).
- Abnormal, equivocal and a random sample of normal scans (30 in year 1 and year 2) must be sent to the VGH Eye Care Centre for secondary review and validation.
- The three study team retinal specialists (DALM, KP-V and SDL) will be considered as the gold standard. Two of them (KP-V and SDL) will review the images of all patients reported as equivocal or abnormal by the 'retina specialist network of the INTACT study' in addition to the random sample of normal scans (30 in year 1 and year 2) from them. Confirmation of diagnosis is based on the agreement between two reviewers at the VGH Eye Care Centre.
- The third retina specialist (DALM) will only review images with any discrepancy in the diagnosis. Eventually, the final decision will be achieved by the third masked reviewer (agreement between DALM and one of the first two reviewers).

III. Severity stages of disease (ie, classification of HCQ retinopathy into mild, moderate and severe).
   - Retina specialists at their clinics will not need to classify the severity staging.
   - The two study team retina specialists (KP-V and SDL) will classify HCQ retinopathy as mild, moderate or severe HCQ retinal toxicity after confirmation of diagnosis.
   - Again, with any discrepancy in the severity staging by the first two reviewers, the third masked reviewer (DALM) will assess and make the final decision, which is based on agreement of his and one of the two other reviewers' assessment.

IV. Data collection training of MOA and research staff at the clinics.
   - There will be a main research lead (ND) for all clinics and one research lead assigned at each clinic (eg, nurse, research coordinator, research assistant). The main research lead will be responsible for the training the other centre leads and the coordination of the overall flow at each centre.

V. Data storage and transfer to the VGH Eye Care Centre and Arthritis Research Canada:
   - There are two types of data to be stored and transferred to Arthritis Research Canada and the VGH Eye Care Centre, specifically the patient self-report and retina specialist report questionnaires and the ocular imaging (ie, SD-OCT and automated VF assessment or FAF).
   - Questionnaires, including both patient self-report and retina specialist reports will be stored in individual patient files in a locked filing cabinet at Arthritis Research Canada. This data will be linked to provincial administrative health data by PopData on completion of the study. The research team will be unable to identify individuals after linkage.
   - A cloud server will be used to store the data including the SD-OCT digital images as well as automated VF assessments, from the retina clinics, which will be accessible to the three readers at the VGH Eye Care Centre. Briefly, there will be a separate folder allocated for each retina clinic, wherein each clinic will only be able to access and upload the images and data of their own patients. The three readers at the VGH Eye Care Centre will be able to access all folders through a secure website.

Data analysis plan

1. Determine the incidence rate of retinopathy in HCQ users with ≥5 years duration of treatment: We will calculate the overall incidence and dose-specific risk (ie, cumulative incidence) of HCQ retinal toxicity. Each eligible and consenting individual will be followed from the study baseline until the end of the 5-year study period, disenrolment or death, whichever occurs first. These person-time data with events will then be used to calculate the cumulative incidence, employing established methods for left truncated data and the competing risk of death.
2. Determine the risk factors for HCQ retinopathy: we will examine the relationship of purported risk factors for HCQ retinopathy among participants, including relevant measures of HCQ exposure (daily dose, daily dose in mg/kg for actual body weight (ABW), daily dose in mg/kg for ideal body weight (IBW), total cumulative lifetime dose and duration of exposure), other putative predictors (ie, older age, female sex, chronic kidney disease, other concomitant drug use with potential retinal toxicity (ie, tamoxifen, anastrozole) or underlying retinal disease), and any other factors that emerge during the study period. First, we will compare the age-standardised incidence rates of HCQ retinopathy according to the risk factor categories. Then, we will obtain the point and interval estimates of the HR of each candidate risk factor for the risk of incident HCQ retinopathy, mutually adjusting for potential risk factors. Also, we will use Cox proportional hazard regression models, accounting for the competing risk of death and left truncation of event time.[52–56]
3. Describe the clinical course of retinopathy following HCQ discontinuation: we will follow all newly identified HCQ retinal toxicity cases on an annual basis during the study period (5 years) and assess the rate of pathological progression of retinopathy, defined as any worsening of both SD-OCT imaging and VF assessment. We will estimate the risk of progression according to initial retinopathy stage (mild, moderate and severe) accounting for the competing risk of death.[57 58]
4. Determine the level of agreement between the reviewers at the reading centre (gold standard) and the network of retina specialists: we will use Cohen's kappa statistic to measure agreement on the HCQ retinopathy diagnosis (normal vs equivocal vs abnormal) between the reviewer's at the reading centre and the network of retina specialists (inter-rater). We will also measure the level of agreement both on the HCQ retinopathy diagnosis and on the HCQ retinopathy staging, between the reviewers at the reading centre (intrarater).

Strengths and limitations

To the best of our knowledge, this is the first prospective, population-based cohort study designed to examine the incidence rate, risk factors and clinical course progression (after discontinuation) of HCQ-induced retinal toxicity in Canada. Our access to province-wide administrative health data for the total 5 million residents of BC is a significant strength. Our estimated sample size is 5508 patients (including 1346 patients with SLE and 4162 patients with RA) of those who have been on HCQ treatment for 5 years or more. In this prospective study, we will have person-time data with events and risk factors including but not limited to HCQ dose for ABW versus IBW, chronic renal failure, comorbidities and others, with

annual updates of data for five consecutive years. We will be able to calculate the cumulative incidence of HCQ-induced retinopathy considering the competing risk of death as well as HRs for each risk factor. These results will provide vital information for patients, physicians and policy makers.

Our study benefits from the collaboration of retinal specialists from urban and rural parts of BC. Our province-wide retinal specialist network developed a novel SOP during a consensus meeting for screening and follow-up of the patients based on the most recent AAO guidelines. Our study is not without potential limitations. First, there may be participant loss, due to declining to participate, emigration and study drop-out. We include patients with 5 years or more of HCQ use in both SLE and RA cohorts, but there is a potential limitation for 18% of patients in the RA cohort to have a false positive diagnosis of RA due to the 82% PPV by the algorithm we are using to identify patients with RA. Another limitation of our study is possible non-adherence to the amount of prescribed HCQ treatment. PharmaNet data will capture medication dispensed, however, participants taking less than the prescribed dose, will not be captured. This issue can only be mitigated through evaluation of the serum level of HCQ, which should be taken into account in future studies. Another potential limitation of our study is that we may not be able to collect adequate information to evaluate HCQ retinopathy in patients with concurrent retinal disease because they may have already avoided starting HCQ medication.

Privacy and confidentiality

We have implemented measures to keep all personal information of patients secure, including names, contact information, Personal Health Numbers, self-report questionnaires and medical reports. These will be kept in secure locations accessible only to a restricted number of study personnel at Arthritis Research Canada and retinal clinics. Patients' names will be replaced by a unique ID code on patient's informed consent and enrolment in the study that will be consistent on every study document and imaging, throughout the study. The digital information including the imaging will be housed on a secure cloud server with the most up-to-date security protections.

Ethics and dissemination

The INTACT study was approved by the University of British Columbia's Clinical Research Ethics Board (H20-00736) and the Vancouver Coastal Health Research Institute (V20-00736). All participants will provide informed consent before inclusion in this study. Study results will be disseminated via peer-reviewed scientific journals and will be presented to academics and researchers at scientific conferences. A plain language summary of study results will be disseminated among participants following study completion.

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Acknowledgements All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

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Contributors Substantial contributions to the conception or design of the work: JAA-Z, JE, SDL, DALM. Substantial contributions to the planning and implementation of the work: BA, RDB, SBB, MB, LC, MD, MErasmus, MEtminan, DG, EH, HH, MH, AJ, AL, ZM, EN, KP-V, SS, KS. Consensus meeting chair persons/moderators: JAA-Z, AH, DALM, JE, KP-V, KS. Drafting of the work: ND, AL, SM, DO. Revising the work critically for important intellectual content: JAA-Z, ND, MD, JE, AH, SDL, DALM. All authors gave final approval of the submitted manuscript.

Funding This work was supported by the Canadian Institutes for Health Research (grant numbers: PJT-162133 and PCS-164995). Dr. Avina-Zubieta is the BC Lupus Society and the Walter and Marilyn Research Scholar Awards

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Bertsias G, Ioannidis JPA, Boletis J, *et al*. EULAR recommendations for the management of systemic lupus erythematosus. Report of a task force of the EULAR standing Committee for international clinical studies including therapeutics. *Ann Rheum Dis* 2008;67:195–205.
2 Ruiz-Irastorza G, Khamashta MA. Hydroxychloroquine: the cornerstone of lupus therapy. *Lupus* 2008;17:271–3.
3 Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med* 1991;324:150–4.
4 Bernatsky S, Boivin J-F, Joseph L, *et al*. Mortality in systemic lupus erythematosus. *Arthritis Rheum* 2006;54:2550–7.
5 Yurkovich M, Vostretsova K, Chen W, *et al*. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. *Arthritis Care Res* 2014;66:608–16.
6 Jorge A, McCormick N, Lu N, *et al*. Hydroxychloroquine and mortality among patients with systemic lupus erythematosus in the general population. *Arthritis Care Res* 2021;73:1219–23.
7 Hoque MR, Aviña-Zubieta JA, De Vera MA, *et al*. Impact of antimalarial adherence on mortality among patients with newly diagnosed systemic lupus erythematosus: a population-based cohort study. *Arthritis Care Res* 2021. doi:10.1002/acr.24550. [Epub ahead of print: 07 Jan 2021]. Online ahead of print).
8 Feldman CH, Yazdany J, Guan H, *et al*. Medication nonadherence is associated with increased subsequent acute care utilization among Medicaid beneficiaries with systemic lupus erythematosus. *Arthritis Care Res* 2015;67:1712–21.
9 Adams EM, Yocum DE, Bell CL. Hydroxychloroquine in the treatment of rheumatoid arthritis. *Am J Med* 1983;75:321–6.
10 The HERA Study Group. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA study. *Am J Med* 1995;98:156–68.
11 Dos Reis Neto ET, Kakehasi AM, de Medeiros Pinheiro M, *et al*. Revisiting hydroxychloroquine and chloroquine for patients with chronic immunity-mediated inflammatory rheumatic diseases. *Adv Rheumatol* 2020;60:32.
12 Worth C, Yusuf IH, Turner B, *et al*. An audit of the use of hydroxychloroquine in rheumatology clinics. *Rheumatol Adv Pract* 2018;2:rky013.
13 Abarientos C, Sperber K, Shapiro DL, *et al*. Hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. *Expert Opin Drug Saf* 2011;10:705–14.
14 Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, *et al*. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. *Circulation* 2012;126:76–82.
15 Tsakonas E, Joseph L, Esdaile JM, *et al*. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian hydroxychloroquine Study Group. *Lupus* 1998;7:80–5.
16 Alarcón GS, McGwin G, Bertoli AM, *et al*. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). *Ann Rheum Dis* 2007;66:1168–72.
17 Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. *Curr Rheumatol Rep* 2011;13:77–80.
18 Clowse MEB, Magder L, Witter F, *et al*. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum* 2006;54:3640–7.
19 Marmor MF, Kellner U, Lai TYY, *et al*. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology* 2016;123:1386–94.
20 Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol* 2014;132:1453–60.
21 Aviña-Zubieta JA, Galindo-Rodriguez G, Newman S, *et al*. Long-Term effectiveness of antimalarial drugs in rheumatic diseases. *Ann Rheum Dis* 1998;57:582–7.
22 Mavrikakis I, Sfikakis PP, Mavrikakis E, *et al*. The incidence of irreversible retinal toxicity in patients treated with hydroxychloroquine: a reappraisal. *Ophthalmology* 2003;110:1321–6.
23 Levy GD, Munz SJ, Paschal J, *et al*. Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. *Arthritis Rheum* 1997;40:1482–6.
24 Costedoat-Chalumeau N, Amoura Z, Hulot J-S, *et al*. Very low blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of systemic lupus erythematosus. *Ann Rheum Dis* 2007;66:821–4.
25 Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G, *et al*. Adherence to treatment in systemic lupus erythematosus patients. *Best Pract Res Clin Rheumatol* 2013;27:329–40.
26 Iudici M, Pantano I, Fasano S, *et al*. Health status and concomitant prescription of immunosuppressants are risk factors for hydroxychloroquine non-adherence in systemic lupus patients with prolonged inactive disease. *Lupus* 2018;27:265–72.
27 Liu LH, Fevrier HB, Goldfien R, *et al*. Understanding nonadherence with hydroxychloroquine therapy in systemic lupus erythematosus. *J Rheumatol* 2019;46:1309–15.
28 Costedoat-Chalumeau N, Houssiau F, Izmirly P, *et al*. A prospective international study on adherence to treatment in 305 patients with flaring SLE: assessment by drug levels and self-administered questionnaires. *Clin Pharmacol Ther* 2018;103:1074–82.
29 Jorge A, Ung C, Young LH, *et al*. Hydroxychloroquine retinopathy - implications of research advances for rheumatology care. *Nat Rev Rheumatol* 2018;14:693–703.
30 Jorge A, Rai SK, Choi HK. The risk of hydroxychloroquine toxic retinopathy and its risk factors in the treatment of rheumatic diseases: a systematic review. *Arthritis Rheumatol* 2017;69 https://acrabstracts.org/abstract/the-risk-of-hydroxychloroquine-toxic-retinopathy-and-its-risk-factors-in-the-treatment-of-rheumatic-diseases-a-systematic-review/
31 Rosenbaum JT, Costenbader KH, Desmarais J, *et al*. American College of rheumatology, American Academy of dermatology, rheumatologic dermatology Society, and American Academy of ophthalmology 2020 joint statement on hydroxychloroquine use with respect to retinal toxicity. *Arthritis Rheumatol* 2021;73:908–11.
32 Mangione CM, Lee PP, Gutierrez PR, *et al*. Development of the 25-item National eye Institute visual function questionnaire. *Arch Ophthalmol* 2001;119:1050–8.
33 Aviña-Zubieta JA, Abrahamowicz M, Choi HK, *et al*. Risk of cerebrovascular disease associated with the use of glucocorticoids in patients with incident rheumatoid arthritis: a population-based study. *Ann Rheum Dis* 2011;70:990–5.
34 Avina-Zubieta JA, McCormick N, Sayre EC, *et al*. FRI0425 Longitudinal analysis of direct medical costs for systemic lupus erythematosus in british columbia, canada: A population-based study. *Ann Rheum Dis* 2013;71:458.1–458.
35 Solomon DH, Love TJ, Canning C, *et al*. Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. *Ann Rheum Dis* 2010;69:2114–7.
36 Solomon DH, Massarotti E, Garg R, *et al*. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. *JAMA* 2011;305:2525–31.
37 Etminan M, Forooghian F, Brophy JM, *et al*. Oral fluoroquinolones and the risk of retinal detachment. *JAMA* 2012;307:1414–9.
38 McCormick N, Reimer K, Famouri A, *et al*. Filling the gaps in SARDs research: collection and linkage of administrative health data and self-reported survey data for a general population-based cohort of individuals with and without diagnoses of systemic autoimmune rheumatic disease (SARDs) from British Columbia, Canada. *BMJ Open* 2017;7:e013977.
39 Bernatsky S, Lix L, O'Donnell S, *et al*. Consensus statements for the use of administrative health data in rheumatic disease research and surveillance. *J Rheumatol* 2013;40:66–73.
40 Population data BC. British Columbia Ministry of Health [creator] (2017): Medical Services Plan (MSP) Payment Information File, 2020. Available: https://www.popdata.bc.ca/data/health/msp
41 Population data BC. Canadian Institute for Health Information [creator] (2017): Discharge Abstract Database (Hospital Separations), 2020. Available: http://www.popdata.bc.ca/data/health/dad
42 BC Ministry of Health. BC Ministry of Health [creator] (2018): PharmaNet, 2020. Available: http://www.popdata.bc.ca/data/health/PharmaNet
43 Population Data BC. BC Vital Statistics Agency [creator] (2017): Vital Statistics Deaths, 2020. Available: http://www.popdata.bc.ca/data/population/vsdeaths
44 Population Data BC. BC cancer registry data (2017), 2020. Available: http://www.popdata.bc.ca/data/health/bccancer
45 Chang J, Rogers P, Lacaille D. Can American College of Rheumatology Criteria for Rheumatoid Arthritis Be Assessed Using Self-Report Data?-Comparison of Self-Reported Data with Chart Review. *Arthritis & Rheumatology* 2011:S49 https://www.researchgate.net/publication/296022043_Can_American_College_of_Rheumatology_Criteria_for_Rheumatoid_Arthritis_Be_Assessed_Using_Self-Report_Data-Comparison_of_Self-Reported_Data_with_Chart_Review
46 Arkema EV, Jönsen A, Rönnblom L, *et al*. Case definitions in Swedish register data to identify systemic lupus erythematosus. *BMJ Open* 2016;6:e007769.

47 Aviña-Zubieta JA, Vostretsova K, De Vera MA, *et al*. The risk of pulmonary embolism and deep venous thrombosis in systemic lupus erythematosus: a general population-based study. *Semin Arthritis Rheum* 2015;45:195–201.
48 McCormick N, Marra CA, Sadatsafavi M, *et al*. Excess productivity costs of systemic lupus erythematosus, systemic sclerosis, and Sjögren's syndrome: a general population-based study. *Arthritis Care Res* 2019;71:142–54.
49 Eisner A, Luoh S-W, Medications BC. Breast cancer medications and vision: effects of treatments for early-stage disease. *Curr Eye Res* 2011;36:867–85.
50 Melles RB, Marmor MF. Pericentral retinopathy and racial differences in hydroxychloroquine toxicity. *Ophthalmology* 2015;122:110–6.
51 Lally DR, Heier JS, Baumal C, *et al*. Expanded spectral domain-OCT findings in the early detection of hydroxychloroquine retinopathy and changes following drug cessation. *Int J Retina Vitreous* 2016;2:18.
52 Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016;133:601–9.
53 Geskus RB. Cause-Specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. *Biometrics* 2011;67:39–49.
54 Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med* 2004;23:2109–23.
55 Thiébaut ACM, Bénichou J. Choice of time-scale in COX's model analysis of epidemiologic cohort data: a simulation study. *Stat Med* 2004;23:3803–20.
56 Beyersmann J, Schumacher M. Time-Dependent covariates in the proportional subdistribution hazards model for competing risks. *Biostatistics* 2008;9:765–76.
57 Gaynor JJ, Feuer EJ, Tan CC, *et al*. On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. *J Am Stat Assoc* 1993;88:400–9.
58 Beiser A, D'Agostino RB, Seshadri S, *et al*. Computing estimates of incidence, including lifetime risk: Alzheimer's disease in the Framingham study. The practical incidence estimators (PIE) macro. *Stat Med* 2000;19:1495–522.