Are the Current Recommendations for Chloroquine and Hydroxychloroquine Screening Appropriate?

Sergio Schwartzman, MD[a,*], C. Michael Samson, MD, MBA[b]

KEYWORDS

• Antimalarials • Hydroxychloroquine • Quinacrine • Ocular toxicity • Retinopathy

KEY POINTS

- Hydroxychloroquine and quinacrine are frequently used to treat rheumatic diseases.
- Ocular toxicity, although infrequent, is one of the potential side effects of antimalarial therapies.
- Current recommendations are unifocal in being developed by only ophthalmologists who do not treat patients for their rheumatic diseases.
- The data used to create the recommendations are meager and retrospective.
- Comanagement of patients with rheumatic disease who are exposed to antimalarial therapies requires a greater interaction between ophthalmologists and rheumatologists.

Antimalarial medications, primarily hydroxychloroquine, have become a cornerstone of treatment of chronic rheumatic diseases. Chloroquine is used uncommonly in the United States because it may have an increased incidence of gastrointestinal and ocular adverse reactions.[1] Bark from the chinchona tree native to the Andes and grown in South America, Indonesia, and Congo containing the quinoline alkaloids quinine and quinidine was the first known source of treatment of malaria.[2] In 1834, quinine was first used to treat systemic lupus erythematosus (SLE).[3] Antimalarial prophylaxis given to soldiers in the Pacific Theater during World War II serendipitously confirmed that this therapeutic class was an effective treatment of arthritis and SLE. Over time, antimalarials have been used to treat patients with numerous rheumatic diseases,

[a] Hospital for Special Surgery, Weill Medical College of Cornell University, New York Presbyterian Hospital, 535 East 70th Street, New York, NY 10021, USA; [b] Department of Ophthalmology, Manhattan Eye, Ear, and Throat Hospital, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA
* Corresponding author.
E-mail address: ssrheum@gmail.com

Rheum Dis Clin N Am 45 (2019) 359–367
https://doi.org/10.1016/j.rdc.2019.04.008
rheumatic.theclinics.com

including SLE, rheumatoid arthritis, palindromic rheumatism, Sjogren syndrome, and some forms of vasculitis.

Currently, hydroxychloroquine is the predominant antimalarial therapy used in the management of patients with rheumatic diseases. The US Food and Drug Administration has approved this medication for the treatment of SLE, polymorphous light eruption, and rheumatoid arthritis.[4] Hydroxychloroquine has become a critical therapy for patients with SLE and is the drug most widely prescribed for this condition. Importantly, in SLE, it improves survival and has the capacity to prevent disease flares.[5] The rationale for the popularity of hydroxychloroquine is not only that it is effective but also that the risks associated with this medication are very low. Ocular toxicity is an accepted complication of antimalarial therapy. However, monitoring for ocular adverse events is evolving and not universally used according to published recommendations.

Chloroquine was reported to cause retinal toxicity in 1957.[6] This first report by Cambiaggi[6] described retinal findings of a black spot in the macula of both eyes with a small whitish area in the center in a patient with SLE. Discontinuation of chloroquine and initiation of hydroxychloroquine did not result in improvement of the lesion, and the investigators attributed the lesion to active lupus. In retrospect, the published fundoscopic findings were the classic bull's-eye maculopathy due to antimalarial toxicity. In other early reports, 2 patients with retinal damage and constricted visual fields (VFs) in the setting of chloroquine therapy were described.[7] Hydroxychloroquine has since largely replaced chloroquine as the primary antimalarial drug used to treat rheumatologic diseases; however, likewise it is associated with retinal toxicity (**Fig. 1**).

Chloroquine and hydroxychloroquine have affinity for pigmented tissues, particularly in the eye, which is a possible explanation for the ocular toxicity associated with these drugs. With prolonged exposure to hydroxychloroquine or chloroquine, studies in animals demonstrate higher concentrations in the pigmented ocular structures and retina compared with those in other parts of the body.[8,9] Low levels of chloroquine have been detected in plasma and urine, even 5 years after discontinuing the drug.[8]

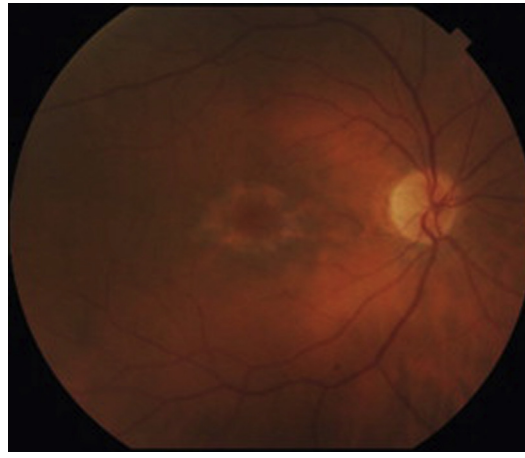

Fig. 1. Bulls retinopathy with bull's-eye macular lesion. *From* Duker JS, Waheed NK, Goldman DR. Hydroxychloroquine Toxicity. In: Handbook of Retinal OCT: Optical Coherence Tomography. Philadelpha, PA: Elsevier; 2014. p. 72–3; with permission.

With current screening technology, hydroxychloroquine toxicity can be detected in advance of obvious retinal damage and visual compromise. Although the ophthalmologist generally assumes primary responsibility of screening for hydroxychloroquine toxicity, it is important for the rheumatologist to have some level of familiarity with which ophthalmologic tests are appropriate and when to use these. Furthermore, it is the rheumatologist's responsibility to assure that proper screening procedures and timing are implemented to assure that retinal toxicity is identified early. Interestingly, a survey study showed that only 5% of rheumatologists and 15% of ophthalmologists were familiar with published screening guidelines.[10] This may be due to the fact that recommendations for monitoring are formulated by ophthalmologists and published in ophthalmology journals rheumatologist screening and self screening by patients using the Amsler grid, a self-administered VF test, has been used in the past but is no longer used because this is an unreliable predictor of toxicity.[11] There is a wide range of methods to screen for ocular toxicity (**Table 1**). Optical coherence tomography (OCT) and VF testing are the current recommended primary screening tests. OCT is a noninvasive imaging test that images the retina in cross-section. The technique uses low-coherence light and is based on low-coherence interferometry. It allows imaging of the entire thickness of the retina with resolution in microns. Its introduction in the 1990s has had a major impact on retinal imaging and has significantly reduced the use of fluorescein angiography and other older testing modalities, such as the Amsler grid, in the diagnosis and management of retinal diseases. Advances in OCT technology have led to increasing resolution of the retina and hence to improved specificity and sensitivity of identifying retinal abnormalities. OCT devices initially were primarily used by retina subspecialists, but, because of their use in both retinal disease and glaucoma, are now commonly used in general ophthalmology practice.

Table 1
Methods to screen for ocular toxicity

Test Name	Description
Visual acuity	Acuity of vision as tested with a Snellen chart; normal visual acuity based on the Snellen chart is 20/20
Color plate testing	Using pseudoisochromic plates with letters or numbers hidden in a maze of dots
Fundus examination	Ophthalmoscopy evaluation of the retina, optic disc, macula, fovea, and posterior pole
Full field ERG and multifocal ERG	Measurement of the electrical activity generated by neural and nonneuronal cells in the retina in response to a light stimulus
Electrooculogram	Measurement of the eye movements through electrodes placed on the skin around the eyes
FAF	A generated image based on the distribution pattern of lipofuscin, which is a fluorescent pigment with a distribution pattern that is disturbed by retinal pathologic condition
Fluorescein angiogram	A retinal image generated by a systemically administered fluorescent dye
OCT	Noninvasive imaging test that uses light waves to take high-resolution cross-sectional tomographic images of the retina
10-2 automated VF testing	VF testing uses fixed points of light, which are shown at different intensity levels, which then correspond to the topographic arrangement of photoreceptors

VF testing was the earliest test used for the screening of antimalarial toxicity. Automated VF testing most commonly tests 30° or 24° of field, but screening for hydroxychloroquine toxicity often focuses on the central 10°, because it is the paracentral foveal region (leading to a paracentral scotoma) that is the most common abnormal early finding. The typical VF examination will be a 10-2 humphrey visual field using a red target, because using red test objects improves the sensitivity of field testing.[12] Asian patients may develop toxicity further from the fovea than do Caucasian patients, and that 10-2 testing would miss early VF changes. Thus, in the Asian population, it is important consider performing standard 30-2 or 24-2 HVF testing.[13]

There are commercially available laboratory tests to measure hydroxychloroquine and its metabolites in whole blood. These tests are infrequently ordered, and, when used, the predominant rationale is either to identify noncompliance or to monitor therapeutic drug levels. In SLE patients, low whole blood hydroxychloroquine concentrations can predict flares and have been associated with active disease.[14] In a study of 300 patients with cutaneous lupus erythematosus, those who failed treatment had significantly lower blood concentrations of hydroxychloroquine than those who achieved complete remission.[15] Because adverse events are very uncommon with this therapy, no studies correlated hydroxychloroquine drug levels with toxicity.

The American Academy of Ophthalmology has published recommendations in 2002, 2011, and 2016 addressing the importance of monitoring for chloroquine and hydroxychloroquine toxicity.[16–18] Interestingly, rheumatologists were not included as collaborators in any of the 3 publications. Systematic literature reviews were not performed; pharmacoeconomic evaluations were not conducted, and patient perspectives were not included. Although several different processes may be used to develop recommendations, such as the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology[19] and Delphi methodology, none was used to develop these recommendations.

In the 2002 recommendations,[16] it was surmised that there was minimal risk of ocular toxicity in patients receiving less than 6.5 mg/kg of hydroxychloroquine or 3 mg/kg of chloroquine for less than 5 years. Therefore, it was recommended that, if a baseline examination was normal, screening be performed over the ensuing 5 years at the frequency of the age-appropriate general ophthalmic recommendations as suggested by the American Academy of Ophthalmology. For example, patients who are between 40 and 64 years old should have an ophthalmologic examination every 4 to 6 years. In addition to the routine examination, the 2002 recommendations suggested that for potential antimalarial toxicity VF and multifocal and full-field electroretinogram (ERG) be performed. This descriptive analysis cited only 12 references, and, although briefly described, none was analyzed critically. These recommendations were based on the opinions of only 5 ophthalmologists who reviewed only descriptive studies.

The 2011 recommendations[17] supported the guideline that a baseline examination be performed, but were more liberal in recommending that screening should then occur after 5 years of use with the caveat that screening should only occur more frequently if other risk factors, such as new visual symptoms, new retinal disease, major weight loss, and liver or kidney disease, were present. Patients who were at increased risk were also identified. These patients were those whose duration of use was more than 5 years, and whose daily dose exceeded 400 mg per day or those who had received more than 1000 mg of hydroxychloroquine. Furthermore, the "elderly," those with prior maculopathy or retinal disease, and those who had kidney or liver dysfunction were identified as being at greater risk of developing retinal toxicity. These investigators recommended that, in addition to 10-2 VF, multifocal

ERG, spectral-domain optical coherence tomography (SD-OCT), or fundus autofluorescence (FAF) be used for screening. Similar to the 2002 guideline, a maximum daily hydroxychloroquine dose of 6.5 mg/kg was recommended. The 2011 recommendations supported the 2002 recommendations but were more definitive in identifying high risks patients and supporting more careful follow up of theses patients. These recommendations were not based on critical data, but rather were presented as the opinion of the authors based on the descriptive studies reviewed.

In a pivotal 2014 publication by Melles and Marmor,[20] the Kaiser Permanente Northern California integrated health organization database was queried using a retrospective case-controlled design. At the time of the study, this organization had electronic medical records on 3.4 million members. Digital ophthalmologic images had been collected since 2009. Inclusion criteria were use of hydroxychloroquine for at least 5 years and having undergone a documented central VF examination or SD-OCT imaging. Exclusion criteria included patients with no evidence of screening, other causes of retinal disease, prior chloroquine use, or those with only fundus examination. Identified were 2361 hydroxychloroquine users, of whom 177 had been diagnosed as having retinal toxicity. The investigators assigned outcomes based on fundoscopic photograph, SD-OCT, and 10-2 pattern deviation and threshold.

The overall prevalence of hydroxychloroquine retinopathy was 7.5%, predominantly in long-term users. This relatively high number was probably due to the fact that modern imaging techniques were able to detect disease much earlier than older diagnostic modalities.[20] Using Kaplan-Meier survival analysis, patients who received a mean daily hydroxychloroquine dose exceeding 5.0 mg/kg had a 10% risk of developing retinal toxicity within 10 years and a 40% risk after 20 years. Patients being treated with hydroxychloroquine doses between 4.0 and 5.0 mg/kg/d had an approximately 2% risk of developing retinal toxicity within 10 years and a 20% risk after 20 years. When patients were treated with hydroxychloroquine at daily doses of less than 5 mg/kg, the risk of developing retinopathy was low at first but then increased with duration of use: from less than 1% during the first 5 years, to less than 2% at 10 years, and to 20% after 20 years. Risk factors for developing retinopathy included higher hydroxychloroquine doses and longer duration of therapy. For those patients receiving hydroxychloroquine doses of more than 5 mg/kg, the development of ocular toxicity was dose dependent. Other major risk factors that were identified included concomitant renal disease, tamoxifen therapy, and prior retinal disease.

There are many recognized risk factors for toxicity. The most important risk factor is daily dose. Studies suggest risk of retinal toxicity is low at dosages of 5 mg/kg (eg, for 70-kg person, 350-mg daily dose) or less. Duration of use is also relevant, with risk increasing with duration of treatment. Annual risk is less than 1% up to 10 years of treatment and increases to around 3% to 4% at 20 years. The presence of renal disease and concomitant use of tamoxifen are identified risks, presumably because of their effect on actual dosage.[21] Other potential factors for increased toxicity include concomitant breast cancer therapy.[22]

Studies have confirmed that retinal damage (and associated vision loss) is less when toxicity is detected early. In a study by Allahdina and colleagues,[23] 22 patients with hydroxychloroquine retinopathy were monitored for 6 to 82 months after drug cessation. Multiple evaluations were performed, and involved eyes were categorized into 4 separate severity stages by qualitative grading OCT. Changes in outcome measures between drug cessation and last follow-up visit were compared between different severity stages. Of the 44 eyes, the distribution noted: stage 1 (subtle changes confined to parafoveal region; n = 14), stage 2 (clear localized changes in parafovea; n = 17), stage 3 (extensive parafoveal changes; n = 7), and stage 4 (foveal

involvement, n = 6). Findings revealed that visual acuity measurements across follow-up were stable in stage 1 and stage 2 eyes but decreased significantly in stage 3 and 4 eyes. The investigators concluded that hydroxychloroquine retinal toxicity correlates with retinopathy severity at the time of cessation. After cessation, eyes with only subtle and localized retinopathy were mostly stable, whereas more severely affected eyes continued to progress. Patients with evidence of moderate to severe toxicity have been shown to have progression of retinal damage even after cessation of treatment.[23]

The most recent recommendations published by the American Academy of Ophthalmology in 2016[18] (**Box 1**) were based predominantly on the 2014 publication by Melles and Marmor.[20] The investigators recommended use of 10-2 VF and SD-OCT. A baseline examination was advised as a reference, and annual screening should begin after 5 years. The same risk factors delineated in the prior recommendations were again supported: a daily hydroxychloroquine dose greater than 5 mg/kg, longer duration of use, and renal and hepatic disease (**Table 2**). However, as identified in the Melles and Marmor study, concomitant use of tamoxifen was identified as an independent risk for ocular toxicity. The American College of Rheumatology published a position paper (**Box 2**) that supported the American Academy of Ophthalmology statement.

The recommendation to not use a dose of hydroxychloroquine greater than 5 mg/kg is challenging in that many rheumatologists frequently use a higher dose than recommended. In a study that investigated the use of hydroxychloroquine in the United Kingdom, the Health Improvement Network, an electronic medical record database that represents 6.2% of the UK population, was queried, and 20,933 individuals were identified who initiated hydroxychloroquine between 2007 and 2016. Forty-seven percent of women and 7% of men had excess dosing.[24] In addition, there are inconsistencies in the practices of rheumatologists as they pertain to ophthalmologic screening based on lack of appropriate studies and education. Many rheumatologists recommend at least once yearly ophthalmologic evaluations, and some insist on twice yearly examinations.

The new recommendations were based predominantly on a single albeit robust large retrospective analysis,[20] and there was no input from a rheumatologist. In all probability, none of the investigators had ever prescribed antimalarial therapy and hence were not aware of the needs to adjust therapy in patients with rheumatic diseases. A logistic regression analysis was used to define risk factors, but an analysis of variables, such as individual disease states, ethnicity, and race, was not undertaken. Hydroxychloroquine toxicity was determined based on VF loss or retinal thinning and photoreceptor damage, but not both. Because there currently is no

Box 1
Screening frequency

Baseline screening
- Fundus examination within first year of use
- Add VFs and SD-OCT if maculopathy is present

Annual screening
- Begin after 5 years of use
- Sooner in the presence of major risk factors

From Marmor MF, Kellner U, Lai TY, et al. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. From Ophthalmology. 2011 Feb;118(2):415-22. https://doi.org/10.1016/j.ophtha.2010.11.017.

Table 2
Major risk factors for toxic retinopathy

	Daily Dosage
HCQ	>5.0 mg/kg real weight
CQ	>2.3 mg/kg real weight
Duration of use	>5 years, assuming no other risk factors
Renal disease	Subnormal glomerular filtration rate
Concomitant drugs	Tamoxifen use
Macular disease	May affect screening and susceptibility to HCQ/CQ

Abbreviations: CQ, chloroquine; HCQ, hydroxychloroquine.

From Marmor MF, Kellner U, Lai TY, et al. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. From Ophthalmology. 2011 Feb;118(2):415-22. https://doi.org/10.1016/j.ophtha.2010.11.017.

treatment to reverse the vision loss from hydroxychloroquine retinal toxicity, efforts need to be focused on prevention by appropriate screening. Understanding the impact of daily dosage, duration of therapy, and concomitant risk factors on the development of hydroxychloroquine toxicity has dramatically reduced the incidence of

Box 2
American College of Rheumatology position statement subject: screening for hydroxychloroquine retinopathy

1. Patients beginning therapy should be informed of potential adverse events, including retinal toxicity and that periodic monitoring and early recognition can limit the impact of macular toxicity.
2. All individuals initiating therapy should undergo a complete ophthalmologic evaluation, including the following elements:
   a. Examination of the retina with a dilated examination and VFs by an automated threshold central VF test (Humphrey 10-2).
   b. If available, objective testing, such as multifocal electroretinography, SD-OCT, or FAF testing
   c. If the patient is considered low risk and baseline examination results are normal, no further specialized ophthalmologic testing is needed for 5 years.
3. Some ophthalmologists may elect to screen more often based on the patient's risk factors. Recognized risk factors include the following:
   a. Macular degeneration and retinal dystrophy and cataracts may increase susceptibility to toxicity.
   b. Reduced kidney function.
   c. Tamoxifen use also been identified as risk factors for retinopathy.
   d. Asian patients demonstrate an early pattern of retinal toxicity that is different from patients of European descent.
4. For patients who are considered high risk, annual eye examination is recommended without the 5-year gap.

Presented by: Committee on Rheumatologic Care FOR DISTRIBUTION TO: Members of the American College of Rheumatology Medical Societies Centers for Medicare and Medicaid Services Managed Care Organizations/Third-Party Carriers Arthritis Foundation.

Data from American College of Rheumatology. Screening for Hydroxychloroquine Retinopathy - 08/2016. Available at: https://www.rheumatology.org/Practice-Quality/Administrative-Support/Position-Statements

antimalarial drug eye toxicity. However, for many rheumatologic conditions, the dose of hydroxychloroquine tends to be greater than 5 mg/kg. Further data are required for a more rational approach to screening.

In the future, it will be important to identify other risk factors predisposing to retinal toxicity. New ophthalmic diagnostic tools, such as OCT angiography, can image the retinal microvasculature without the use of an intravenous contrast dye.[25] It is possible that evolving fields, such as pharmacogenetics, will play an important role in defining both potential risk and potential benefit of antimalarial use. The current literature includes only retrospective studies. Hence, a prospective trial comparing different screening paradigms in uniform patient populations could provide further important information. Screening recommendations should be developed by first performing a systematic literature review and then using GRADE methodology and the Delphi method. Existing literature supports the lack of dialogue between rheumatologists and ophthalmologists. Only limited publications have used the perspectives of both specialties.[26] It is critical that both physician groups open a dialogue and develop screening strategies that are based on collaboration.

REFERENCES

1. Rainsford KD, Parke AL, Clifford-Rashotte M, et al. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology 2015;23(5):231–69.
2. Schlitzer M. Malaria chemotherapeutics part I: history of antimalarial drug development, currently used therapeutics, and drugs in clinical development. ChemMedChem 2007;2(7):944–86.
3. Dubois EL, Hahn BH, Wallace DJ. Dubois' lupus erythematosus. Philadelphia: Lippincott Williams & Wilkins; 2007.
4. Physicians' desk reference. Montvale (NJ): Thomson PDR; 2005.
5. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, et al. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann Rheum Dis 2010;69(1):20–8.
6. Cambiaggi A. Unusual ocular lesions in a case of systemic lupus erythematosus. AMA Arch Ophthalmol 1957;57(3):451–3.
7. Goldman L, Preston RH. Reactions to chloroquine observed during the treatment of various dermatologic disorders. Am J Trop Med Hyg 1957;6:654.
8. Bernstein H, Zvaifler N, Rubin M, et al. The ocular deposition of chloroquine. Invest Ophthalmol 1963;2(384):384–92.
9. Rosenthal RA, Kolb H, Bergsma D, et al. Chloroquine retinopathy in the rhesus monkey. Invest Ophthalmol Vis Sci 1978;17(12):1158–75.
10. Shulman S, Wollman J, Brikman S, et al. Implementation of recommendations for the screening of hydroxychloroquine retinopathy: poor adherence of rheumatologists and ophthalmologists. Lupus 2017;26(3):277–81.
11. Pluenneke AC, Blomquist PH. Utility of red Amsler grid screening in a rheumatology clinic. J Rheumatol 2004;31(9):1754–5.
12. Percival SP, Behrman J. Ophthalmological safety of chloroquine. Br J Ophthalmol 1969;53(2):101–9.
13. Giocanti-Auregan A, Couturier A, Girmens JF, et al. Variability of chloroquine and hydroxychloroquine retinopathy among various ethnicities. J Fr Ophtalmol 2018;41(4):363–7.

14. Costedoat-Chalumeau N, Dunogue B, Leroux G, et al. A critical review of the effects of hydroxychloroquine and chloroquine on the eye. Clin Rev Allergy Immunol 2015;49(3):317–26.
15. Frances C, Cosnes A, Duhaut P, et al. Low blood concentration of hydroxychloroquine in patients with refractory cutaneous lupus erythematosus: a French multicenter prospective study. Arch Dermatol 2012;148(4):479–84.
16. Marmor MF, Carr RE, Easterbrook M, et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American Academy of Ophthalmology. Ophthalmology 2002;109(7):1377–82.
17. Marmor MF, Kellner U, Lai TY, et al. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology 2011;118(2):415–22.
18. Marmor MF, Kellner U, Lai TY, et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology 2016;123(6):1386–94.
19. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(4):383–94.
20. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol 2014;132(12):1453–60.
21. Kim JW, Kim YY, Lee H, et al. Risk of retinal toxicity in longterm users of hydroxychloroquine. J Rheumatol 2017;44(11):1674–9.
22. Sharma AMA, Tucker WR, Cuckras C. Accelerated onset of retinal toxicity from hydroxychloroquine use with concomitant breast cancer therapy. Retin Cases Brief Rep 2018;16:98–102.
23. Allahdina AM, Chen KG, Alvarez JA, et al. Longitudinal changes in eyes with hydroxychloroquine retinal toxicity. Retina 2019;39(3):473–84.
24. Jorge AM, Melles RB, Zhang Y, et al. Hydroxychloroquine prescription trends and predictors for excess dosing per recent ophthalmology guidelines. Arthritis Res Ther 2018;20(1):133.
25. Goker YS, Ucgul Atilgan C, Tekin K, et al. The validity of optical coherence tomography angiography as a screening test for the early detection of retinal changes in patients with hydroxychloroquine therapy. Curr Eye Res 2019;44(3):311–5.
26. Rosenbaum JT, Mount GR, Youssef J, et al. New perspectives in rheumatology: avoiding antimalarial toxicity. Arthritis Rheumatol 2016;68(8):1805–9.