LUPUS SCIENCE & MEDICINE™

Rheumatologists' perspective on hydroxychloroquine guidelines

James Winebrake,[1] Leila Khalili ,[2] Julia Weiner,[2] Yevgeniya Gartshteyn ,[2] Lisa Park,[3] Anca D Askanase [2]

To cite: Winebrake J, Khalili L, Weiner J, *et al*. Rheumatologists' perspective on hydroxychloroquine guidelines. *Lupus Science & Medicine* 2020;**7**:e000427. doi:10.1136/lupus-2020-000427

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/lupus-2020-000427).

JW and LK contributed equally.

LP and ADA are joint senior authors.

Received 20 July 2020
Revised 15 October 2020
Accepted 15 October 2020

[1]Weill Cornell Medical College, New York City, New York, USA
[2]Rheumatology, Columbia University Irving Medical Center, New York City, New York, USA
[3]Ophthalmology, Columbia University Irving Medical Center, New York City, New York, USA

Correspondence to
Dr Anca D Askanase; ada20@cumc.columbia.edu

ABSTRACT

Objective Hydroxychloroquine (HCQ) retinal toxicity is an ongoing concern for rheumatologists. The revised 2016 American Academy of Ophthalmology (AAO) guidelines created controversy regarding the correct dosing and evaluation of HCQ toxicity. The current study was initiated to further understand rheumatologists' practices regarding HCQ.

Methods A questionnaire-based survey was distributed electronically to rheumatologists. We collected information on HCQ dosing, clinical decision-making processes, familiarity with the AAO 2016 guidelines, and perceived disparities between the AAO 2016 guidelines and rheumatological clinical practice.

Results 78 rheumatologists completed the survey (49% from USA, 90% academic practices, 82% self-identified as lupus experts). Only lupus expert (n=64) data were included in subsequent analysis. The mean cohort size was 747 (50–6571), a total cohort 45 612 patients. HCQ was prescribed to >75% of patients with SLE by 81.3% of SLE experts, with routine counselling about ophthalmic risks. The typical dose of HCQ used was 200–400 mg/day. 17% of rheumatologists use doses up to 600 mg/day, while 6.2% use up to 6.5 mg/kg/day. HCQ adherence is routinely assessed. 479 cases of HCQ retinal toxicity (1.05%) and 9 cases of HCQ-associated blindness (1.8 per 10 000 patients) were reported. 89.1% of respondents reported familiarity with the AAO guidelines. Those aware of the guidelines cited limited dosing options (54.7%), lack of supporting evidence (57.8%) and low patient adherence (43.8%) as obstacles to greater implementation of the guidelines.

Conclusion These data suggest that HCQ toxicity and blindness are rare in patients with SLE. Rheumatologists treating patients with SLE are aware of the guidelines and appreciate the importance of partnering with ophthalmologists in preventing retinal toxicity.

INTRODUCTION

SLE is an autoimmune disease of unknown aetiology, characterised by bouts of immune-mediated inflammation and tissue injury. Hydroxychloroquine (HCQ) is the main drug used to treat lupus; HCQ has been shown to reduce flares[1 2] and confer a protective effect on survival.[2 3] Additionally, HCQ use is associated with reduced frequency and severity of organ damage.[2 4] Recent data show that HCQ reduces SLE flares by 57% and disease activity by 32%.[5–7] HCQ is classified as a disease-modifying antirheumatic drug due to its ability to alter 'antigen-processing' by antigen-presenting cells. This is thought to decrease SLE activity at a molecular level and has direct anti-inflammatory effects.

HCQ is generally a well-tolerated drug. That said, HCQ use is linked to a number of adverse effects, which may be broadly classified by severity. While more common, gastrointestinal distress, aquagenic pruritus and other dermatological complaints rarely necessitate discontinuation of treatment. On the other hand, retinal, neuromuscular and cardiac effects usually dictate withdrawal and are occasionally irreversible.[8]

Retinal toxicity and blindness are the most concerning side effects of HCQ. HCQ toxicity is dependent on daily dose, duration of use and total consumption.[9] The exact pathophysiology of retinal toxicity attributed to HCQ is speculated but remains unclear. Binding of the agent to melanin in the retinal pigment epithelium (RPE) may concentrate the drug in this region, but it has also been suggested that toxicity originates in the photoreceptor layer with secondary RPE damage. In either case, impairment of lysosomal function and autophagy contributes to RPE degeneration and photoreceptor loss.[10]

The American Academy of Ophthalmology (AAO) has provided formal recommendations on screening for chloroquine (CQ) and HCQ retinopathy, the most recent iteration of which was released in 2016.[9] These guidelines provide a framework for ophthalmologists and rheumatologists by reviewing patient risk factors, predictors of toxicity, dosage recommendations, preferred screening methodology and management following diagnosis. These guidelines recommend a weight-based dosing (≤5 mg/kg real weight), but also state that although the risk of HCQ toxicity 'is smaller with low doses, it is not clear that there is any truly 'safe' dosage for

long durations of use'. In making these guidelines, the risk assessments were based on outcomes of characteristic visual field pattern defects combined with retinal findings on optical coherence tomography (OCT).[11] It is unclear whether rheumatologists are familiar and compliant with the 2016 AAO guidelines and the risk factors associated with blindness, including duration of use, medical history of renal or macular disease, and tamoxifen use.

Previous studies have estimated the frequency of HCQ retinal toxicity between 1.0% and 7.5%.[9] Additionally, the proportion of patients with retinal toxicity is under 1% for the first 5 years, increases to 2% after 10 years, and increases to about 20% after 20 years of exposure. For patients taking ≥5 mg/kg dose, the risk of retinal toxicity is two to three times higher for the same time frame increments.[9] Additionally, higher HCQ blood levels are associated with increased risk of HCQ retinopathy.[12]

While HCQ-related blindness is uncommon, the potential for these harmful side effects raises concern among patients, rheumatologists and ophthalmologists. Whether retinal toxicity measured by OCT has the same ominous prognosis as decreased visual fields resulting in long-term damage and possible blindness remains to be determined.[11] There are limited data on the actual risk and prevalence of HCQ-induced blindness in patients with SLE.

This study was initiated to investigate the frequency of HCQ retinal toxicity and blindness in the experience of self-reported lupus experts, and to assess the knowledge of and adherence to the 2016 AAO guidelines.

METHODS

A questionnaire regarding HCQ prescribing practice, clinical decision-making processes and familiarity with current AAO guidelines was designed by an ophthalmology/rheumatology team. Additionally, the survey included questions regarding participant demographics, SLE cohort size, number of patients taking HCQ, and the number of patients with HCQ-induced retinal toxicity and blindness.

A group of 277 international rheumatologists who were members of the Systemic Lupus Erythematosus International Collaborating Clinics, the Lupus Clinical Investigators Network, the Asia Pacific Lupus Collaboration, and the Columbia University Irving Medical Center, Division of Rheumatology were invited to respond to the survey by email. A total of 78 responded (49% from USA, 90% academic practices). Of the 78, 14 rheumatologists' responses were eliminated as they did not identify as SLE expert rheumatologists. These 14 rheumatologists were from the Columbia University Irving Medical Center, Division of Rheumatology. None of the rheumatologists who responded to the survey were involved in the study design.

Data analysis was conducted based on survey results. Measures of central tendency and spread were used to describe responses. Summary statistics, counts and percentages were calculated. Statistical calculations were performed using Microsoft Excel.

Table 1 Respondent demographics and cohort size

Location	
North America	29 (45.3)
South America	5 (7.8)
Europe	12 (18.8)
Asia	10 (15.6)
Australia	6 (9.4)
Other	2 (3.1)
Type of practice, n (%)	
Solo	5 (7.8)
Group	3 (4.7)
Academic	56 (87.5)
Cohort size, n (%)	
0–100	2 (3.1)
101–1000	53 (82.8)
>1000	9 (14.1)
Number of patients with SLE per month, n (%)	
0–10	1 (1.6)
11–50	36 (56.3)
51–100	21 (32.8)
>100	6 (9.3)

Patient and public involvement

This research was conducted without patient involvement. Patients were not involved in the study design, interpretation of results or writing of the manuscript.

RESULTS

Demographics and prescribing practices

Completed surveys were available for 64 self-identified SLE experts. The demographics of the respondents and cohort information are presented in table 1. HCQ prescribing practices are described in table 2.

The 64 lupus experts cared for a cohort of approximately 45 612 patients with SLE. The majority prescribed HCQ at a dose of 200–400 mg/day. The maximum dose of HCQ was 600 mg/day or 6.5 mg/kg/day. Of the rheumatologists, 17.2% use doses up to 600 mg/day, while 6.2% use up to 6.5 mg/kg/day.

Clinical decision-making

Clinical decision-making processes were assessed and are presented in table 3. Dose adjustments for patient weight are done by 50 (78%) physicians and 'sometimes' by 12 (19%) responders, respectively; 54 (84%) and 9 (14%) responders adjust using actual and ideal body weight, respectively. All the replies stated that HCQ adherence is routinely assessed through questioning during the clinical encounter, formal questionnaire or serum HCQ levels.

Table 2 Characteristics of the cohorts and HCQ practices

Percentage of patients with SLE prescribed HCQ, n (%)	
60%–75%	12 (18.7)
>75%	52 (81.3)
Number of patients with SLE with retina toxicity, n (%)	
0	8 (12.5)
1–5	27 (42.2)
6–10	17 (26.5)
11–50	12 (18.8)
Typical HCQ dose, n (%)	
200–400 mg/day	22 (34.4)
400 mg/day	22 (34.4)
5 mg/kg/day	15 (23.4)
5–6.5 mg/kg/day	5 (7.8)
Maximum HCQ dose, n (%)	
200 mg/day	1 (1.5)
400 mg/day	44 (68.8)
600 mg/day	11 (17.2)
5 mg/kg/day	1 (1.6)
6 mg/kg/day	3 (4.7)
6.5 mg/kg/day	4 (6.2)

HCQ, hydroxychloroquine.

Table 3 Clinical decision-making processes

For which side effects do you provide counselling to patients prior to starting them on HCQ, if any? Mark all that apply, n (%)	
Ophthalmological	64 (100)
Gastrointestinal	44 (68.8)
Dermatological	44 (68.8)
Other	8 (12.5)
Do you adjust HCQ dose for patient weight? n (%)	
Yes	50 (78.1)
No	2 (3.1)
Sometimes	12 (18.8)
If you adjust for weight, which strategy do you use? n (%)	
Actual body weight	54 (84.4)
Ideal body weight	9 (14.1)
I do not adjust for weight	1 (1.5)
Do you routinely monitor blood levels of HCQ? n (%)	
Yes	6 (9.4)
No	58 (90.6)
How do you assess HCQ adherence? n (%)	
Blood level	7 (10.9)
Question during history and physical	54 (84.4)
Other	3 (4.7)

HCQ, hydroxychloroquine.

Several clinical vignettes and multiple-choice questions were used to evaluate familiarity with the AAO 2016 guidelines. The responses to these vignettes/questions are presented in online supplemental table 1.

Knowledge and attitudes

Multiple-choice and select-all-that-apply questions were used to evaluate knowledge and attitudes regarding HCQ prescribing practices and usage (table 4).

Risk factors

Risk factors for the development of retinal toxicity associated with HCQ/CQ use were evaluated on a scale of 0–4 (0: no risk; 4: strong risk/presumed causation). The rheumatologists identified the following risk factors to be less, more and highly associated with the development of retinal toxicity, respectively: age, race, high body mass index, low body mass index, familial predisposition; pre-existing retinal/macular disease, renal disease, concomitant tamoxifen use; excessive daily dose of HCQ/CQ and cumulative dose of HCQ/CQ. A table demonstrating responses to evaluation of risk factors associated with retinal toxicity can be found in online supplemental table 2.

Familiarity with AAO guidelines

Of the rheumatologists, 57 (89.1%) responded that they were aware of the 2016 AAO guidelines regarding HCQ use (table 5). The rheumatologists identified limited dosing options (35 rheumatologists, 54.7%), evidence not supporting the guidelines (37 rheumatologists, 57.8%), low patient adherence to HCQ (28 rheumatologists, 43.8%) and other issues (8 rheumatologists, 12.5%) as the foremost concerns with the AAO 2016 revised guidelines. There were 479 cases of HCQ retinal toxicity (1.05%) and 9 cases of HCQ-associated blindness (1.8 per 10 000 patients) reported.

DISCUSSION

This is the first study evaluating rheumatologists' familiarity with the updated AAO guidelines. These data show that rheumatologists are familiar with weight-based dosing recommendations and risk factors outlined in the 2016 AAO guidelines. However, ubiquitous adoption of strict weight-adjusted dosing regimens is hindered by multiple factors, including market availability, patient compliance and some degree of scepticism about supporting literature. Additionally, there were inconsistencies in identifying the clinical risk factors associated with retinal toxicity and the suggested screening methodology.

Our data suggest that blindness from retinal toxicity associated with HCQ use is rare. The results of the survey estimate that blindness occurs in less than 0.1% of patients and retinal toxicity occurs in approximately 1% of patients. These data are consistent with previously

Table 4 Knowledge and attitudes

Which ophthalmological side effects are associated with HCQ use? Mark all that apply, n (%)	
Periorbital oedema	0 (0)
Keratopathy	21 (32.8)
Cataract formation	2 (3.1)
Retinopathy	64 (100)*
None of the above	0 (0)
What are the common symptoms of progressive retinal toxicity associated with CQ/HCQ use? Mark all that apply, n (%)	
Visual colour deficits	49 (76.6)*
Paracentral scotoma	54 (84.4)*
Glare	14 (21.9)
Flashing lights	18 (28.1)
Metamorphopsia (visual distortion)	26 (40.6)
A 37-year-old woman with no significant past medical history (PMH) is newly diagnosed with SLE and started on HCQ. What is her approximate risk of retinal toxicity after 5 years of treatment at recommended dosages? n (%)	
<1%	46 (71.9)*
3%–5%	15 (23.4)
5%–10%	3 (4.7)
10%–20%	0 (0)
>20%	0 (0)
A 37-year-old woman with no significant PMH is newly diagnosed with SLE and started on HCQ. At what point should she be considered at high risk for developing retinal toxicity? n (%)	
1 month intro treatment	0 (0)
1 year into treatment	1 (1.6)
5 years into treatment	17 (26.5)
20 years into treatment	44 (68.8)*
No significant temporal relationship	2 (3.1)
When might you refer your patient prescribed HCQ to an ophthalmologist? n (%)	
Prior to initiating therapy	17 (26.6)
Non-urgent within first year of treatment	40 (62.5)*
Non-urgent within first 5 years of treatment	6 (9.4)
Only after complaint of reduced visual acuity	1 (1.5)

*Per the American Academy of Ophthalmology guidelines.
CQ, chloroquine; HCQ, hydroxychloroquine; PMH, past medical history.

Table 5 Familiarity with the AAO guidelines

Are you aware of the most recent guidelines proposed by the American Academy of Ophthalmology (AAO) regarding HCQ use (2016)? n (%)	
Yes	57 (89.1)
No	2 (3.1)
Unsure	5 (7.8)
AAO guidelines recommend ophthalmological screening how frequently for patients on long-term (>5 years) CQ/HCQ regimen, if ever? n (%)	
Every 3 months	0 (0)
Every 6 months	7 (10.9)
Every year	48 (75.0)*
Every 5 years	8 (12.5)
Never	0 (0)
Unsure	1 (1.6)
AAO guidelines recommend which of the following as primary test(s) for retinal toxicity in patients taking CQ/HCQ? Mark all that apply, n (%)	
Fundus examination	30 (46.9)
Fluorescein angiography	8 (12.5)
Automated visual field	40 (62.5)*
Optical coherence tomography	56 (87.5) *
Colour testing	9 (14.1)
Full-field ERG	8 (12.5)
Amsler grid	5 (7.8)
Unsure	2 (3.1)

*Per the American Academy of Ophthalmology guidelines.
CQ, chloroquine; ERG, electroretinography; HCQ, hydroxychloroquine.

published literature suggesting that retinal toxicity occurs in 1% of patients.[9] While larger studies on the outcome of HCQ-related blindness in SLE are needed, the low prevalence of this complication should be considered as rheumatologists and ophthalmologists monitor and counsel patients on the risk of retinal toxicity.

The AAO recommendations on screening for HCQ and CQ retinopathy were initially published in 2002 but would be revised multiple times in the following decades to account for new findings in the literature. Shortly afterwards, a prospective cohort study of 526 patients from Greece treated with HCQ for rheumatoid arthritis or SLE described a 0.5% prevalence of related retinopathy among those receiving recommended dosages (≤6.5 mg/kg/day) for at least 6 years. Ophthalmological evaluation entailed best-corrected visual acuity, colour vision testing, static and central visual field testing, funduscopy, electroretinography, and fluorescein angiography when indicated.[13] In 2010, another group reported an incidence rate of 0.65% for definite or probable retinopathy among 3995 patients receiving HCQ for rheumatoid arthritis or SLE. Diagnosis was based on the presence of bull's eye maculopathy on funduscopy or suspicious aberration on visual field examination. While <0.3% exhibited such signs within the first 5 years of treatment, point estimates

of risk at later intervals were approximately 2% at 10–15 years of usage and 3.1% at 20 years.[14]

Revisions of the guidelines made in 2011 accounted for the above findings of cumulative dose-dependent risk and advances in available ophthalmological screening modalities: multifocal electroretinogram, spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence. New recommendations encouraged addition of at least one of the above to supplement routine screening with 10–2 automated fields and capping of daily dose at 400 mg or 6.5 mg/kg ideal body weight. They also cautioned against over-reliance on funduscopic examination due to the late-stage nature of visible bull's eye maculopathy.[15] In 2014, a large retrospective case–control study of 2361 patients on long-term HCQ reported higher prevalence of retinopathy than previously recognised: 7.5% overall and approaching 20% in those receiving longer term (>20 years) therapy based on visual field or OCT.[11] This landmark study played a role in prompting the 2016 guideline revision, which recommended a maximum daily HCQ dose of 5.0 mg/kg actual body weight, with citation of risk factors including high/excess dose, longer duration of use, and concomitant renal disease or tamoxifen use. Furthermore, updated guidelines emphasised baseline fundus examination, annual screening after 5 years of treatment using automated visual fields and SD-OCT, and additional consideration of patient ethnicity and medical history.[9]

Several recent studies aimed to investigate temporal shifts in HCQ dosing in the context of revised guidelines, producing rather mixed results. One group reviewed prescription patterns in a large health network from 2007 to 2016 and reported reduced dosing over time with a marked decrease in percentage of patients receiving at least 400 mg HCQ daily in light of the 2011 guideline revisions.[16] On the other hand, a retrospective review of electronic medical records of another health system documented that approximately 50% and 47% of patients seen from 2009 to 2016 were placed on excess initial doses according to the 2011 and 2016 guidelines, respectively. Of the patients, 56% were currently on excess maintenance doses per the 2016 guidelines. The authors concluded that the 2011 revisions had little impact on clinical practice and similarly tempered expectations for that of subsequent revisions.[17]

Studies have found that concern for adverse effects is a significant cause of non-adherence to medication in patients with SLE.[18] Fear over HCQ toxicity has been a limiting factor in prescribing HCQ for both patients and rheumatologists. There is a lack of data regarding non-reversible HCQ retinopathy/retinal blindness from HCQ use. The current AAO recommendations do not alleviate these fears. The lower dosing suggested by the new guidelines does not consider the limited therapeutic options for the treatment of SLE or the risk/benefit profile of HCQ compared with that of immunosuppressive medications. While rheumatologists understand the 2016 AAO recommendations, the results of the survey expressed appropriate concern that the guidelines lack sufficient evidence to support the change in practice that has ensued. The 2016 AAO guidelines and screening recommendations may be a step forward towards improving patient safety, but not necessarily improved outcomes in SLE. Technological advancements should continue to shape opinions on prevalence of retinopathy and suggest solutions for diagnosis and management. In any case, there is certainly a need for continued multidisciplinary collaboration between clinicians using HCQ to treat debilitating illnesses and ophthalmologists seeking to avoid potentially devastating consequences of overuse.

The strengths of the current study include a large number of responses from experienced rheumatologists/lupus experts who regularly prescribe HCQ to their patients, and an estimated cohort of 45 612 patients with SLE. The questionnaire was extensive and used multiple modalities (multiple-choice questions, ranking questions, clinical vignettes) to capture rheumatologists' familiarity with dosing, screening/monitoring and risk factors outlined in the 2016 AAO guidelines.

Limitations of this study included the following: (1) the cross-sectional survey-based data from a convenience sample of self-identified lupus experts may not be representative of the rheumatology community as a whole and thus limit the generalisability of our findings; (2) responses to questions were limited to the options presented to responders in the multiple-choice forms; and (3) the estimation of the occurrence of retinal toxicity did not explore potential associations with blindness (such as cumulative dose of HCQ or comorbidities). Moreover, while the response rate was close to 28%, individuals who chose not to respond may have done so because of their lack of familiarity with the guidelines. The study estimated the occurrence of retinal toxicity and HCQ-associated blindness from reports from rheumatologists. The next steps should include observational data from other large cohorts to confirm the accuracy of the data presented in this study.

Acknowledgements We acknowledge the rheumatologists who contributed to this survey.

Contributors ADA and LP were involved in the planning/development of the study, study design, survey development, data collection, data analysis and interpretation, as well as drafting of the manuscript. JM, LK and JW were involved in data analysis, interpretation of data and drafting of the manuscript. YG was involved in interpretation of data and drafting of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was determined to be exempt by the Columbia University Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Requests may be made to ADA at ada20@cumc.columbia.edu.

ORCID iDs
Leila Khalili http://orcid.org/0000-0002-1070-0997
Yevgeniya Gartshteyn http://orcid.org/0000-0001-5547-4658
Anca D Askanase http://orcid.org/0000-0003-4597-5023

REFERENCES

1 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.
2 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;69:20–8.
3 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.
4 Akhavan PS, Su J, Lou W, *et al*. The early protective effect of hydroxychloroquine on the risk of cumulative damage in patients with systemic lupus erythematosus. *J Rheumatol* 2013;40:831–41.
5 Hsu C-Y, Lin Y-S, Cheng T-T, *et al*. Adherence to hydroxychloroquine improves long-term survival of patients with systemic lupus erythematosus. *Rheumatology* 2018;57:1743–51.
6 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.
7 Geraldino-Pardilla L, Perel-Winkler A, Miceli J, *et al*. Association between hydroxychloroquine levels and disease activity in a predominantly Hispanic systemic lupus erythematosus cohort. *Lupus* 2019;28:862–7.
8 Costedoat-Chalumeau N, Dunogué B, Morel N, *et al*. Hydroxychloroquine: a multifaceted treatment in lupus. *Presse Med* 2014;43:e167–80.
9 Marmor MF, Kellner U, Lai TYY, *et al*. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology* 2016;123:1386–94.
10 Yusuf IH, Sharma S, Luqmani R, *et al*. Hydroxychloroquine retinopathy. *Eye* 2017;31:828–45.
11 Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol* 2014;132:1453–60.
12 Petri M, Elkhalifa M, Li J, *et al*. Hydroxychloroquine blood levels predict hydroxychloroquine retinopathy. *Arthritis Rheumatol* 2020;72:448–53.
13 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.
14 Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res* 2010;62:775–84.
15 Marmor MF, Kellner U, Lai TYY, *et al*. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology* 2011;118:415–22.
16 Melles RB, Jorge AM, Marmor MF, *et al*. Sharp decline in hydroxychloroquine dosing-analysis of 17,797 initiators from 2007 to 2016. *Clin Rheumatol* 2018;37:1853–9.
17 Braslow RA, Shiloach M, Macsai MS. Adherence to hydroxychloroquine dosing guidelines by rheumatologists: an electronic medical Record-Based study in an integrated health care system. *Ophthalmology* 2017;124:604–8.
18 Daleboudt GMN, Broadbent E, McQueen F, *et al*. Intentional and unintentional treatment nonadherence in patients with systemic lupus erythematosus. *Arthritis Care Res* 2011;63:342–50.