Screening for Hydroxychloroquine Toxicity by Texas Ophthalmologists

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ABSTRACT. ***Objective.*** To determine current practice patterns for screening for hydroxychloroquine (HCQ) toxicity by Texas ophthalmologists.

Methods. A survey was sent to all comprehensive ophthalmologists and retina specialists in the state of Texas. Questions included need for baseline examinations, frequency of followup, tests used to monitor for toxicity, and influences on monitoring regimen.

Results. Two hundred ninety of 577 surveys were returned correctly completed (response rate = 50.3%). Two hundred fifty-seven respondents (88.6%) felt a baseline examination was necessary prior to beginning HCQ therapy, and 223 (76.9%) followed patients every 6 months during HCQ therapy. Visual acuity, slit lamp examination, and dilated fundus examination were performed on almost all patients, and about three-quarters of respondents also checked visual fields and color vision. While 183 ophthalmologists (63.1%) used the Ishihara pseudoisochromatic plates to check color vision, there was no consensus on the preferred visual field test. One hundred twenty-two respondents (42.1%) stated they had diagnosed a patient with HCQ ocular toxicity.

Conclusion. Most ophthalmologists in Texas continue to perform baseline examinations and follow HCQ patients semiannually for the development of ocular toxicity despite recent recommendations questioning the need for such close followup. The majority check visual acuity, perform slit lamp and dilated fundus examinations, and test color vision and visual fields, although there is no consensus on the preferred method to test visual fields. (J Rheumatol 2002;29:1665–70)

Key Indexing Terms:
HYDROXYCHLOROQUINE ADVERSE EFFECTS ANTIRHEUMATIC AGENTS
CHEMICALLY INDUCED RETINAL DISEASES DRUG MONITORING

Antimalarials are widely used by rheumatologists and dermatologists for the treatment of rheumatoid arthritis, systemic lupus erythematosus, and cutaneous (discoid) lupus. Hydroxychloroquine (HCQ) has come to be favored over chloroquine due to the decreased incidence of ocular toxicity[1,2]. Chloroquine retinal toxicity presents initially as asymptomatic paracentral scotomas[1]. With longterm use permanent damage to the central retina occurs ("bull's eye" maculopathy) with resultant visual loss. HCQ is a 4-aminoquinolone derivative similar in structure to chloroquine except for the substitution of a hydroxyethyl group for an ethyl group on the tertiary aminohydrogen. The hydroxy group limits the ability of HCQ to cross the blood-retinal barrier, which may help to explain HCQ's decreased ocular toxicity[3].

Since Crews reported the first well documented case of HCQ retinopathy in 1964[4], there has been a low incidence of toxicity and only a few cases of the classic bull's eye maculopathy associated with HCQ[5-8]. Patients with bull's eye maculopathy were either overdosed by today's standards or were taking HCQ for over 6 years, with one exception. Bienfang, *et al* reported a 75-year-old Caucasian woman taking 200 mg of HCQ daily (4 mg/kg/day) for 5–6 years who developed visual symptoms, and HCQ was stopped. A bull's eye maculopathy first appeared 2 years after discontinuing HCQ[8]. The incidence of retinal toxicity from HCQ at today's recommended dosages (≤ 400 mg) is exceedingly low. In 7 case series with 1547 patients studied, only 5 cases of possible toxicity were identified[6,9-15]. In a study of 1207 patients taking HCQ, only one case of definite toxicity was identified (in a patient taking 6.98 mg/kg/day)[16].

Although quarterly eye examinations are recommended in the manufacturer's product description for HCQ[17], most authors in the past have recommended less frequent ophthalmologic examinations, usually once or twice yearly[9,18-20]. In 1998 a Canadian Consensus Conference recommended ophthalmologic examinations every 12–18 months for patients without liver or renal dysfunction[21]. The Royal College of Ophthalmologists guidelines recommend referral to an ophthalmologist only if the patient develops visual symptoms or if the prescribing rheumatologist or dermatologist detects visual abnormalities on annual evaluation. The working party for the development of the guidelines believed that if HCQ was newly introduced today, no

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Supported in part by an unrestricted research grant from Research to Prevent Blindness, Inc., New York, New York.

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Submitted September 26, 2001; revision accepted March 5, 2002.

evidence based case for the cost effectiveness of a screening program could be justified[22]. However, patients who develop visual symptoms may not have resolution of defects on discontinuing HCQ[7]. There is no consensus as to which tests are best to screen for HCQ ocular toxicity[23]. The American Academy of Ophthalmology has formed a task force on antimalarials, which is expected to suggest a recommended screening strategy. We sought to determine the current practice patterns for HCQ screening in Texas.

MATERIALS AND METHODS

A survey (Appendix) was sent to all ophthalmologists in the state of Texas with a practice focus of comprehensive ophthalmology or retina subspecialty listed in the 2000 Member Directory of the American Academy of Ophthalmology. Fulltime faculty members of the University of Texas Southwestern Medical Center were excluded from participation. Questions included need for baseline examinations and tests performed at baseline, frequency of followup, and tests used to monitor for HCQ toxicity assuming a hypothetical patient with normal renal function, 70 inches tall and weighing 70 kg, taking 400 mg of HCQ daily for 5 years or less. Ophthalmologists were also asked about the influences on their screening practices and whether they had ever diagnosed HCQ ocular toxicity. Participants were eligible to receive a copy of the results upon survey completion. The survey was sent only once, and reminders and second chance reply forms were not used.

Fisher exact test, chi-square test, and Student's t test were used to assess statistical significance between groups as appropriate.

RESULTS

Five hundred seventy-seven ophthalmologists (of which 141 had a practice focus of a retinal subspecialty) were identified and sent a survey. Three hundred twenty-two responses were received, but 32 were deemed ineligible due to the respondent having retired from practice, moved from Texas, or incompletely filled out the survey. Thus 290 surveys were analyzed (response rate = 50.3%). Two hundred twenty-seven responses (78.3%) were from comprehensive ophthalmologists, while 63 (21.7%) were from retina specialists. The respondents had practiced ophthalmology on average for 18.4 years (range 1–51 yrs, standard deviation 10.2). Two hundred four (70.3%) respondents saw less than 50 HCQ patients per year, and 276 (95.2%) saw less than 100 HCQ patients per year.

Two hundred fifty-seven ophthalmologists (88.6%) felt a baseline ophthalmologic examination was necessary prior to beginning HCQ therapy. Table 1 shows the tests performed at time of baseline and followup examination. Table 2 shows the recommended interval of followup after baseline. Visual field tests used are shown in Table 3 and color vision tests used are given in Table 4. Eighty-nine respondents (30.7%) use home Amsler grid monitoring. Table 5 shows the primary influence on the respondent's monitoring regimen. There was no difference between comprehensive ophthalmologists and retina specialists in this regard except for an increased primary concern about litigation on the part of retina specialists (14.3% vs 3.5%; p = 0.0029, Fisher exact test).

Table 1. Baseline and followup testing to screen for hydroxychloroquine ocular toxicity.

	Baseline Number (%)	Followup Examination Number (%)	p
Test			
Visual acuity	289 (99.7)	289 (99.7)	
Slit lamp	286 (98.6)	276 (95.2)	0.0284*
Dilated fundus	284 (97.9)	273 (94.1)	0.0312*
Visual field	222 (76.6)	224 (77.2)	
Color vision	222 (76.6)	220 (75.9)	
Fundus photos	67 (23.1)	22 (7.6)	< 0.0001*
Undilated fundus	23 (7.9)	28 (9.7)	
Electrooculography	2 (0.7)	4 (1.4)	
Electroretinography	0 (0.0)	0 (0.0)	
Visual evoked potentials	0 (0.0)	0 (0.0)	

* Fisher exact test, comparing testing at baseline with testing at followup examination.

Table 2. Recommended interval of followup.

	Number (%), n = 290
Followup interval	
3 mo	15 (5.2)
6 mo	223 (76.9)
9 mo	10 (3.5)
1 yr	41 (14.1)
6 yrs	1 (0.3)
As needed (prn)	0 (0)
Never	0 (0)

Table 3. Visual field (VF) tests used to screen for HCQ ocular toxicity.

	Number (%), n = 290
Visual field test*	
None	45 (19.0)
Automated 10° VF, red	67 (23.1)
Automated 30° VF, white	57 (19.7)
Amsler grid, white	50 (17.2)
Automated 10° VF, white	34 (11.7)
Automated 30° VF, red	32 (11.0)
Red Amsler grid	25 (8.6)
Tangent screen	11 (3.8)
Other	16 (5.5)

* Some respondents use more than one test.

Table 6 shows the factors that would influence an ophthalmologist to increase the frequency of screening examinations. One hundred twenty-two respondents (42.1%) had diagnosed a patient with HCQ ocular toxicity. The average length of practice for ophthalmologists that had diagnosed a patient with HCQ ocular toxicity was 20.0 years as opposed to 17.3 years for ophthalmologists that had not

Table 4. Color tests used to screen for HCQ ocular toxicity.

	Number (%), n = 290
Color test*	
None	57 (19.7)
Ishihara	183 (63.1)
Hardy Rand Rittler	39 (13.4)
Farnsworth D-15	26 (9.0)
Lanthony desaturated 15 hue	3 (1.0)
Farnsworth-Munsell 100 hue	1 (0.3)
Standard Pseudoisochromatic Plates, Part 2	1 (0.3)
Other	4 (1.4)

* Some respondents use more than one test.

Table 5. Primary influence on monitoring regimen.

	Number (%), n = 290
Influence*	
Desire to detect retinopathy before changes irreversible	146 (50.3)
Doing what was taught during residency/fellowship	76 (26.2)
Doing what referring physician asked as per monitoring†	44 (15.2)
Manufacturer's monitoring guidelines	34 (11.7)
Professional society guidelines	20 (6.9)
Threat of litigation	17 (5.9)

* Some respondents gave more than one primary influence. † While the other options were presented on the survey as choices, this influence was written by a significant number of respondents on the "Other" line.

Table 6. Factors that would influence the ophthalmologist to increase the frequency of screening.

	Number (%), n = 290
Factor	
Abnormal ophthalmic examination	168 (57.9)
Daily dose > 400 mg or 6.5 mg/kg lean body weight	92 (31.7)
None (all patients screened the same)	70 (27.2)
Daily dose > 400 mg	67 (23.1)
Duration of treatment > 10 yrs	51 (17.6)
Duration of treatment > 8 yrs	39 (13.4)
Daily dose > 6.5 mg/kg lean body weight	35 (12.1)
Duration of treatment > 6 yrs	32 (11.0)
Abnormal renal function	23 (7.9)
Abnormal liver function	12 (4.1)

(p = 0.0284, Student t test). Of the ophthalmologists who had diagnosed HCQ ocular toxicity, 80 (65.6%) recommended discontinuation of HCQ after evaluation by or discussion with the physician prescribing the patient's HCQ, 42 (34.4%) stopped the HCQ immediately, and 2 ophthalmologists (1.6%) continued the HCQ with close observation (a few respondents chose more than one option). Table 7 gives the findings seen in patients with HCQ ocular toxicity identified by the 122 ophthalmologists. Thirty-seven (30.3%) of the 122 ophthalmologists who had diagnosed HCQ toxicity had had a patient with permanent visual loss from HCQ.

Table 7. Findings seen in patients diagnosed with HCQ by responding ophthalmologists.

	Number (%), n = 122
Finding*	
Fundus abnormality	57 (46.7)
Visual field defect	43 (35.2)
Visual acuity decrease	27 (22.1)
Color vision defect	14 (11.5)
Electrophysiologic study abnormality	7 (5.7)
Fluororescein angiographic defect	5 (4.1)
Corneal deposits	3 (2.5)
No information provided	27 (22.1)

* Some respondents provided more than one finding.

DISCUSSION

While we are pleased with the 50.3% response rate to the survey, it is possible that recipients that responded may not be representative of Texas ophthalmologists as a whole. Despite recent recommendations to the contrary[9,18-22], most ophthalmologists responding continue to perform baseline examinations prior to beginning HCQ and then screen patients semiannually. Visual acuity, slit lamp examination, and dilated fundus examination are performed on almost all patients, and about three-quarters of respondents also checked visual field and color vision. Easterbrook argues that examination prior to beginning HCQ is not necessary, as retinopathy has never been described in patients taking antimalarial therapy for less than 6 months[24]. Our recommendations for screening have been published elsewhere[25].

Perhaps the earliest sign of HCQ retinal toxicity is the development of paracentral scotomas within 10 degrees of fixation[26]. There was no consensus in this survey on the type of visual field test that was preferable to detect early visual field defects. A plurality of respondents performed an automated central 10° visual field with a red test object, but 6% of the normal population may have scotomas to red test objects[27]. An Amsler grid, especially the red grid, may detect absolute or relative paracentral scotomas before they can be detected by conventional perimetry[12,28,29]. Easterbrook suggests obtaining an automated central 10° visual field with a white test object if the Amsler grid examination is abnormal prior to diagnosing retinal toxicity[30,31]. He found that patients presenting with relative scotomas had an excellent visual prognosis if antimalarial therapy was discontinued, but 63% of eyes presenting with absolute scotomas lost visual acuity and 63% lost visual field despite stopping antimalarials[32]. An Amsler grid was given to

Appendix. Hydroxychloroquine (HCQ) screening survey.

1. What is your specialty?
   - ❑ Comprehensive or general ophthalmology
   - ❑ Retina subspecialty
   - ❑ Other _____
2. How many years have you been in practice? _____
3. About how many patients do you see for hydroxychloroquine screening per year?
   - ❑ <50 ❑ 50-100 ❑ 100-200 ❑ >200

For questions 4 through 9, base your answers as if you were examining a HCQ patient with normal renal function, 70 inches tall and weighing 70 kg, taking 400 mg of HCQ daily for 5 years or less.

4. Do you feel a baseline ophthalmologic exam prior to beginning therapy is necessary?
   - ❑ Yes ❑ No
5. What tests do you routinely perform for baseline exam? Check all that apply.
   - ❑ Visual acuity ❑ Slit lamp exam
   - ❑ Undilated ophthalmoscopy ❑ Dilated ophthalmoscopy
   - ❑ Color vision testing ❑ Visual field testing
   - ❑ Fundus photography ❑ Electroretinography (ERG)
   - ❑ Electro-oculography (EOG) ❑ Visual evoked potential (VEP)
   - ❑ Other _____
6. When do you see a new HCQ patient again after baseline exam?
   - ❑ 3 months ❑ 6 months ❑ 9 months ❑ 1 year ❑ 6 years
   - ❑ Only if visual symptoms occur ❑ Never again
7. What tests do you routinely perform on a patient taking HCQ for 1 year back for annual exam?
   - ❑ Visual acuity ❑ Slit lamp exam
   - ❑ Undilated ophthalmoscopy ❑ Dilated ophthalmoscopy
   - ❑ Color vision testing ❑ Visual field testing
   - ❑ Fundus photography ❑ Electroretinography (ERG)
   - ❑ Electro-oculography (EOG) ❑ Visual evoked potential (VEP)
   - ❑ Other _____
8. If you routinely test color vision at either baseline or follow-up exam, what test(s) do you routinely use? Check all that apply.
   - ❑ Ishihara plates ❑ HRR plates
   - ❑ SPP-2 plates ❑ Farnsworth D-15
   - ❑ Farnsworth-Munsell 100 hue ❑ Lanthony desaturated 15 hue
   - ❑ Other _____
9. If you routinely test visual fields at either baseline or follow-up exam, what test(s) do you routinely use? Check all that apply.
   - ❑ Tangent screen ❑ Amsler grid (white)
   - ❑ Red Amsler grid ❑ Automated 30° VF, white target
   - ❑ Automated 30° VF, red target ❑ Automated 10° VF, white target
   - ❑ Automated 30° VF, red target ❑ Other _____
10. Do you give patients an Amsler grid to use to monitor vision at home?
    - ❑ Yes ❑ No
11. What factor has primarily influenced your monitoring regimen (choose only one)?
    - ❑ Manufacturer's monitoring guidelines
    - ❑ Professional society guidelines
    - ❑ Threat of litigation
    - ❑ Desire to detect retinopathy before changes irreversible
    - ❑ Just doing what I was taught to do in residency/fellowship
    - ❑ Other _____
12. When do you increase frequency of screening of HCQ patients? Check all that apply.
    - ❑ If daily dose > 6.5 mg/kg lean body weight
    - ❑ If daily dose > 400 mg, irrespective of patient's height and weight
    - ❑ If duration of treatment > 6 years
    - ❑ If duration of treatment > 8 years
    - ❑ If duration of treatment > 10 years
    - ❑ If patient's renal function is abnormal
    - ❑ If patient's liver function is abnormal
    - ❑ If abnormality found on ophthalmic screening exam
    - ❑ Never; all patients screened the same
13. Have you ever diagnosed HCQ toxicity? ❑ Yes ❑ No (skip remaining questions)
    If so, how: _____
14. What action did you take?
    - ❑ Instructed patient to stop HCQ immediately
    - ❑ Recommended discontinuation of HCQ after evaluation by or discussion with the physician prescribing the patient's HCQ
    - ❑ Continue HCQ with close observation and follow-up of abnormal exam
    - ❑ Other_____
15. Did any of your patients with HCQ toxicity have permanent visual loss?
    - ❑ Yes ❑ No

patients so they could check their vision at home between examinations by over 30% of respondents, although there are no formal studies demonstrating the utility of this practice[33].

Color vision loss usually follows the appearance of scotomas on visual field testing[34]. Initially the retinopathy produces a blue-yellow defect with an associated protan defect in the longer wavelengths, but becomes predominantly red-green as the disease progresses. Commonly available color plates like the Ishihara pseudoisochromatic plates are designed to detect red-green defects and often miss the earliest color vision defects in quinolone retinopathy[35]. The widespread availability of the Ishihara plates, however, may explain their prevalent use in this survey for testing for color vision defects associated with HCQ toxicity.

For half of the respondents the primary influence on their monitoring regimen was the desire to detect toxic retinopathy before the changes are irreversible. Stopping drug therapy at the earliest signs of toxicity often causes disappearance of the scotomas, or at least stabilization of the visual defects[1,7,23,32]. Another quarter of respondents selected that they were "just doing" what they were taught to do during their training, despite the (unintended) bias in the way the choice was worded. Fifteen percent wrote on the "Other" choice line that they relied on the referring physician to guide their monitoring regimen. Although 34 ophthalmologists stated the manufacturer's monitoring guidelines were the primary influence on their monitoring regimen, only 15 actually performed quarterly examinations as recommended by the manufacturer[17]. Less than 6% of respondents claimed to be primarily motivated by the threat of litigation. In contrast, a recent random sampling of members of the American College of Rheumatology found that 74% would continue to recommend routine ophthalmologic screening for HCQ ocular toxicity because of legal liability and 56% felt that their patients would insist on being screened[36]. We did not specifically ask whether patients' preferences for testing influenced ophthalmologists' screening practices, nor did we ask about a possible profit motive behind routine screening.

Bernstein reviewed all published cases to date as well as US Food and Drug Administration reports of HCQ retinopathy and concluded that, in the absence of chronic renal disease, permanent visual field scotomas did not occur if the daily dose was less than 6.5 mg/kg/day for less than 10 years[37]. About 60% of HCQ is excreted by the kidney, so significant renal insufficiency would lead to increased tissue retention of the drug. Since little of the drug is bound to fat, brain, or bone, Mackenzie recommended basing dosage on lean body weight[12]. Mavrikakis, *et al* described 2 cases of irreversible HCQ retinopathy (permanent paracentral scotomas) among 360 patients without renal dysfunction examined prospectively. No retinopathy was observed in patients using HCQ less than 6 years in this series[38]. Despite the apparent relationship of daily dosage, duration of treatment, and renal dysfunction to HCQ toxicity, over a quarter of respondents screened all of their patients in the same way despite differences in drug regimen and medical status.

Despite an incidence of HCQ ocular toxicity well under 1% in recent studies, 122 respondents (42.1%) stated they had diagnosed a patient with HCQ ocular toxicity. Of these ophthalmologists, almost two-thirds recommended discontinuation of HCQ after evaluation by or discussion with the physician prescribing the patient's HCQ. HCQ is among the best tolerated of the drugs used in rheumatology[39]. Patients may experience a substantial increase in disease activity when HCQ is discontinued[15,40,41]. The adverse effects of discontinuing HCQ when it has been effective in controlling the underlying disease, or of substituting a more toxic medication for HCQ, may sway all parties concerned to follow the patient a little longer until the diagnosis of retinal toxicity can be definitely affirmed.

Ophthalmologists who had diagnosed HCQ ocular toxicity tended to have been in practice longer than those who had not, yet the large number of respondents who claimed to have diagnosed toxicity surprised us. Granted the survey tool accepted a "yes" response for having made the diagnosis of toxicity without defining what constitutes HCQ ocular toxicity, but in an open ended question respondents were asked how they made the diagnosis. While 22.1% provided no information to this query, almost half of the ophthalmologists had seen fundus abnormalities, yet less than one-third of ophthalmologists who had diagnosed toxicity had had a patient with permanent visual loss from HCQ use. This self-reported data, obtained from the ophthalmologists' best recollections as opposed to chart review, is suspect at best, but despite the low overall incidence of HCQ ocular toxicity, many ophthalmologists may see cases during their professional careers.

In summary, most ophthalmologists in Texas continue to perform baseline examinations and follow HCQ patients semiannually for the development of ocular toxicity despite recent recommendations questioning the need for such close followup. The majority check visual acuity, perform slit lamp and dilated fundus examinations, and test color vision and visual fields, although there is no consensus on the best way to perform visual field testing.

REFERENCES

1. Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. Am J Med 1983;75:25-34.
2. Houpt JB. A rheumatologist's verdict on the safety of chloroquine versus hydroxychloroquine. Liability in off-label prescribing. J Rheumatol 1999;26:1864-6.
3. Raines MF, Bhargava SK, Rosen ES. The blood-retinal barrier in chloroquine retinopathy. Invest Ophthalmol Vis Sci 1989; 30:1726-31.
4. Crews SJ. Chloroquine retinopathy with recovery in early stages.

Lancet 1964;2:436-41.
5. Shearer RV, Dubois EL. Ocular changes induced by long-term hydroxychloroquine (Plaquenil) therapy. Am J Ophthalmol 1967;64:245.
6. Johnson MW, Vine AK. Hydroxychloroquine therapy in massive total doses without retinal toxicity. Am J Ophthalmol 1987;104:139-44.
7. Weiner A, Sandberg MA, Gaudio AR, Kini MM, Berson EL. Hydroxychloroquine retinopathy. Am J Ophthalmol 1991; 112:528-34.
8. Bienfang D, Coblyn JS, Liang MH, Corzillius M. Hydroxychloroquine retinopathy despite regular ophthalmologic evaluation: a consecutive series. J Rheumatol 2000;27:2703-6.
9. Rynes RI, Krohel G, Falbo A, Reinecke RD, Wolfe B, Bartholomew LE. Ophthalmologic safety of long-term hydroxychloroquine treatment. Arthritis Rheum 1979;22:833-6.
10. Mikkelsen J. Ocular complications of treatment with antimalarial drugs in dermatology [in Danish]. Ugeskr Laeg 1979;141:2316-8.
11. Tobin D, Krohel G, Rynes R. Hydroxychloroquine. Seven-year experience. Arch Ophthalmol 1982;100:81-3.
12. Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. Am J Med 1983;75:40-5.
13. Mantyjarvi M. Hydroxychloroquine treatment and the eye. Scand J Rheumatol 1985;14:171-4.
14. Finbloom DS, Silver K, Newsome DA, Gunkel R. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. J Rheumatol 1985;12:692-4.
15. Morsman CDG, Livesay SJ, Richards IM, Jessop JD, Mills PV. Screening for hydroxychloroquine retinal toxicity: is it necessary? Eye 1990;4:572-6.
16. Levy GD, Munz SJ, Paschal J, Cohen HB, Pince KJ, Peterson T. Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. Arthritis Rheum 1997;40:1482-6.
17. Physicians' desk reference. Montvale, NJ: Medical Economics Company; 2001:2860-2.
18. Easterbrook M. Is corneal deposition of antimalarial any indication of retinal toxicity? Can J Ophthalmol 1990;5:249-51.
19. Ruiz RS, Saatci OA. Chloroquine and hydroxychloroquine retinopathy: how to follow affected patients. Ann Ophthalmol 1991;23:290-1.
20. Bray VJ, Enzenauer RJ, Enzenauer RW, West SG. Antimalarial ocular toxicity in rheumatic disease. J Clin Rheumatol 1998; 4:168-9.
21. Esdaile JM. Canadian Consensus Conference on Hydroxychloroquine. J Rheumatol 2000;27:2919-21.
22. Fielder A, Graham E, Jones S, Silman A, Tullo A. Royal College of Ophthalmologists guidelines: ocular toxicity and hydroxychloroquine. Eye 1998;12:907-9.
23. Silman A, Shipley M. Ophthalmological monitoring for hydroxychloroquine toxicity: a scientific review of available data. Br J Rheumatol 1997;36:599-601.
24. Easterbrook M. Detection and prevention of maculopathy associated with antimalarial agents. Int Ophthalmol Clin 1999;39:49-57.
25. Blomquist PH. Screening for hydroxychloroquine toxicity. Comp Ophthalmol Update 2000;1:245-50.
26. Hart WM, Burde RM, Johnston GP, Drews RC. Static perimetry in chloroquine retinopathy: perifoveal patterns of visual field depression. Arch Ophthalmol 1984;102:377-80.
27. Percival SPB, Meancock I. Chloroquine: ophthalmological safety and clinical assessment in rheumatoid arthritis. BMJ 1968; 3:579-84.
28. Easterbrook M. The use of Amsler grids in early chloroquine retinopathy. Ophthalmology 1984;91:1368-72.
29. Easterbrook M. The sensitivity of Amsler grid testing in early chloroquine retinopathy. Trans Ophthal Soc UK 1985;104:204-7.
30. Easterbrook M. Chloroquine retinopathy. Arch Ophthalmol 1991;109:1362.
31. Easterbrook M. The ocular safety of hydroxychloroquine. Semin Arthritis Rheum 1993;23 Suppl 1:62-7.
32. Easterbrook M. Long-term course of antimalarial maculopathy after cessation of treatment. Can J Ophthalmol 1992;27:237-9.
33. Grierson DJ. Hydroxychloroquine and visual screening in a rheumatology outpatient clinic. Ann Rheum Dis 1997;56:188-90.
34. Brinkley JR Jr, Dubois EL, Ryan SJ. Longterm course of chloroquine retinopathy after cessation of medication. Am J Ophthalmol 1979;88:1-11.
35. Vu BL, Easterbrook M, Hovis JK. Detection of color vision defects in chloroquine retinopathy. Ophthalmology 1999;106:1799-803.
36. Fraenkel L, Felson DT. Rheumatologists' attitudes toward routine screening for hydroxychloroquine retinopathy. J Rheumatol 2001;28:1218-21.
37. Bernstein HN. Ocular safety of hydroxychloroquine. Ann Ophthalmol 1991;23:292-6.
38. Mavrikakis M, Papazoglou S, Sfifakis PP, Vaiopoulos G, Rougas K. Retinal toxicity in longterm hydroxychloroquine treatment. Ann Rheum Dis 1996;55:187-9.
39. Block JA. Hydroxychloroquine and retinal safety. Lancet 1998;351:771.
40. Pinckers A, Broekhuyse RM. The EOG in rheumatoid arthritis. Acta Ophthalmol Copenh 1983;61:831-7.
41. The 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.