JCS Yam 任卓昇
AKH Kwok 郭坤豪

Ocular toxicity of hydroxychloroquine

羥基氯奎引致的眼毒疾病

Objectives. To review the types, incidence, pathogenesis, risk factors, and clinical characteristics of hydroxychloroquine ocular toxicity and current views about its screening and management.

Data sources. Literature search of Medline up to May 2005.

Study selection. Key words for the literature search were 'hydroxychloroquine', 'chloroquine', 'ocular', 'toxicity', 'retinopathy', and 'screening'.

Data extraction. Original articles and review papers were examined.

Data synthesis. Hydroxychloroquine ocular toxicity includes keratopathy, ciliary body involvement, lens opacities, and retinopathy. Retinopathy is the major concern: others are more common but benign. The incidence of true hydroxychloroquine retinopathy is exceedingly low; less than 50 cases have been reported. Although its pathogenesis is unclear, risk factors include: daily dosage of hydroxychloroquine, cumulative dosage, duration of treatment, coexisting renal or liver disease, patient age, and concomitant retinal disease. Patients usually complain of difficulty in reading, decreased vision, missing central vision, glare, blurred vision, light flashes, and metamorphopsia. They can also be asymptomatic. Most patients have a bull's eye fundoscopic appearance. All patients have field defects including paracentral, pericentral, central, and peripheral field loss. Colour vision is usually undisturbed in early retinopathy, but is impaired in the advanced stage. Most patients have visual loss. Some patients with advanced retinopathy may experience deteriorating visual acuity even after cessation of treatment. There is no consensus on the definition of retinopathy, most-effective ophthalmological assessment, or frequency of screening. Regular screening may be necessary to detect reversible premaculopathy. Cessation of the drug is the only effective management of the toxicity.

Conclusion. Consensus with regard to various important aspects of hydroxychloroquine ocular toxicity is limited, especially the definition of true hydroxychloroquine retinopathy, the most effective ophthalmological assessment, and frequency of screening. Decisions to stop medication must be made in conjunction with the rheumatologist or physician managing the patient. Management of hydroxychloroquine retinopathy remains a clinical challenge.

目的：檢討羥基氯奎引致眼毒疾病的種類、病發情況、病發原理、風險因素和臨床特徵，以及現時對此病症檢查和治療方法的論點。

資料來源：在醫學資料庫 Medline 搜索 2005 年 5 月或以前的文獻。

研究選項：以「羥基氯奎」(hydroxychloroquine)、「氯奎」(chloroquine)、「眼的」(ocular)、「毒性」(toxicity)、「視網膜病」(retinopathy) 和「檢查」(screening) 作關鍵字，搜索有關的文獻。

資料選取：以論著及綜述文章作研究。

資料綜合：羥基氯奎引致的眼毒疾病包括角膜病、睫狀體侵入、晶狀體混濁和視網膜病，其中以視網膜病最受關注，其他病症雖然較普遍但病情輕微。真正由羥基氯奎引致的視網膜病極少出現，只有不多於 50 宗病例報告。雖然未清楚其病發原理，但其風險因素則包括每日使用羥基氯奎的劑量、累積劑量、用藥期長短、是否同時有腎病或肝病、病人年齡和是否有併發性視網膜病。病人通常表示自己閱讀困難、視力減弱、失去中央視力、感覺光線太強、視力模糊、光線閃動和出現變視症；亦有病人是無徵狀的。大部分病人會有大瞳孔及眼底顯露。所有病人的視野都受損害，包括中央旁視野受損、中央環狀視野受損、中央和外圍視野受損。早期視網膜病通常不會影響分辨顏色的能力，但隨著病情轉重，色覺亦會受損。大部分病人視覺受損，部分嚴重的病人若停止治療會出現視敏度受損。現時醫學界對視網膜病的定義、最有效的視力評估方法和檢查次數都未有共識。定期檢查可能偵查到可

Key words:
Chloroquine;
Hydroxychloroquine;
Mass screening;
Retinal diseases

關鍵詞：
氯奎；
羥基氯奎；
大規模檢查；
視網膜病

Hong Kong Med J 2006;12:294-304

Department of Ophthalmology, Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong
JCS Yam
AKH Kwok, MD, FRCS (Edin)

Correspondence to: Dr AKH Kwok (e-mail: alvinkwok@hksh.com)

治療的前視網膜病。停止使用羥基氯奎是唯一有效的治療方法。

結論：醫學界對羥基氯奎引致眼毒疾病的很多重要問題，尤其是此病症的確實定義、最有效的視力評估方法和檢查次數，共識仍很有限。醫生在決定停藥時，必須與病人的風濕病科醫生或治療人員配合。治療羥基氯奎引致的視網膜病仍是臨床醫學上的挑戰。

Introduction

Since the 1950s, the antimalarial agents chloroquine and hydroxychloroquine have been used with increasing popularity to treat systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, Sjogren's syndrome, and other diseases.[1] Hydroxychloroquine is less toxic than chloroquine and other disease-modifying drugs, and is one of the most efficacious and safe therapeutic options.[1] Various side-effects of hydroxychloroquine such as gastro-intestinal upset, skin rash, and headache are common,[1] but the major concern is retinopathy with consequent permanent visual loss. Patients deprived of hydroxychloroquine because of this ocular concern are typically treated with far more toxic therapy to control disease activity.[2] Thus, it is important to understand the incidence, pathogenesis, risk factors, clinical presentation, and current concepts about screening for hydroxychloroquine ocular toxicity.

Ocular side-effects of antimalarials

Ocular side-effects of antimalarial agents include keratopathy, ciliary body involvement, lens opacities and retinopathy.[3] This review will focus mainly on retinopathy, the major manifestation of ocular toxicity. Although other ocular side-effects are more common, they are benign.

Keratopathy

Corneal deposits have been chemically shown to be composed of unchanged antimalarial salts.[4] They are limited to the corneal epithelium and the pattern can vary from diffuse punctate opacities to an aggregation of radial and whirling lines that converge and coalesce on a zone just beneath the centre of the cornea. Pigmented lines are often present as large, isolated, and circumscribed opacities.[3] Visual acuity is not reduced, but patients may complain of halos around a light source and photophobia.[3] Keratopathy occurs in 90% of patients taking appropriate doses of chloroquine but very rarely in those taking hydroxychloroquine.[4] This difference may reflect a lower tissue accumulation of hydroxychloroquine or a difference in the tendency of chloroquine and hydroxychloroquine to bind to the cornea.[4] Since the recommended hydroxychloroquine dose has decreased over the last 30 years, corneal problems now occur much less frequently. In 1967, corneal infiltration was reported in 28% of 94 patients receiving 800 mg/day hydroxychloroquine.[5] Fifteen years later, no corneal changes were observed in 99 patients treated with 400 mg/day hydroxychloroquine for longer than 7 years in a prospective study.[6] Easterbrook[4] reported a less than 5% incidence of hydroxychloroquine corneal infiltrate in patients receiving 400 mg/day and none were symptomatic. He concluded that those with hydroxychloroquine corneal deposits should be considered overdosed, and should be assessed carefully for any disturbance of macular function. These findings were supported by another prospective study of 758 patients who received hydroxychloroquine, with only six cases of corneal deposits reported (incidence, 0.8%).[7] In four patients, the daily dosage was higher than 6.5 mg/kg per day and in one the cumulative dosage was 514.6 g. Corneal deposits may appear as early as 2 to 3 weeks following commencement of antimalarial treatment.[3] They are completely reversible on drug discontinuation and no residual corneal damage ensues regardless of the duration of therapy. As such they are usually not a reason to stop therapy.[3]

Ciliary body and ocular muscle imbalance

Long-term administration of antimalarials may rarely disturb accommodation. Difficulty in quickly changing focus may occur soon after administration of chloroquine.[3] The dose can be decreased if symptoms are bothersome. In an earlier study, no loss of accommodation was observed in patients who received hydroxychloroquine.[6] Another study more than 10 years later implicated hydroxychloroquine as a cause of ocular muscle imbalance in four patients, though no firm conclusions could be drawn.[7]

Lens

Cataracts have been associated with chloroquine therapy in more than 20% of patients.[3] They are described as tiny white flakes axially placed beneath the posterior lens capsule, and do not resemble the central posterior

Table 1. Premaculopathy versus true retinopathy[3]

	Premaculopathy	True retinopathy
Visual field loss	Red only	White + red test object
Visual symptoms	Rarely if ever present	Usually present
Visual acuity	Never affected	May or may not be affected
Macula	Fine pigmentary stippling, loss of foveal light reflex	Hypo- or hyper-pigmentary change Bull's eye
Reversibility after drug discontinuation	Almost always	Very rare
Onset or progression after drug discontinuation	Almost never	Sometimes

Table 2. Review of published reports of hydroxychloroquine retinopathy with details[5,8-30]

Case No.	Series	Sex/age (years)	Diagnosis*	Dose (mg/day)	Dose/wt (mg/kg/day)	Duration (years)	Total (g)	Symptoms
1	Braun-Vallon,[8] 1963	-/84	Horton's syndrome	400	-	1.5	200	-
2	Perdriel,[8] 1965	-/53	-	600	-	0.25	54	-
3		-	-	500	-	0.50	129	-
4		-	-	600	-	0.75	90	-
5	Reed and Karlinsky,[9] 1967	F/40	SLE CRF	400	-	5	730	'Smoky' vision
6	Shearer and Dubois,[5] 1967	F/37	SLE	600-1200	13.6-33.4	2.20	770	Difficulty in seeing
7	Brinkley et al,[10] 1979	-/38	SLE	800	15.3	3.50	1032	-
8		-/47	SLE	900	24.1	2.50	886	-
9		-/40	SLE	300	7.8	3.75	396	-
10	Stillman,[8] 1981	-	-	400	7.7	4.75	684	-
11	Douche,[8] 1983	-/66	-	600	-	0.50	86	-
12	Hart et al,[11] 1984	F/54	-	400	-	7	1022	Difficulty in reading
13	Johnson and Vine,[12] 1987	F/43	RA	500	10.6	4	730	-
14	Easterbrook,[13] 1988	F/38	RA	600	12.2	1.5	329	-
15		F/41	SLE	400	10.2	6.5	949	-
16		F/34	RA	400	8.8	4.0	584	-
17		F/28	SLE	200	3.79	0.16	12	-
18	Raines et al,[14] 1989	F/69	RA	400	7.27	4.0	584	Asymptomatic
19		F/72	RA	400	5.2	19.0	1734	Asymptomatic
20	Weiner et al,[15] 1991	F/49	SLE	400-800	6.1-12.2	10	1788	Glare
21		F/60	SLE	400	6.1	20	2920	Asymptomatic
22	Falcone et al,[16] 1993	F/70	RA	200	3.92	7	511	-
23	Mavrikakis et al,[17] 1996	F/39	RA	200-400	3.57	6.5	700	-
24		F/58	SLE	200-400	2.90-5.80	8	730	-
25	Levy et al,[18] 1997	F/48	SLE	400	6.98	7.3	1066	-
26	Thorne and Maguire,[19] 1999	F/61	RA	400	6.3	10	1460	Glare
27	Maturi et al,[20] 1999	F/45	RA	400	8.5	6	876	↓central vision
28	Wang et al,[21] 1999	-/-	SLE	200-400	6.5	12.8	1700	-
29	Bienfang et al,[22] 2000	F/66	RA	400	8.70	11	1606	Central vision 'off'
30		F/50	SLE	400	7.27	15	2190	↓vision
31		F/64	RA	400	6.56	11	1606	↓vision
32		F/60	RA	200	3.40	15	1095	↓reading vision
33		F/75	Inflammatory arthritis	800	16	5	1460	Difficulty in reading
34	Warner,[23] 2001	F/45	SLE	400	5.9	9	1314	Flashing lights circling around central vision
35	Shroyer et al,[24] 2001	-/-	RA	400	-	7	1060	Visual impairment
36		-/-	Sjogren	400	-	5.5	803	Visual impairment
37	Wei et al,[25] 2001	F/42	SLE	200-400	4-8	-	657	-
38	Browning,[26] 2002	-/45	RA	400	6.9	20	2920	-
39		F/48	RA	400	6.8	13	1861	Blurring vision
40		-/53	SLE	400	6.3	3	432	-
41		-/58	RA	550	9.1	8	1606	-
42		-/78	SCL	400	11.0	6	876	-
43	Herman et al,[27] 2002	F/67	RA	250	3.2	17	1551	↓central vision
44	Alarcon,[28] 2002	F/35	SLE	400	3	0.8	122	Difficulty in reading
45	So et al,[29] 2003	-/52	Dm	400	-	7	1022	'Cloudy area', donut shaped
46		-/45	SLE	500	-	5	913	Glare
47	Penrose et al,[30] 2003	F/46	SLE	400	6.5	7	1022	Bilateral metamorphopsia

* SLE denotes systemic lupus erythematosus, CRF chronic renal failure, RA rheumatoid arthritis, SCL scleroderma, and Dm dermatomyositis
† CF denotes count fingers
‡ Colour tests include Hardy-Rand-Rittler colour plate (HRR), Ishihara colour plate, Farnsworth Panel D-15 test, and Pseudoisochromatic plate

subcapsular plaques found in steroid-induced cataracts. Nonetheless, differentiating such changes from the normal effects of ageing is difficult.[3] Again, none have been observed in patients prescribed hydroxychloroquine.[6]

Definitions of hydroxychloroquine retinopathy

Hydroxychloroquine retinopathy may be classified as premaculopathy and true retinopathy.[3] Their differences

Final visual acuity		Colour vision test‡	Fundus appearance	Visual field loss	Prognosis after treatment cessation
R	L				
20/20	Decrease	-	Macular degeneration	-	-
-	-	-	-	-	-
-	-	-	-	-	-
-	-	-	-	-	-
CF† at 5 feet	CF at 2 feet	-	Fine pigmented stippling	Central + peripheral constriction	Delay onset 1 year after termination of therapy, with deterioration over 2 years
20/50	20/50	Abnormal HRR	Bull's eye	Severely constricted	Stable
20/20	20/20	Abnormal HRR	Mild pigment mottling	Constricted	Regression
20/60	20/50	Abnormal HRR	Advanced bull's eye	Markedly constriction	Deterioration over 10 years
20/30	20/25	Abnormal HRR	Mild pigment mottling	Central	Stable
-	-	-	-	-	-
-	-	-	-	-	-
20/25	20/30	-	Bull's eye in right, minor granularity in left	Central	-
20/25	20/20	Normal Farnsworth	Bull's eye	Pericentral	-
-	-	-	-	-	-
-	-	-	-	-	-
-	-	-	-	-	-
-	-	-	-	-	-
6/12	3/60	Abnormal Ishihara	Bull's eye	Present	-
6/12	6/24	Abnormal Ishihara	Bull's eye	Present	-
20/25	20/25	Abnormal Ishihara Normal Farnsworth	Bull's eye	Pericentral	Stable
20/25	20/25	Abnormal Ishihara Normal Farnsworth	Bull's eye	Pericentral	Stable
20/25	20/25	Abnormal tests (not specified)	Bull's eye	Pericentral	Stable
20/20	20/20	Normal Farnsworth	Bull's eye in right	Unilateral paracentral	Stable
20/20	20/20	Normal Farnsworth	Bull's eye	Pericentral	Stable
-	-	-	-	-	-
20/20	20/20	Normal pseudoisochromatic plate	Subtle pigmentary changes, early bull's eye	Pericentral	Slight improvement
20/50	20/50	Abnormal Ishihara	Bull's eye	Central	Stable
20/30	20/25	-	Bull's eye	Central	Stable
20/20	20/20	Abnormal HRR	Bull's eye	Central	Stable
20/50	CF at 1 foot	Abnormal HRR	Bull's eye	Central	Deterioration over 3 years
20/100	CF at 3 feet	Abnormal HRR	Bull's eye	Central	Deterioration over 4 years
20/30	20/30	Abnormal HRR	Bull's eye	Central	Stable
20/200	20/200	Abnormal HRR	Bull's eye	Central	Deterioration over 3 years
20/20	20/20	Abnormal Ishihara Abnormal Farnsworth	Bull's eye	Pericentral	Stable
-	-	-	-	-	-
-	-	-	-	-	-
Present	Present	-	Bull's eye	-	Deterioration continued for more than 5 years
-	-	-	Bull's eye	Pericentral	-
20/50	20/50	Abnormal Ishihara Normal Farnsworth	Bull's eye	Pericentral	Stable
-	-	-	Bull's eye	Pericentral	-
-	-	-	Bull's eye	Pericentral	-
-	-	-	Bull's eye	Pericentral	-
5/10	4/10	-	Bull's eye	Pericentral	Stable
-	-	-	Bull's eye	-	-
20/25	20/25	-	Normal	Paracentral	-
20/20	20/20	-	Normal	Central	-
20/20	20/20	Normal Ishihara	Normal	Paracentral	-

are summarised in Table 1.[3] Despite this, there is no general consensus on the definition of true hydroxychloroquine retinopathy. Two definitions are commonly cited. Bernstein[8] requires the development of persistent paracentral or central visual field scotoma to suprathreshold white stimuli and a duration of treatment of more than 9 months. In the absence of visual field defects, a bull's eye lesion also suggests true retinopathy. Easterbrook[4] advocates the use

Table 3. Summary of all important case series for the incidence of hydroxychloroquine retinopathy[5-7,12,18,21,31-41]

Case Series	Authors	Type of the study	Duration of the study	No. of patients (%)	Dosages	Treatment period
1	Shearer and Dubois,[5] 1967	Prospective	-	1 in 94 (1)	800 mg/day	<4.5 years
2	Mikkelsen,[41] 1979	-	-	0 in 338 (0)	-	-
3	Frenkel,[32] 1982	-	15 years	0 in 100 (0)	200-400 mg/day	3 years
4	Adams et al,[33] 1983	Retrospective	-	2 in 108 (1.8)	400 mg/day	>6 months
5	Mackenzie,[34] 1983	Prospective	7 years	0 in 311 (0)	<6.5 mg/kg/day	6.8 years
6	Rynes,[6] 1983	Prospective	7 years	4 in 99 (4)	400 mg/day	>1 year
7	Runge,[35] 1983	Retrospective	7 years	0 in 101 (0)	400 mg/day	20 months
8	Finbloom et al,[36] 1985	Retrospective	15 years	0 in 66 (0)	280 mg/day	>1 year
9	Mantyjarvi,[37] 1985	Prospective	-	1 in 63 (1.6)	300 mg/day	3-95 months
10	Johnson and Vine,[12] 1987	Retrospective	-	0 in 9 (0)	<600 mg/day	7-26 months
11	Morsman et al,[31] 1990	Prospective	9 years	0 in 73 (0)	200-400 mg/day	>18 months
12	Morand et al,[38] 1992	Prospective	8 years	0 in 403 (0)	200-400 mg/day	-
13	Spalton,[39] 1996	Retrospective	-	0 in 82 (0)	235.3 (100-441) mg/day	38.6 months
14	Grierson,[7] 1997	Prospective	12 years	0 in 758 (0)	400 mg/day	1-11 years
15	Levy et al,[18] 1997	Retrospective	2 years	1 in 1207 (0.08)	>350 mg/day	4.1-3.3 years
16	Wang et al,[21] 1999	Prospective	-	1 in 77 (1.3)	200-400 mg/day	>6 years
17	Mavrikakis et al,[40] 2003	Prospective	15 years	2 in 400 (0.5) 2 in 526 (0.38)	<6.5 mg/kg/day <6.5 mg/kg/day	>6 years >1 years

of bilateral, reproducible, positive field defects that can be shown by two different visual field tests—Amsler grid test and an automated 10-degree visual field test—as definitive evidence of retinal toxicity.

Incidence of hydroxychloroquine retinopathy

Cases of true hydroxychloroquine retinopathy were reviewed by Medline literature search. Only patients receiving hydroxychloroquine therapy and never chloroquine, together with a detailed description of clinical characteristics were selected. In this review, Bernstein's[8] or Easterbrook's[4] definition are used to define true hydroxychloroquine retinopathy. Between 1960 and 2005, 47 cases of true hydroxychloroquine retinopathy have been reported (Table 2).[5,8-30]

All published case series on the incidence of hydroxychloroquine retinopathy identified by Medline literature search are summarised in Table 3.[5-7,12,18,21,31-41] Out of 17 case series, the incidence ranges from 0 to 4%, such variation being mainly due to the different definitions of retinopathy and use of different drug doses. Combining all the data, out of a total of 4415 patients who received hydroxychloroquine therapy, only 12 developed retinopathy. Among all series, nine prospective studies, with a total of 2404 patients, reported only nine cases of hydroxychloroquine retinopathy. However, combining such data is complicated by the variation of definitions and types of study. The highest incidence of 4% occurred in a prospective study of 99 patients over 7 years[6] (case series 6), but all their cases appeared to be reversible premaculopathy rather than true retinopathy, when the above-mentioned definitions were applied. The largest retrospective study (case series 15) of 1207 patients found only one patient (dosed with hydroxychloroquine 6.98 mg/kg per day) with definite toxicity, with an overall incidence of 0.08%.[18] The lack of appropriate controls in this study, nevertheless makes the assessment of baseline retinopathy risk impossible.[2] In the most recent large prospective study of 526 patients (case series 17), the overall incidence of irreversible hydroxychloroquine retinopathy was 0.38%.[40] For 400 patients who received long-term treatment (over 6 years), the incidence was 0.5%. Whatever the true incidence, all studies support the view that hydroxychloroquine retinopathy is rare.

Pathogenesis of retinopathy

Although the pathogenesis of retinopathy due to hydroxychloroquine is not well established, the similarity of its chemical structure to chloroquine and the characteristics of the retinopathy, suggest that the mechanisms may be analogous.[15] Chloroquine is highly concentrated in the pigmented ocular tissues such as retinal pigment epithelium (RPE), binds to melanin, and remains there for prolonged periods of time even after cessation of therapy.[42]

Two histopathological studies[43,44] of advanced chloroquine retinopathy in humans revealed destruction of rods and cones with sparing of the foveal cones. This explains the fundoscopic appearance of the bull's eye maculopathy. Attenuation of the retinal arterioles is thought to be secondary to extensive retinal damage.[44] An accumulation of pigment laden cells, possibly due to their migration from RPE, has also been demonstrated in the outer nuclear and outer plexiform layers.[44] It is suggested that the metabolism of the RPE is first affected, with disturbance of its function of phagocyting the physiologically shed outer segments of the photoreceptor cells.[44] This results in degenerative changes to the RPE leading to migration,[43] followed by photoreceptor degeneration.

Animal studies have shown that the earliest reversible histopathological changes are membranous cytoplasmic bodies that accumulate in ganglion cells and degenerative

Table 4. Criteria for low and high risk of developing retinopathy[45]

Criterion	Low risk	High risk
Dosage	<6.5 mg/kg hydroxychloroquine <3 mg/kg chloroquine	>6.5 mg/kg hydroxychloroquine >3 mg/kg chloroquine
Duration of use (years)	<5	>5
Habitus	Lean or average fat	High fat level (unless dosage is appropriately low)
Renal/liver disease	None	Present
Concomitant retinal disease	None	Present
Age (years)	<60	>60

changes in photoreceptor outer segments. Thus, initially the drug may destroy ganglion cells and photoreceptors, with later involvement of the RPE.[42]

Hydroxychloroquine is less ocular toxic than chloroquine,[36] which may be due to the addition of the hydroxyl group that limits the ability of hydroxychloroquine to cross the blood-retinal barrier. Breakdown of the blood-retinal barrier by chloroquine, but not by hydroxychloroquine, has been demonstrated.[14]

Risk factors

Factors that contribute to the development of hydroxychloroquine retinopathy include: the daily and cumulative dosage, duration of treatment, coexisting renal or liver disease, patient age, and concomitant retinal disease. The American Academy of Ophthalmology (AAO) guidelines have developed criteria to indicate low and high risk of retinopathy (Table 4).[45]

Daily dosage

Daily dosage is believed to be the most important factor in the development of hydroxychloroquine retinopathy.[34] It is extremely important to take into account lean (ideal) body weight when calculating the optimal dose, since very little of the drug is bound to fat, brain, and bone.[34] Thus obesity is a risk factor if patients are dosed according to their actual weight.[46] Lean body weight has been defined as 50 kg plus 2.3 kg per inch (2.54 cm) over 5 feet (152.4 cm) for men and 45.5 kg plus 2.3 kg per inch over 5 feet for women.[46]

Based on a review of a large population with a zero incidence of retinopathy at a dosage of <6.5 mg/kg lean body weight/day, Mackenzie[34] (case series 5) suggested this to be the recommended dosage at which patients would not be at risk. Bernstein's[8] extensive review of the world literature (1960 to 1989) also revealed no published cases of hydroxychloroquine retinopathy among patients with normal renal function who received less than this recommended dose for up to 10 years. In the largest cohort (case series 15) of 1207 patients, a zero incidence was also found among those receiving less than 6.5 mg/kg of hydroxychloroquine per day.[18] Moreover, a scientific review of all available data also concluded that the risk of retinopathy in patients taking hydroxychloroquine less than 6.5 mg/kg per day is very small.[47] The AAO committee guidelines also recommended that maintenance dosages should be less than 6.5 mg/kg per day (Table 4).[45] Despite this, 14 cases of hydroxychloroquine retinopathy occurring at this dosage are reported in this review, and up to 21 cases have been reported elsewhere.[46]

Cumulative dosage

It has been suggested that a cumulative dosage of more than 100 g carries a significant risk of retinopathy.[39] In this review, 43 cases of hydroxychloroquine retinopathy with cumulative dosages exceeding 100 g were identified, although several studies revealed conflicting results. In one study, among 900 patients treated with either chloroquine or hydroxychloroquine (case series 5), 84 patients received more than 1000 g of either chloroquine or hydroxychloroquine over a mean of 14 years without developing retinopathy.[34] Similar results were reported by Rynes[6] (case series 6). Another study (case series 10) found no retinopathy in nine patients who received massive total doses of hydroxychloroquine ranging from 1054 to 3923 g.[12]

The importance of cumulative dosage as a risk factor for toxicity therefore remains controversial[40] and has not been mentioned in guidelines by the AAO[45] or the Royal College of Ophthalmologists.[48]

Duration of treatment and renal/liver function

The duration of treatment and renal/liver function (Table 4[45]) are contributing factors but less significant than the daily dosage.[8] Among the 47 cases of hydroxychloroquine retinopathy cited in this review, the duration of therapy ranged from 1.9 months (case 17) to 20 years (cases 21, 38) with a mean of 7.0 years. Bernstein[8] concluded that the risk of retinopathy was virtually zero among those with normal renal function prescribed hydroxychloroquine at or below the recommended dosage and with treatment duration of less than 10 years. Once again though, this review identified nine patients who received less than the recommended dosage and developed retinopathy with therapy for less than 10 years and in three after less than 5 years of treatment.

Since the kidney and liver are responsible for excretion (60%[8]) and metabolism of hydroxychloroquine,[34] respectively, increased tissue retention of the drug and consequent increased risk of retinopathy will ensue in

Table 5. Clinical presentation of true hydroxychloroquine retinopathy (n=47)[5,8-30]

Clinical presentation*	No. of cases
Symptoms (n=23)	
Asymptomatic	3
Difficulty in reading	5
Decreased vision	4
Missing in central vision	3
Glare	3
Blurring of vision	3
Light flashes	1
Metamorphopsia	1
Final visual acuity (n=29)	
Normal vision	8
Visual loss with visual acuity better than 20/40	10
Visual acuity worse than 20/40	11
Fundoscopic appearance (n=34)	
Normal	3
Pigment mottling/stippling	4
Bull's eye	27
Visual field status (n=32)	
Normal	0
Paracentral/pericentral only	16
Central only	10
Peripheral constriction only	3
Central and peripheral	1
Visual field defects present but not specified	2
Colour vision status† (n=22)	
Normal colour vision test	5
Abnormal colour vision test	16
Abnormal colour vision test(s) but not specified	1

* n denotes the total number of cases with respective category reported
† Colour tests include Hardy-Rand-Rittler colour plate, Ishihara colour plate, Farnsworth Panel D-15 test, and Pseudoisochromatic plate

the presence of significant renal or liver impairment (case 5).

Age, concomitant retinal disease, and genetic predisposition

Older patients may be more susceptible to the toxic effects of hydroxychloroquine due to malfunctioning of retinal pigment that results in reduced drug clearance and thus greater accumulation.[16] In Johnson and Vine's study[12] (case series 10), out of the 47 cases (age range, 28-84 years), none of the nine patients younger than 60 years developed retinopathy, in contrast to 13 who were aged 60 years or older.

Patients with concomitant retinal disease appear to be at higher risk, although no specific data have shown diseased retinas to be more susceptible.[45]

Individuals with an *ABCR* mutation may be genetically predisposed to hydroxychloroquine retinopathy even at the recommended daily dosage,[24] but this remains to be verified.

Clinical presentation and prognosis of hydroxychloroquine retinopathy

The clinical presentations of 47 cases of true hydroxychloroquine retinopathy described in the literature[5,8-30] are summarised in Table 5. Five variables are described: symptoms, final visual acuity, fundoscopic appearance, visual field status, and colour vision status. Owing to the absence of standardised reporting patterns and differences of focus in the various studies, not all variables were reported for all cases. Patients with true retinopathy may be asymptomatic despite abnormal fundi or visual field, but most complained of difficulty in reading, decreased vision, missing central vision, glare, blurring of vision, light flashes, and metamorphopsia. Most patients had a fundoscopic bull's eye appearance. All cases reported visual field defects, possibly the first indication of retinopathy.[45] The presence of a visual field defect correlates well with degree of retinal damage,[49] and begins as paracentral scotoma that may become confluent and form pericentral ring scotoma. It may progress to form a central scotoma, leading to a marked decrease in visual acuity (cases 5, 30, 31, 33). Peripheral field loss occurs in advanced retinopathy. Colour vision is essentially undisturbed in early antimalarial retinopathy but impaired in the presence of extensive macular damage.[50] Of the 22 patients in whom colour vision status was reported, 17 had abnormal colour vision testing. Nonetheless their abnormal response to Ishihara or Hardy-Rand-Rittler colour plate testing may in turn be due to their visual field defects.[4] Only one case (case 34) with abnormal Farnsworth Panel D-15 test result was reported.

Visual prognosis of hydroxychloroquine retinopathy may depend on the severity of the retinopathy when therapy was discontinued,[10] but the small number of cases makes this difficult to establish.[4] Of 29 patients in whom visual acuity was reported, only eight had normal final visual acuity. In the worst case (case 5), the patient could only count fingers at a distance of 5 feet with the right eye and at 2 feet with the left eye. While premaculopathy is mostly reversible,[6,51] most cases of true retinopathy remain stable after therapy is discontinued and advanced cases may even progress. In 22 cases where prognosis was reported (Table 2), six showed deterioration of vision after stopping treatment. Case 8 showed deterioration over a period of up to 10 years. Delayed onset of hydroxychloroquine retinopathy, 1 year after discontinuation of treatment, has also been reported (case 5), which suggests a need to follow-up patients after treatment is stopped.

Fundoscopic abnormalities and differential diagnoses

Premaculopathy consists of fine pigmentary stippling of the macula and loss of foveal reflex. It may progress to true retinopathy that usually consists of stippled hyperpigmentation of the macula, and is surrounded first by a clear zone of depigmentation and then by a second ring of pigment, giving a bull's eye appearance (Table 1).[3] Uncommonly, with more extensive retinal damage, the arterioles may show generalised attenuation and segmental constriction with disk pallor.[3] In the peripheral fundus, a prominent choroidal pattern and fine granularity of the retina may be seen. A high degree of symmetry between the eyes is usually found.[3] Hydroxychloroquine retinopathy shares phenotypic similarities with several

maculopathies.[27] Hydroxychloroquine premaculopathy should be differentiated from age-related macular degeneration. True hydroxychloroquine retinopathy should be differentiated from combined cone and rod dystrophies, classical cone dystrophies, neuronal ceroid lipofuscinosis, Stargardt's disease, and fenestrated sheen macular dystrophy.[27]

Diagnosis of early antimalarial toxicity

The rarity of hydroxychloroquine ocular toxicity makes it impossible to determine the most effective ocular examinations. Several methods have been recommended and include ophthalmological examination, visual field testing, colour vision testing, fluorescein angiography, and electrophysiological tests.

Ophthalmological examination

Best-corrected visual acuity should be measured.[45] Slit lamp examination with dilated pupils is useful in the detection of corneal deposits that may indicate overdose.[4] Careful fundoscopic examination (including retinal periphery and vasculatures) is important to detect early maculopathy.[45] Nonetheless early fundoscopic changes are non-specific[27] and may not be noticed until permanent damage has occurred,[52] thus other retinal function studies that detect early reversible abnormalities should be performed.

Visual field testing

Central field testing is the most important test for the early diagnosis of hydroxychloroquine toxicity, since paramacular functional loss may appear before definite fundoscopic changes.[45] The Amsler grid and Humphrey field test are the two most commonly used methods. With superior sensitivity[52] to and good correlation[53] with static and kinetic perimetry, the Amsler grid is simple, quick, inexpensive, reproducible, and self-administrable by a cooperative patient, making it an excellent screening test for antimalarial retinopathy.[52] A disadvantage is the appearance of faded or absent squares that is entirely subjective. Moreover, the Amsler grid provides a suprathreshold target with high contrast to examine the central visual field, thus it may fail to detect subtle scotomata.[54] The threshold Amsler grid (TAG) decreases perceived luminance by using cross-polarising filters, thereby it decreases the image contrast and serves as a more sensitive test to detect such subtle scotomas.[54] A recent prospective study of 56 patients taking hydroxychloroquine and 12 controls showed that TAG was 12.5 times as likely to identify a patient with a scotoma compared with Amsler grid, which provides an alternative means of detecting central visual field defects in patients receiving hydroxychloroquine.[54] The Humphrey 10-2 white programme is an automated static threshold perimetry, testing 68 points in the central 10 degrees of vision. Studies show that it has greater sensitivity than non-automated static and kinetic perimetry in assessing macular function in patients with retinopathy,[27] but its relative sensitivity compared with the Amsler grid has yet to be determined.[52] Since it is expensive and time-consuming, it is mainly used to confirm a positive Amsler test.[4]

Colour vision testing

The widely available colour vision tests, such as Ishihara plates, are mainly used to detect scotomata rather than colour vision defects in early retinopathy.[3] They may be a useful adjunct to central visual field testing, particularly in patients with short attention spans for whom visual field testing is unreliable.[52] For advanced maculopathy, antimalarials tend to affect the blue-yellow tritan axis of confusion rather than the red-green, so the Farnsworth Panel D-15 test may be useful.[45] Male patients should have a baseline colour vision test performed to exclude any underlying congenital colour deficiency that may otherwise be confused with toxicity.[45]

Fluorescein angiography and fundus photography

Fluorescein angiography can demonstrate striking macular uptake and identify subtle pigmentary alterations. As in the development of scotoma, visual loss, or macular stippling precedes the abnormalities detected by fluorescein angiography.[53] It therefore has little role in diagnosing early retinopathy. However, it is useful in patients who find visual field testing difficult,[52] and in assessing pre-existing maculopathy (eg age-related macular degeneration).[52] Fundus photography can provide a record of the appearance for later comparison.[45]

Electrophysiological tests

Electrophysiological tests such as electro-oculogram and electroretinogram (ERG) play a limited role in screening, but remain useful in evaluating the severity of antimalarial retinopathy.

Electro-oculography (EOG) reflects the metabolic integrity of the RPE and was believed to detect early antimalarial-induced retinal changes.[53] Regrettably, the poor correlation between macular changes and EOG, high inter-individual variability of EOG , pre-existing low EOG values among rheumatoid arthritis patients and the influence of the disease activity on EOG results—limit its prognostic significance and usefulness as a screening test.[53]

Electroretinogram readings are normal when macular damage alone is present, and decrease only in the presence of diffuse retinal damage.[53] A newer technique, the multifocal ERG, may be more suitable for the evaluation of hydroxychloroquine toxicity, but its role as a screening test remains to be established.[45]

Screening for antimalarial toxicity: differing opinions

Screening recommendations for antimalarial drug toxicity vary in different regions. The dilemma of whether to screen for retinopathy lies in its rare occurrence, despite its seriousness and irreversibility. The manufacturer's

Summary of the American Academy of Ophthalmology screening recommendations for chloroquine and hydroxychloroquine retinopathy[45]

Baseline examination for all patients taking either chloroquine or hydroxychloroquine within the first year
- Baseline examination to establish the risk status (low or higher)
- Complete ophthalmologic examination (best-corrected visual acuity and dilated pupillary examination of the cornea and retina)
- Baseline field testing with an Amsler grid, or Humphrey 10-2 fields
- Optional colour testing (especially important in male patients for later screening)
- Optional fundus photography when the fundus shows any pigmentary changes confusing with early toxicity
- Optional specialised tests such as fluorescein angiography or multifocal electroretinogram for those with underlying maculopathy indistinguishable from antimalarial drug toxicity, or those with unusual risk factors for early or rapid toxicity

Low-risk patients
- No further special ophthalmologic testing required, but regular ophthalmologic examinations as usual
- Dilated pupillary examination of the cornea and retina and visual field testing (Amsler grid or Humphrey 10-2 fields) in each examination
- Other tests are optional (colour testing, fundus photography, fluorescein angiography, multifocal electroretinography)
- Patient counselling on the very small risk of toxicity within initial 5-year period
- Patient counselling to promptly return upon (1) visual status changes (visual acuity, Amsler grid appearance, colour sensations, or adjustment to the dark), (2) increased drug dosage, (3) major weight loss, and (4) hepatic or renal dysfunction

Higher-risk patients
- Annual screening with a complete ophthalmologic examination and visual field testing (Amsler grid testing or Humphrey 10-2 field testing)
- Periodic Humphrey 10-2 testing may be added to Amsler grid results
- Other tests are optional (colour testing, fundus photography, fluorescein angiography, multifocal electroretinography)
- Patient education on home use of the Amsler grid on a regular basis (eg monthly)
- Patient counselling to promptly return upon visual status changes

Patients with suggestive visual symptoms or fundus findings
- Repeated fundoscopic examination and Amsler grid testing with a Humphrey 10-2 test for confirmation
- Further evaluation with fundus photography, fluorescein angiography, multifocal electroretinography, and full-field electroretinography
- Immediate cessation of drug for confirmed cases
- Re-evaluation in 3 months for doubtful cases

recommendation of quarterly ophthalmological examination is obviously not cost-effective in relation to its low incidence.[46]

Based on the zero (or approaching zero) incidence of hydroxychloroquine retinopathy found in their studies, Morsman et al[31] (case series 11), Morand et al[38] (case series 12), Grierson[7] (case series 14), and Levy et al[18] (case series 15) suggested that routine screening for ocular toxicity be abandoned when recommended dosages are prescribed. Silman and Shipley[47] also concluded that the available scientific evidence is insufficient to recommend routine monitoring in patients on a dosage of less than 6.5 mg/kg per day. In their editorial, Blyth and Lane[55] suggested that ophthalmological examination is not necessary unless patients become symptomatic. The Royal College of Ophthalmologists found that there was no evidence-based justification for the cost-effectiveness of a screening programme for hydroxychloroquine ocular toxicity, and thus recommends ophthalmological referral only if the patient develops visual symptoms or if the prescribing rheumatologist or dermatologist detects visual abnormalities on annual evaluation.[48] Furthermore, screening programmes are costly, may make patients unnecessarily anxious, and generate unnecessary work for clinicians. More importantly, screening may not identify reversible toxicity as (a) there is no reliable screening test to identify them before ophthalmoscopic changes develop, and (b) it is difficult to distinguish toxicity from age-related macular degeneration.

Other researchers believe that screening can detect early signs of toxicity and thus permit discontinuation of the drug before irreversible damage occurs. They support screening after a baseline examination, although opinions on the timing of screening varies. Rynes[56] suggests screening every 6 months, Ruiz and Saatci[57] every 9 to 12 months, the Canadian Consensus Conference on Hydroxychloroquine[58] every 12 to 18 months, and Browning[26] yearly. Spalton[39] suggests screening after 3 years of treatment and Block[2] after 5 years. After examining the available evidence, the AAO recently developed screening recommendations in accordance with both modern knowledge and the economic realities of practice. It suggests different screening approaches, according to risk status (Table 4). This recommendation is summarised in the Box.[45]

Despite the varying screening recommendations for antimalarial retinopathy, surveys of practitioners suggest that some screening may be indicated, as cases of definite retinopathy have been reported in patients receiving less than the recommended dosage.[46] In a survey of 325 British dermatologists (response rate, 70%), 60% routinely referred patients for ophthalmological follow-up.[59] In another survey of 300 American rheumatologists (response rate, 56%), 75% would continue to screen because they were unwilling to accept any risk of visual loss among their patients, and 74% would continue to screen because of legal liability.[60] In the third survey of all ophthalmologists (response rate, 50.3%) in Texas, 77% would assess patients receiving hydroxychloroquine therapy every 6 months.[61]

Management of toxicity

There is no effective treatment for hydroxychloroquine ocular toxicity other than cessation of medication.[45] Management depends on the presence of retinal damage and the patient's medical status.[45] Decisions to stop medication, which can lead to worsening of underlying disease, must be made in conjunction with the physician caring for the patient.

Conclusion

Hydroxychloroquine ocular toxicity is becoming increasingly important due to the increasing popularity of the drug. Retinopathy is the major concern although the incidence of true retinopathy is extremely low. Fewer than 50 cases have been reported. The important risk factors are: excessive daily dosage, increasing cumulative dosage, the duration of treatment and patient age as well as coexistent renal or liver disease and concomitant retinal disease. There is no consensus on the definition of retinopathy, the most-effective method of ophthalmological assessment, or screening frequency. Frequent screening may be necessary to detect reversible premaculopathy. Cessation of the drug is the only effective management of the toxicity.

References

1. Rynes RI. Antimalarial drugs in the treatment of rheumatological diseases. Br J Rheumatol 1997;36:799-805.
2. Block JA. Hydroxychloroquine and retinal safety. Lancet 1998;351:771.
3. Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. Am J Med 1983;75:25-34.
4. Easterbrook M. The ocular safety of hydroxychloroquine. Semin Arthritis Rheum 1993;23(2 Suppl 1):62S-67S.
5. Shearer RV, Dubois EL. Ocular changes induced by long-term hydroxychloroquine (plaquenil) therapy. Am J Ophthalmol 1967;64:245-52.
6. Rynes RI. Ophthalmologic safety of long-term hydroxychloroquine sulfate treatment. Am J Med 1983;75:35-9.
7. Grierson DJ. Hydroxychloroquine and visual screening in a rheumatology outpatient clinic. Ann Rheum Dis 1997;56:188-90.
8. Bernstein HN. Ocular safety of hydroxychloroquine. Ann Ophthalmol 1991;23:292-6.
9. Reed H, Karlinsky W. Delayed onset of chloroquine retinopathy. Can Med Assoc J 1967;97:1408-11.
10. Brinkley JR Jr, Dubois EL, Ryan SJ. Long-term course of chloroquine retinopathy after cessation of medication. Am J Ophthalmol 1979;88:1-11.
11. Hart WM Jr, Burde RM, Johnston GP, Drews RC. Static perimetry in chloroquine retinopathy. Perifoveal patterns of visual field depression. Arch Ophthalmol 1984;102:377-80.
12. Johnson MW, Vine AK. Hydroxychloroquine therapy in massive total doses without retinal toxicity. Am J Ophthalmol 1987;104:139-44.
13. Easterbrook M. Ocular effects and safety of antimalarial agents. Am J Med 1988;85:23-9.
14. Raines MF, Bhargava SK, Rosen ES. The blood-retinal barrier in chloroquine retinopathy. Invest Ophthalmol Vis Sci 1989;30:1726-31.
15. Weiner A, Sandberg MA, Gaudio AR, Kini MM, Berson EL. Hydroxychloroquine retinopathy. Am J Ophthalmol 1991;112:528-34.
16. Falcone PM, Paolini L, Lou PL. Hydroxychloroquine toxicity despite normal dose therapy. Ann Ophthalmol 1993;25:385-8.
17. Mavrikakis M, Papazoglou S, Sfikakis PP, Vaiopoulos G, Rougas K. Retinal toxicity in long term hydroxychloroquine treatment. Ann Rheum Dis 1996;55:187-9.
18. 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.
19. Thorne JE, Maguire AM. Retinopathy after long term, standard doses of hydroxychloroquine. Br J Ophthalmol 1999;83:1201-2.
20. Maturi RK, Folk JC, Nichols B, Oetting TT, Kardon RH. Hydroxychloroquine retinopathy. Arch Ophthalmol 1999;117:1262-3.
21. Wang C, Fortin PR, Li Y, Panaritis T, Gans M, Esdaile JM. Discontinuation of antimalarial drugs in systemic lupus erythematosus. J Rheumatol 1999;26:808-15.
22. Bienfang D, Coblyn JS, Liang MH, Corzillius M. Hydroxychloroquine retinopathy despite regular ophthalmologic evaluation: a consecutive series. J Rheumatol 2000;27:2703-6.
23. Warner AE. Early hydroxychloroquine macular toxicity. Arthritis Rheum 2001;44:1959-61.
24. Shroyer NF, Lewis RA, Lupski JR. Analysis of the *ABCR* (ABCA4) gene in 4-aminoquinoline retinopathy: is retinal toxicity by chloroquine and hydroxychloroquine related to Stargardt disease? Am J Ophthalmol 2001;131:761-6.
25. Wei LC, Chen SN, Ho CL, Kuo YH, Ho JD. Progression of hydroxychloroquine retinopathy after discontinuation of therapy: case report. Chang Gung Med J 2001;24:329-34.
26. Browning DJ. Hydroxychloroquine and chloroquine retinopathy: screening for drug toxicity. Am J Ophthalmol 2002;133:649-56.
27. Herman K, Leys A, Spileers W. (Hydroxyl)-chloroquine retinal toxicity: two case reports and safety guidelines. Bull Soc Belge Ophthalmol 2002;284:21-9.
28. Alarcon GS. How frequently and how soon should we screen our patients for the presence of antimalarial retinopathy? Arthritis Rheum 2002;46:561.
29. So SC, Hedges TR, Schuman JS, Quireza ML. Evaluation of hydroxychloroquine retinopathy with multifocal electroretinography. Ophthalmic Surg Lasers Imaging 2003;34:251-8.
30. Penrose PJ, Tzekov RT, Sutter EE, et al. Multifocal electroretinography evaluation for early detection of retinal dysfunction in patients taking hydroxychloroquine. Retina 2003;23:503-12.
31. Morsman CD, Livesey SJ, Richards IM, Jessop JD, Mills PV. Screening for hydroxychloroquine retinal toxicity: is it necessary? Eye 1990;4:572-6.
32. Frenkel M. Safety of hydroxychloroquine. Arch Ophthalmol 1982;100:841.
33. Adams EM, Yocum DE, Bell CL. Hydroxychloroquine in the treatment of rheumatoid arthritis. Am J Med 1983;75:321-6.
34. Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. Am J Med 1983;75:40-5.
35. Runge LA. Risk/benefit analysis of hydroxychloroquine sulfate treatment in rheumatoid arthritis. Am J Med 1983;75:52-6.
36. 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.
37. Mantyjarvi M. Hydroxychloroquine treatment and the eye. Scand J Rheumatol 1985;14:171-4.
38. Morand EF, McCloud PI, Littlejohn GO. Continuation of long term treatment with hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis. Ann Rheum Dis 1992;51:1318-21.
39. Spalton DJ. Retinopathy and antimalarial drugs—the British experience. Lupus 1996;5(Suppl 1):70S-72S.
40. 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.
41. Mikkelsen J. Ocular complications after treatment with antimalarial agents in dermatology [in Danish]. Ugeskr Laeger 1979;141:2316-8.
42. Rosenthal RA, Kolb H, Bergsma D, Huxsoll D, Hopkins JL. Chloroquine retinopathy in the rhesus monkey. Invest Ophthalmol Vis Sci 1978;17:1158-75.

43. Wetterholm DH, Winter FC. Histopathology of chloroquine retinal toxicity. Arch Ophthalmol 1964;71:82-7.
44. Bernstein HN, Ginsberg J. The pathology of chloroquine retinopathy. Arch Ophthalmol 1964;71:238-45.
45. 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;109:1377-82.
46. Easterbrook M. Screening for antimalarial toxicity: current concepts. Can J Ophthalmol 2002;37:325-8.
47. Silman A, Shipley M. Ophthalmologic monitoring for hydroxychloroquine toxicity: a scientific review of available data. Br J Rheumatol 1997;36:599-601.
48. Royal College of Ophthalmologists. Ocular toxicity and hydroxychloroquine: guidelines for screening. London: The College; 2004.
49. Portnoy JZ, Callen JP. Ophthalmologic aspects of chloroquine and hydroxychloroquine therapy. Int J Dermatol 1983;22:273-8.
50. Vu BL, Easterbrook M, Hovis JK. Detection of color vision defects in chloroquine retinopathy. Ophthalmology 1999;106:1799-804.
51. Crews SJ. Chloroquine retinopathy with recovery in early stages. Lancet 1964;2:436-8.
52. Easterbrook M. Detection and prevention of maculopathy associated with antimalarial agents. Int Ophthalmol Clin 1999;39:49-57.
53. Maksymowych W, Russell AS. Antimalarials in rheumatology: efficacy and safety. Semin Arthritis Rheum 1987;16:206-21.
54. Almony A, Garg S, Peters RK, et al. Threshold Amsler grid as a screening tool for asymptomatic patients on hydroxychloroquine therapy. Br J Ophthalmol 2005;89:569-74.
55. Blyth C, Lane C. Hydroxychloroquine retinopathy: is screening necessary? BMJ 1998;316:716-7.
56. Rynes RI. Ophthalmologic considerations in using antimalarials in the United States. Lupus 1996;5(Suppl 1):73S-74S.
57. Ruiz RS, Saatci OA. Chloroquine and hydroxychloroquine retinopathy: how to follow affected patients. Ann Ophthalmol 1991;23:290-1.
58. Canadian rheumatology association. Canadian Consensus Conference on Hydroxychloroquine. J Rheumatol 2000;27:2919-21.
59. Cox NH, Paterson WD. Ocular toxicity of antimalarials in dermatology: a survey of current practice. Br J Dermatol 1994;131:878-82.
60. Fraenkel L, Felson DT. Rheumatologists' attitudes toward routine screening for hydroxychloroquine retinopathy. J Rheumatol 2001;28: 1218-21.
61. Blomquist PH, Chundru RK. Screening for hydroxychloroquine toxicity by Texas ophthalmologists. J Rheumatol 2002;29:1665-70.