Retinal toxicity in long term hydroxychloroquine treatment

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Abstract
Objective—To report clinical experience from patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) who were receiving recommended doses of hydroxychloroquine for more than six years, and were monitored for evidence of hydroxychloroquine related retinopathy every six months.

Methods—A prospective (and continuing) evaluation was made of the potential retinal toxicity of hydroxychloroquine in a cohort of 360 Greek patients followed for RA and SLE, 58 of whom have received long term treatment (> six years). Fundoscopy, colour vision tests, dark adaptation tests, visual field testing, automated perimetry, and electroretinogram were performed every six months.

Results—Among 58 patients receiving hydroxychloroquine for more than six years, two relatively young women (3.5%), one treated for RA and the other treated for SLE, developed characteristic hydroxychloroquine related toxic retinal lesions after cumulative doses of 700 g (6.5 years) and 730 g (8 years) of hydroxychloroquine, respectively. Bilateral visual acuity was 6/6 and 6/7.5, respectively; both patients had normal colour perception. Despite an early diagnosis and cessation of treatment, permanent visual field paracentral scotomata in both patients, and persisting lesions in fluorescein angiography in the patient with SLE, were observed at 4.5 and 3 years of follow up, respectively. No other specific cases of hydroxychloroquine related retinopathy have to date been identified in the remaining 302 patients.

Conclusion—Cases of irreversible, hydroxychloroquine related retinopathy in patients who did not receive overdoses have not been reported previously. The present observations in two relatively young patients should raise our concern regarding the long term usage of an increasingly popular medication in rheumatology practice.

Patients and methods

STUDY POPULATION
This prospective study included consecutive patients with RA or SLE, followed at the Departments of Clinical Therapeutics and Internal Medicine of the Athens University Medical School and the Rheumatology Department of the General Hospital, Athens, Greece, who were being treated with hydroxychloroquine. Abnormality of visual function or retinal appearance at baseline were the only exclusion criteria. Of 360 patients that have been studied to date, the subgroup who have received long term treatment comprised 58...
Results

LONG TERM TREATMENT

Among the 58 patients treated long term, two middle aged women whose cumulative dosages of hydroxychloroquine were at the top end of the range of cumulative dosage of the whole group developed toxic, irreversible retinopathy lesions that were clearly attributable to hydroxychloroquine.

Patient 1—A 39 year old woman with RA, whose weight varied in the range 56–62 kg over the years of treatment, developed characteristic retinal changes after 6–5 years of treatment with hydroxychloroquine (400 mg/day for three years, then 200 mg/day for 3–5 years, approximately; cumulative dose approximately 700 g). Bilateral best corrected visual acuity (6/6) and colour perception were normal, but fundoscopic lesions (fig 1) and paracentral scotomata (fig 2A) in the right eye were observed. These lesions were also demonstrated in fluorescein angiography with the beginnings of a mask defect on the macula; the respective electroretinogram was suppressed. Comorbidities that could have caused these lesions were not identified.

Despite early diagnosis, cessation of treatment, and attempts to bind hydroxychloroquine with ammonium chloride or dimercaprol, the condition of this patient remained relatively stable, and though a recent fluorescein angiogram appeared normal, unilateral paracentral scotomata were evident in the visual field (fig 2B) in 4·5 years of follow up, while the respective electroretinogram was also suppressed, indicating the presence of retinopathy.

Patient 2—A 58 year old woman with SLE, weighing 69 kg, developed retinal changes after eight years of treatment with hydroxychloroquine (400 mg/day for two years, then 200 mg/day for six years; cumulative dose 730 g). Colour perception was normal, but a slight bilateral decrease in best corrected visual acuity (6/7·5) was observed. Paracentral scotomata on both optical fields, fundoscopic lesions of a characteristic appearance that were similar to the lesions depicted in figure 1, abnormal fluorescein angiography, and suppressed retinograms were also observed.

This second patient's condition, in common with that of the first, did not change during follow up: bilateral visual field tests remained abnormal, the amplitude of the B wave on the retinogram was markedly reduced, and characteristic hydroxychloroquine related retinal changes were evident in fluorescein angiography three years after cessation of treatment (fig 3).

PATIENTS TREATED FOR LESS THAN SIX YEARS

We have not observed any case of hydroxychloroquine related retinal toxicity in the remaining 302 patients of the study population who, at the time of this study, had received the drug in recommended doses for less than six years (mean cumulative dose of 255 g). SLE related changes, or non-specific changes such as senile retinal degeneration, cataracts,
myopic degeneration, chiasmatic syndrome, pigmented retinopathy, and Eales' disease were documented in 10 patients at some time during the frequent evaluations, but these changes were not attributable to hydroxychloroquine.

Discussion

Retinal toxicity was recognised as the main side effect of antimalarial agents in 1957, and since then more than 300 cases have been reported in the literature. The vast majority of these cases were related to chloroquine treatment, probably reflecting the relative use of chloroquine and the other antimalarial agents. Bernstein analysed thoroughly all cases designated as hydroxychloroquine induced retinopathy that were reported in the literature between 1960 and 1989, or reported to the Food and Drug Administration from 1975 to 1990. He found that 20 cases fulfilled validated criteria, but considered that only two of the 20 represented true hydroxychloroquine related retinopathy that was attributable to daily doses not exceeding the recommended dose of 6-5 mg/kg, in the absence of renal insufficiency. However, these two patients had taken the drug for 14 and 10 years, respectively.

Two additional cases of hydroxychloroquine related retinopathy were reported by Weiner et al., one had received excessive dosage (6-1-12-2 mg/kg/day for 10 years), and the other received a dose of 6-1 mg/kg/day over a 20 year period, with a cumulative dose of 2920 g. Whether the cumulative dose, rather than a greater daily dose, is important in determining overdosage, toxicity, or both, remains controversial. Nevertheless, according to Wallace, and to the best of our own knowledge, irreversible retinal changes in patients with normal renal function, taking hydroxychloroquine in recommended doses for less than 10 years, have not been reported previously.

The two cases of hydroxychloroquine retinopathy among 58 long term treated patients (3-5%) represent a substantial prevalence that is clearly greater than that reported in other studies. The difficulty in avoiding exposure to the sun in Greece may represent an additional risk factor that contributed to the retinal toxic effect of hydroxychloroquine in our patients. At present, it remains unclear why such cases have not been reported in other areas with a particularly sunny climate. Unknown factors, including unusual enzymatic deficiencies analogous to glucose-6-phosphate dehydrogenase deficiency, may predispose Greek patients to toxicity.

Our finding of no case of retinal toxicity in our patients during the first six years of hydroxychloroquine treatment is in accordance with other reports, suggesting that frequent and meticulous ophthalmological assessment of patients receiving hydroxychloroquine is not necessary during the first years of treatment. However, we disagree with Bernstein's conclusion that no risk of retinopathy exists during the first 10 years of hydroxychloroquine treatment in recommended doses. In view of the irreversible cases of retinopathy reported above, prolonged use of this drug should be accompanied by mandatory ophthalmological evaluation at least two or three times a year, even if the daily dose is maintained at less than 6-5 mg/kg.

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