Objective: To review the natural history and ocular and systemic adverse effects of patients taking hydroxychloroquine sulfate who attended an ophthalmic screening program.

Design: Retrospective study.

Results: Records of 262 patients who were taking hydroxychloroquine and screened in the Department of Ophthalmology were reviewed. Of the 262 patients, 14 (18%) of 76 who had stopped treatment at the time of the study experienced documented adverse effects. Systemic adverse effects occurred in 8 patients (10.5%) and ocular adverse effects, in 5 (6.5%). Thirty-five patients (13.4%) had visual field abnormalities, which were attributed to hydroxychloroquine treatment in 4 patients (1.5%). Three of the 4 patients were taking less than 6.5 mg/kg per day and all patients had normal renal and liver function test results.

Conclusions: The current study used a protocol of visual acuity and color vision assessment, funduscopy, and Humphrey 10-2 visual field testing and shows that visual field defects appeared before any corresponding changes in any other tested clinical parameters; the defects were reproducible and the test parameters were reliable. Patients taking hydroxychloroquine can demonstrate a toxic reaction in the retina despite the absence of known risk factors. Screening, including Humphrey 10-2 visual field assessment, is recommended 2 years after the initial baseline and yearly thereafter.

Arch Ophthalmol. 2006;124:1729-1733

HYDROXYCHLOROQUINE SULFATE, like chloroquine, is a 4-aminoquinoline compound.1 Alexander Surrey and Henry Hammer synthesized hydroxychloroquine in 1946.2 The first case of hydroxychloroquine retinopathy was described by Braun-Vallon in 1963.3 Screening programs have been developed to minimize the toxic effects of hydroxychloroquine. This article retrospectively reviews the demographic and clinical characteristics of all patients attending such a program over a 10-year period at the tertiary hospital in Christchurch, New Zealand.

METHODS

A database of all patients attending the hydroxychloroquine screening program at Christchurch Hospital was examined for the years 1990 to 2000. All patients who start taking hydroxychloroquine are routinely referred to the Department of Ophthalmology. All patients were examined yearly during the follow-up interval, and this included a Humphrey visual field assessment. The follow-up interval for patients in this retrospective analysis was variable during the 10-year period of observation; the median follow-up for the population was 2.7 years.

The following data were extracted: patient demographics; the number that discontinued treatment and the reasons; visual acuity at the first and last visit; funduscopy results; color vision assessment (Ishihara test) results; analysis of all visual field assessments; concurrent medical problems; other medications that were used by the patients; and renal and liver function. None of the patients had taken chloroquine during the course of treatment.

Diagnosis of a toxic reaction was based on assessment of visual field findings according to the criteria outlined by Bernstein,3 where acceptance of a case as a valid retinopathy requires as a minimum the presence and persistence of central or paracentral visual field scotomas to suprathreshold white stimuli and a duration of treatment of at least 9 months with a daily dose of hydroxychloroquine sulfate of 400 mg or less. Test criteria were chosen on the basis of the analysis conducted by Bernstein3 of all published cases of retinopathy attributed to hydroxychloroquine by the Food and Drug Administration.

Perimetric assessment was performed on the 10-2 Humphrey Visual Field Analyzer (Humphrey Instruments Inc, San Leandro, Calif). Assessment of abnormal visual field results was based on the following criteria: paracentral points were considered defective when their threshold on the total deviation plot had a less than \( P < .01 \) chance of being normal and were therefore marked with a solid black box on StatPac 1 of the Humphrey perimeter. A sco-
 RESULTS

Of 275 patients screened over the 10-year period, 13 were excluded: 11 because of insufficient data; 1, for an intentional overdose of a combination of drugs in addition to hydroxychloroquine; and 1, for discontinuing drug treatment before his follow-up appointment. Therefore, the study population included 262 patients.

The median age of the population was 55 years, and the highest frequency distribution was in the age group 71 to 80 years (56 patients [20%]) (Figure 1). Of the total population, 207 (79%) were female and 55 (21%) were male. The median duration of treatment was 2.7 years. The most frequent diagnoses were rheumatoid arthritis and systemic lupus erythematosus, together affecting 81.6% of the total population.

Of the 262 patients taking hydroxychloroquine, 76 patients (29%) had stopped treatment at the time of the study. Of the 12 patients who had cumulative doses greater than 700 g and of the 71 patients 70 years and older, only 1 patient in each category developed a toxic reaction in the retina to hydroxychloroquine. A comparison between drug cumulative dose and duration of treatment between different populations is summarized in Table 1.

Of the population that discontinued treatment during follow-up, 46 (68%) were diagnosed with rheumatoid arthritis and 8 (12%) with systemic lupus erythematosus. Remission occurred in 12 patients (26%) with rheumatoid arthritis and in 4 patients (50%) with systemic lupus erythematosus. Relapse requiring discontinuation of the hydroxychloroquine treatment and the addition of another anti-inflammatory or an immunosuppressive agent occurred in 12 patients (26%) with rheumatoid arthritis and zero patients with systemic lupus erythematosus.

Nonocular adverse effects occurred in 4 patients (6%). Of the systemic adverse effects, gastrointestinal effects were the most common, diarrhea occurred in 2 (3%), mucous membrane ulcer occurred in 1 (1.5%), and tinnitus, in 1 (1.5%). Eight patients stopped treatment prior to the ocular examination: 4 patients (0.5%) developed nonocular adverse effects; 2, a rash; 1, diarrhea; and 1, headache. Two patients (0.2%) were undergoing only 6 weeks of treatment for dermatological problems. One patient stopped treatment because of remission of rheumatoid arthritis and 1 patient, because of relapse of systemic lupus erythematosus. Another patient did not attend follow-up.

Visual field abnormalities occurred in 35 patients. Five patients developed hydroxychloroquine ocular adverse effects, of which 4 were visual field defects (Table 2) and 1 was significant vortex keratopathy.

Table 1. Comparison of Hydroxychloroquine Cumulative Dose and Treatment Duration Between Different Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Sample Size</th>
<th>Cumulative Dose, g.* Mean (Range)</th>
<th>Duration of Treatment, d, Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who stopped treatment</td>
<td>76</td>
<td>228 (8.4-1206)</td>
<td>986 (30-3287)</td>
</tr>
<tr>
<td>Because of adverse effects</td>
<td>13</td>
<td>273 (9.8-1206)</td>
<td>2.3 (0.08-8.3)</td>
</tr>
<tr>
<td>Ocular adverse effects</td>
<td>5</td>
<td>468.9 (158-1206)</td>
<td>1522 (426-3014)</td>
</tr>
<tr>
<td>Systemic adverse effects</td>
<td>8</td>
<td>121.5 (12.4-304.4)</td>
<td>376.1 (61-789)</td>
</tr>
<tr>
<td>Because they achieved remission</td>
<td>25</td>
<td>233 (9-529)</td>
<td>3 (0.2-9)</td>
</tr>
<tr>
<td>Population still receiving treatment</td>
<td>186</td>
<td>333.5 (0.05-2278)</td>
<td>3.7 (0.07-25.5)</td>
</tr>
</tbody>
</table>

*Given as hydroxychloroquine sulfate.

Table 2. Frequency Distribution of the Causes of Visual Field Abnormalities in the Population

<table>
<thead>
<tr>
<th>Cause of Visual Field Abnormality</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenticular opacities</td>
<td>13 (4.9)</td>
</tr>
<tr>
<td>Unreliable field test results (patient inattentiveness)</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td>Hydroxychloroquine sulfate</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Retinal vascular occlusion</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Trauma/iatrogenic</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Age-related macular degeneration</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Optic disc pit</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

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None of these patients developed visual symptoms, changes in visual acuity, or fundus abnormalities resulting from drug toxic effects nor did they have any color vision defects. All had normal liver and renal function test results during the period of observation. Another 31 patients had visual field defects that were due to other causes, the most common being second-ary to lenticular opacities (Table 3).

The prevalence of ocular toxic effects was 1.9% (95% confidence interval, 2.2-1.6). In the 4 patients with visual field defects, the median age was 51 years, the median duration of treatment was 3.5 years, and the median cumulative dose of hydroxychloroquine sulfate was 328.4 g. Treatment was stopped in this group after a minimum of 2 abnormal visual field test results. An example of the abnormal field test results is shown in Figure 2.

Screening program algorithms are based on known risk factors and the natural history of the disease. The visual field loss with hydroxychloroquine may be permanent, and therefore, it is desirable to detect it before it becomes symptomatic. The issues are who should be screened, how often should the screening occur, and what are the most sensitive methods with which to screen. The current study shows that visual field defects appeared before any corresponding changes in any other tested clinical parameters; the defects were reproducible, and the test parameters were reliable.

Many authors have constructed recommendations for screening. One theme is that retinopathy is highly unlikely if the daily dose of hydroxychloroquine sulfate is less than 6.5 mg/kg and renal function is normal.3,7 For these patients, screening is suggested at baseline and then after 3 years,8 5 or 10 years,7,9 not at all,10-12 or only by an ophthalmologist if there is a problem.13

Bienfang et al14 offer an alternative view, stating that there are 13 cases of retinopathy in the literature where the daily hydroxychloroquine sulfate dose was less than 6.5 mg/kg. Easterbrook15 states that there are 14 such cases but that there are no cases where the retinopathy occurred with less than 2 years of treatment. Both Easterbrook15 and Bernstein3 recommend approximately annual screening.

Screening methods include assessment of visual acuity and color vision, funduscopy, Amsler grids, and visual field testing. The current study used a protocol of visual acuity and color field assessment, funduscopy, and Humphrey 10-2 visual field testing. We detected significant reproducible visual field defects in 4 of 262 patients, which is much more common than other studies. However, none of our patients was symptomatic, none had color vision defects,
and all had a visual acuity of 6/9 or better. This suggests that visual field defects of these patients were detected very early and may reflect the ability of the visual field assessment to detect subtle defects.16

All 4 patients had been receiving treatment for less than 5 years (2.6, 2.8, 4.2, and 4.4 years) and 3 of 4 patients had been taking doses of less than 6.5 mg/kg per day (2.9, 3.6, 3.8, and 8.0 mg/kg per day). All 4 patients developed their visual field defects within the 1-year gap between visual field tests. Data from the cases referred to by Easterbrook15 and Bienfang et al14 are incomplete but suggest a similar time frame in the development of the retinopathy. Annual screening for high-risk patients and a screening frequency stratified according to age has recently been recommended by the American Academy of Ophthalmology.17

Based on data from Bienfang et al,14 Easterbrook,15 Bernstein,3 and the patients in this article, we recommend the following screening guidelines: (1) Baseline observations should be logged. (2) Screening should start 2 years later and be annual thereafter irrespective of the dose of hydroxychloroquine. (3) Other risk factors such as impaired renal or liver function should be considered and may increase the follow-up frequency.

Submitted for Publication: December 5, 2005; final revision received August 5, 2005; accepted August 14, 2006.

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Financial Disclosure: None reported.

REFERENCES