Visual Loss in Patients With Cytomegalovirus Retinitis and Acquired Immunodeficiency Syndrome Before Widespread Availability of Highly Active Antiretroviral Therapy

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Objective: To evaluate rates and causes of visual loss among patients with acquired immunodeficiency syndrome (AIDS) and cytomegalovirus (CMV) retinitis before widespread availability of highly active antiretroviral therapy (HAART).

Methods: Data from 681 patients with AIDS and newly diagnosed or relapsed CMV retinitis who enrolled in 3 clinical trials conducted by the Studies of Ocular Complications of AIDS (SOCA) Research Group (between 1990 and 1996) were combined to evaluate the rates and causes of visual loss. Visual acuity and visual field (Goldmann visual fields) losses were evaluated.

Results: The rates of visual loss in eyes with CMV retinitis were substantial in all 3 clinical trials, ranging from 51.7 to 97.7 events per 100 eye-years for loss of visual acuity to worse than 20/40 and 18.9 to 49.1 events per 100 eye-years for loss of visual acuity to 20/200 or worse. The 2 major causes of visual loss were retinitis, involving either the macula or the optic nerve, and retinal detachment. After 1992, visual outcomes improved significantly. Antiretroviral therapy was associated with a 30% reduction in the risk of visual acuity loss (relative risk, 0.70; \( P = .02 \))

Conclusions: In the pre-HAART era, visual morbidity was substantial. However, there was a secular trend for improved outcomes. The principal causes of visual loss were CMV involvement of the posterior retina and retinal detachment.


Prior to the advent of highly active antiretroviral therapy (HAART), cytomegalovirus (CMV) retinitis was estimated to affect 30% of people with acquired immunodeficiency syndrome (AIDS) at some point during their shortened lifetimes and was associated with high rates of visual loss. More recently, the incidence of CMV retinitis has decreased by 55% to 95%, with current estimates of the incidence at 25% of the rates seen in the early 1990s, presumably because of the widespread use of HAART and the attendant improvement in immune function. Data from 3 clinical trials were evaluated for information on the rates, secular trends, and causes of visual loss before the widespread availability of HAART. These data provide a comparative base to evaluate the changes in both the rates and causes of visual loss among patients with CMV retinitis that have occurred with improvements in therapy for human immunodeficiency virus (HIV), ie, HAART. Historical comparisons will be important for such evaluations because clinical trials may not be feasible or ethical. Furthermore, patients with CMV retinitis who fail to respond to HAART or develop resistant virus after responding may be expected to experience visual loss, much like the group, described here.

Data were analyzed from 3 completed clinical trials conducted by the Studies of Ocular Complications of AIDS (SOCA) Research Group: the Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial (FGCRT), the Cytomegalovirus Retinitis Retreatment Trial (CRRT), and the Monoclonal Antibody Cytomegalovirus Retinitis Trial (MACRT). Patients with either newly diagnosed retinitis or relapsed retinitis enrolled in these trials during 7 years (1990 through 1996). The first 2 trials were completed before the introduction of HAART. The third trial was conducted just as HAART was introduced outside clinical trials but before its widespread use.
PATIENT CHARACTERISTICS

Baseline characteristics of patients enrolled in the 3 trials are presented in Table 1, and ocular characteristics of eyes with retinitis at baseline are presented in Table 2. Two hundred thirty-four patients with newly diagnosed CMV retinitis were enrolled in the FGCRT; 279 patients with relapsed retinitis were enrolled in the CRRT; and 209 patients were enrolled in the MACRT, of whom 83 patients had newly diagnosed retinitis and

The protocols for each of the 3 trials were reviewed and approved by institutional review boards at the coordinating center and at each participating clinical center; each patient signed an institutional review board–approved consent statement.

In the FGCRT, patients with AIDS and newly diagnosed CMV retinitis were enrolled and followed at 11 clinical centers. Patients were assigned randomly to treatment with either intravenous (IV) foscarnet sodium or IV ganciclovir sodium. The treatment protocol was suspended in October 1991 because of an excess of mortality among patients assigned to ganciclovir; visual outcomes were similar between the two groups.7,8

In the CRRT, patients with AIDS and relapsed CMV retinitis were enrolled; relapsed retinitis was defined as CMV retinitis that had reactivated or that had remained active after at least 1 month of treatment with either IV foscarnet or IV ganciclovir. Patients were enrolled at 12 clinical centers and were assigned randomly to treatment with either high-dose IV foscarnet sodium (90 mg/kg twice daily for the 2-week induction period and 120 mg/kg once daily for maintenance), high-dose IV ganciclovir sodium (5 mg/kg twice daily for the 2-week induction period and 10 mg/kg once daily for maintenance), or both drugs at standard doses. The treatment protocol was suspended in April 1995 owing to differences in time to retinitis progression and visual field loss among the treatment groups. Combination therapy was more effective at controlling retinitis and preserving visual field than either monotherapy.7,8

In the MACRT, patients with AIDS and active CMV retinitis, either newly diagnosed or relapsed, were eligible for enrollment. Patients at 15 clinical centers were assigned randomly to receive adjuvant treatment with either MSL-109, a monoclonal antibody to CMV, or placebo. Patients also received primary treatment for CMV retinitis, eg, IV ganciclovir, IV foscarnet, oral ganciclovir, the ganciclovir implant, IV cidofovir, and/or intravitreal injections of these drugs according to the best medical judgment of the treating physician. For the MACRT, initial treatment for CMV retinitis was defined as the primary therapy recorded at the baseline visit. The treatment protocol was suspended in August 1996 because of a lack of evidence for the efficacy of MSL-109 to control retinitis and a higher rate of mortality among relapsed patients assigned to MSL-109.10

For all 3 trials, study visits were scheduled at baseline and at least once per month for the first 6 months of follow-up. In the FGCRT and CRRT, study visits were scheduled every 2 and 3 months after 6 months, respectively, and in the MACRT visits were monthly for the first year of follow-up. Best-corrected visual acuity assessment, indirect ophthalmoscopic examination, and retinal photography were required at every study visit. Best-corrected visual acuity was measured with logarithmic visual acuity charts.11 The photography protocol used for all the trials specified 8 nonstereoscopic fields and a stereoscopic pair of the optic disc and macula for each eye.11 Fundus photographs were evaluated at the Fundus Photograph Reading Center, University of Wisconsin, Madison.11 The standard definition of retinal zones was used.14

Visual fields were assessed by standard procedures at baseline and after 1 (FGCRT only), 3, 6, 8, or 9, and 12 months by kinetic perimetry along 12 meridians on Goldmann perimeters with a IV-e test object; the degrees of field perceived along each meridian were summed to calculate the visual field score.15 The median scores for total degrees of field in eyes not involved with CMV retinitis at baseline ranged from 715 to 719 for each of the 3 trials.

In all 3 trials, follow-up was continued until either death or a common study close out date. Data collected at all study visits, including long-term follow-up visits conducted after the treat-
126 had relapsed retinitis. These analyses include data from 94% to 96% of patients enrolled in these trials, i.e., those patients for whom data on visual function at baseline and at least one follow-up visit were available. Five patients with unilateral disease enrolled in the FGCRT subsequently enrolled in the CRRT, and 3 patients enrolled in the CRRT, 1 with unilateral disease and 2 with bilateral disease, subsequently enrolled in the MACRT. These 8 patients were included in the analyses for each trial in which they were enrolled.

Median follow-up time for visual acuity outcomes ranged from a median of 5.9 months for the CRRT (range, 0.5-28 months) and MACRT (range, 0.6-13 months) to 7.4 months for the FGCRT (range, 0-24 months). The mortality rates in all trials were high: 0.94 deaths per person-year in the FGCRT, 0.96 deaths per person-year in the CRRT, and 0.94 deaths per person-year in the MACRT.
person-year in the CRRT, and 0.48 deaths per person-year in the MACRT.

Most patients enrolled in the 3 trials were men between the ages of 32 and 44 years. Proportionately more whites and former or current injecting drug users were enrolled in the first trial, the FGCRT (Table 1). Patients enrolled in the FGCRT also reported more opportunistic infections and had a higher mean Karnofsky score at baseline. Newly diagnosed patients were less likely to report extraocular CMV disease than patients with relapsed retinitis. As was expected, antiretroviral regimens were different among the 3 trials. Only patients in the MACRT were receiving HAART at baseline. Patients enrolled in the first 2 trials were assigned to an anti-

### Table 2. Characteristics of Eyes at Baseline*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FGCRT (n = 468 eyes)</th>
<th>CRRT (n = 520 eyes)</th>
<th>MACRT (n = 238 eyes)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV retinitis at baseline</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Location†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foveal avascular zone involved</td>
<td>4.0</td>
<td>7.0</td>
<td>4.8</td>
<td>.39</td>
</tr>
<tr>
<td>Optic disc involved</td>
<td>8.9</td>
<td>6.2</td>
<td>8.7</td>
<td>.001</td>
</tr>
<tr>
<td>Other zone 1 involvement</td>
<td>37.5</td>
<td>41.7</td>
<td>28.9</td>
<td>.12</td>
</tr>
<tr>
<td>Any zone 1 involvement</td>
<td>49.3</td>
<td>53.3</td>
<td>39.4</td>
<td>.08</td>
</tr>
<tr>
<td>Extent of retinitis†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of involved eyes</td>
<td>326</td>
<td>345</td>
<td>96</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Percentage of retina involved, zone 1 or 2, median (IQR)§</td>
<td>9.0 (2.3, 20.0)</td>
<td>20.6 (10.3, 39.6)</td>
<td>8.8 (2.0, 34.2)</td>
<td>19.2 (9.6, 34.6)</td>
</tr>
<tr>
<td>Retinal detachment‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current detachment</td>
<td>4.1</td>
<td>7.3</td>
<td>2.8</td>
<td>.12</td>
</tr>
<tr>
<td>History of detachment</td>
<td>2.6</td>
<td>6.6</td>
<td>0.9</td>
<td>.008</td>
</tr>
<tr>
<td>Either</td>
<td>4.4</td>
<td>12.0</td>
<td>2.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visual acuity‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of eyes</td>
<td>459</td>
<td>520</td>
<td>151</td>
<td>.006</td>
</tr>
<tr>
<td>No. of standard letters, median (IQR)§</td>
<td>84 (78, 88)</td>
<td>82 (71, 88)</td>
<td>85 (80, 89)</td>
<td>85 (75, 90)</td>
</tr>
<tr>
<td>20/40 or better</td>
<td>85.0</td>
<td>76.4</td>
<td>87.4</td>
<td>79.4</td>
</tr>
<tr>
<td>20/200 or worse</td>
<td>3.8</td>
<td>6.9</td>
<td>3.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Visual field‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of eyes</td>
<td>440</td>
<td>513</td>
<td>149</td>
<td>236</td>
</tr>
<tr>
<td>Degree of visual field, median (IQR)§</td>
<td>648 (568, 708)</td>
<td>568 (380, 678)</td>
<td>666 (553, 728)</td>
<td>597 (467, 677)</td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; CRRT, Cytomegalovirus Retinitis Retreatment Trial; FGCRT, Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial; IQR, interquartile range; MACRT, Monoclonal Antibody Cytomegalovirus Retinitis Trial.

*P values were derived from logistic regression models for binary variables and from linear regression for continuous variables; variance was adjusted for 2 eyes from the same patient.

‡For eyes with retinitis at baseline.

§Ranks of data were analyzed in a linear regression model.

### Table 3. Rate of Visual Acuity Loss

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>FGCRT Newly Diagnosed Retinitis (n = 372)</th>
<th>CRRT Relapsed Retinitis (n = 260)</th>
<th>MACRT Newly Diagnosed Retinitis (n = 135)</th>
<th>MACRT Relapsed Retinitis (n = 89)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse than 20/40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All eyes</td>
<td>69.8 (157/225)</td>
<td>72.0 (158/225)</td>
<td>37.5 (24/65)</td>
<td>61.2 (54/89)</td>
<td>.03</td>
</tr>
<tr>
<td>Involved</td>
<td>93.8 (134/260)</td>
<td>97.7 (150/257)</td>
<td>51.7 (21/41)</td>
<td>80.6 (52/64)</td>
<td>.04</td>
</tr>
<tr>
<td>Not involved</td>
<td>22.3 (111/225)</td>
<td>12.2 (8/67)</td>
<td>12.9 (3/24)</td>
<td>8.5 (2/24)</td>
<td>.07</td>
</tr>
<tr>
<td>Better eye‡</td>
<td>34.9 (52/215)</td>
<td>39.8 (58/247)</td>
<td>17.2 (6/70)</td>
<td>20.8 (12/62)</td>
<td>.02</td>
</tr>
<tr>
<td>20/200 or worse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All eyes</td>
<td>35.4 (100/282)</td>
<td>37.4 (107/284)</td>
<td>14.0 (10/148)</td>
<td>23.5 (26/112)</td>
<td>.003</td>
</tr>
<tr>
<td>Involved</td>
<td>49.1 (95/190)</td>
<td>47.4 (103/216)</td>
<td>18.3 (9/52)</td>
<td>29.4 (25/87)</td>
<td>.004</td>
</tr>
<tr>
<td>Not involved</td>
<td>5.6 (5/114)</td>
<td>5.8 (4/94)</td>
<td>4.2 (1/46)</td>
<td>4.4 (1/46)</td>
<td>.98</td>
</tr>
<tr>
<td>Better eye‡</td>
<td>11.8 (19/220)</td>
<td>14.8 (24/161)</td>
<td>10.2 (7/71)</td>
<td>6.6 (4/61)</td>
<td>.33</td>
</tr>
</tbody>
</table>

Abbreviations: CRRT, Cytomegalovirus Retinitis Retreatment Trial; FGCRT, Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial; MACRT, Monoclonal Antibody Cytomegalovirus Retinitis Trial.

*P values were derived from Poisson regression models with adjustment for 2 eyes from the same patient.

†The better eye for the patient at each visit was used for the assessment of events; rates are events per 100 person-years.
CMV treatment. Patients enrolled in the MACRT had their primary anti-CMV treatment selected by their physicians and were most likely to receive IV ganciclovir as the primary treatment for CMV retinitis at baseline.

Patients with newly diagnosed retinitis were less likely to have bilateral retinitis (P = .004) and more likely to have blood and/or urine cultures positive for CMV than were patients with relapsed retinitis (Table 1). Among patients with relapsed retinitis, those enrolled in the CRRT had fewer reported relapses of CMV retinitis and less time from the diagnosis of CMV retinitis than those enrolled in the MACRT.

Characteristics of eyes at baseline were similar across the 3 trials (Table 2). Eyes of patients with relapsed disease had a greater area of retina involved with retinitis and more impaired visual function at baseline.

### RATES OF VISUAL LOSS

The rates of loss of visual acuity (to a visual acuity worse than 20/40 or to one of 20/200 or worse) in all eyes and subsets of eyes are presented in Table 3. In all groups of patients, the rates of visual acuity loss in eyes involved with CMV retinitis were substantial, ranging from 51.7 to 97.7 events per 100 eye-years for a loss to worse than 20/40 and from 18.9 to 49.1 events per 100 eye-years for a loss to 20/200 or worse. The rates of loss in eyes with retinitis at baseline were different among the 4 groups. Although similar rates were observed in the first 2 trials (FGCRT and CRRT), the rates in the third trial (MACRT) were lower in both newly diagnosed and relapsed patients (Table 3). Although in the MACRT, the rates of loss to worse than 20/40 in involved eyes tended to be greater in eyes of patients with relapsed retinitis, the difference was not significant (P = .06). Rates of loss in the better eye estimate the visual acuity loss that patients experience. Between 30% and 40% of patients had a loss of visual acuity to worse than 20/40 in their better eye during the first year of follow-up in the FGCRT and CRRT, whereas only about 20% of patients enrolled in the MACRT experienced such a loss; no difference by stage of disease was observed (P = .68).

The secular trend for rates of loss of visual field (Table 4) was similar to the trend for the rates of visual acuity loss. The rates of loss in eyes with retinitis at baseline were higher in the first 2 trials compared with rates in eyes of newly diagnosed or relapsed patients enrolled in the MACRT. However, no difference in rates of visual field loss were observed by stage of disease (P = .22 for 50% loss; P = .38 for 90% loss).

### CAUSES AND PREDICTORS OF VISUAL ACUITY LOSS

The ocular findings associated with most occurrences of visual acuity loss in all 3 trials were destruction of the retinal tissue at the posterior pole of the eye (ranging from 54% to 84% of cases across the 3 trials) and retinal detachment (ranging from 26% to 63% of cases). In the MACRT, retinal detachment was associated with 63% of the occurrences of visual acuity decline to 20/200 or worse, whereas it was associated with 45% and 36% of the occurrences in the CRRT and FGCRT, respectively (P = .01). In the other 2 trials, zone 1 involvement was associated more frequently with decline in visual acuity to 20/200 or worse than retinal detachment (81% and 84% of cases in the FGCRT and CRRT, respectively, vs 54% of cases in the MACRT). In any one trial, other causes of visual loss, such as vitreitis, hypotony, epiretinal membranes, or macular edema, were infrequent (less than 5% of cases) or not seen.

In univariate analysis, the baseline ocular characteristics associated with increased risk of visual acuity loss to worse than 20/40 included presence of CMV retinitis, measures of zone 1 involvement with CMV retinitis, retinal detachment, and visual function (Table 5). In a multivariate model, the baseline ocular characteristics associated independently with increased risk of visual acuity loss were involvement with CMV retinitis, current or past
Table 5. Baseline Characteristics Associated With Visual Acuity Loss to Worse Than 20/40

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted* RR (95% CI)</th>
<th>P Value</th>
<th>Multivariate† RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV retinitis</td>
<td>5.1 (3.6-7.2)</td>
<td>&lt;.001</td>
<td>2.3 (1.6-3.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Retinal detachment or history of repair</td>
<td>4.5 (2.6-7.7)</td>
<td>&lt;.001</td>
<td>2.7 (1.6-3.5)</td>
<td>.002</td>
</tr>
<tr>
<td>Zone 1 involvement</td>
<td>2.9 (2.3-3.6)</td>
<td>&lt;.001</td>
<td>1.5 (1.1-1.9)</td>
<td>.008</td>
</tr>
<tr>
<td>Foveal avascular zone involvement</td>
<td>2.7 (1.7-4.5)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic nerve involvement</td>
<td>4.0 (1.3-12.5)</td>
<td>.02</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Visual acuity, 1 less line on chart</td>
<td>1.6 (1.5-1.7)</td>
<td>&lt;.001</td>
<td>1.3 (1.2-1.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visual field loss of 100*</td>
<td>1.7 (1.6-1.8)</td>
<td>&lt;.001</td>
<td>1.4 (1.2-1.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Relapsed retinitis stage</td>
<td>1.1 (0.9-1.3)</td>
<td>.36</td>
<td>1.1 (0.7-1.7)</td>
<td>.78</td>
</tr>
<tr>
<td>CD4+ T cells/µL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>1.5 (1.1-2.1)</td>
<td></td>
<td>1.7 (1.2-2.4)</td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>1.8 (1.3-2.5)</td>
<td></td>
<td>2.1 (1.5-3.1)</td>
<td></td>
</tr>
<tr>
<td>10-19</td>
<td>1.3 (0.9-1.8)</td>
<td>.001</td>
<td>1.5 (1.1-2.1)</td>
<td>.004</td>
</tr>
<tr>
<td>≥20 (Reference group)</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level, g/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>1.3 (1.0-1.7)</td>
<td></td>
<td>1.4 (1.1-1.9)</td>
<td></td>
</tr>
<tr>
<td>10-10.9</td>
<td>1.3 (1.0-1.8)</td>
<td>.12</td>
<td>1.0 (0.7-1.4)</td>
<td>.05</td>
</tr>
<tr>
<td>11-11.9</td>
<td>1.1 (0.8-1.4)</td>
<td></td>
<td>1.1 (0.8-0.6)</td>
<td>.12</td>
</tr>
<tr>
<td>≥12 (Reference group)</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Any HIV therapy</td>
<td>0.7 (0.6-0.9)</td>
<td>.009</td>
<td>0.7 (0.6-0.9)</td>
<td>.02</td>
</tr>
<tr>
<td>Trial enrollment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGCRT (Reference group)</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>CRRT</td>
<td>1.0 (0.8-1.3)</td>
<td>.04</td>
<td>0.6 (0.3-1.0)</td>
<td>.05</td>
</tr>
<tr>
<td>MACRT</td>
<td>0.7 (0.6-1.0)</td>
<td></td>
<td>0.6 (0.4-0.9)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; CRRT, Cytomegalovirus Retinitis Treatment Trial; FGCRT, Foscarinet-Ganciclovir Cytomegalovirus Retinitis Trial; HIV, human immunodeficiency virus; MACRT, Monoclonal Antibody Cytomegalovirus Retinitis Trial; RR, relative risk.

*Relative risk, 95% CI for RR, and associated P value estimated from a proportional hazards model with adjustment for 2 eyes from the same patient.

†Relative risk, 95% CI for RR, and associated P value estimated from a proportional hazards model including all the listed covariates except foveal avascular zone involvement and optic nerve involvement and with adjustment for 2 eyes from the same patient. Ellipses indicate parameters were not estimated because the variable was not included in multivariate models.

Patient characteristics at baseline that were associated with increased risk of visual acuity loss after adjustment (presence of CMV retinitis, current or past retinal detachment, zone 1 involvement, visual acuity, visual field, trial enrollment, and stage of retinitis) were lower CD4+ T cell counts, lower hemoglobin levels, and the absence of antiretroviral treatment. The same set of risk factors was selected when the risk set was restricted to eyes with CMV retinitis involvement at baseline (data not shown).

Patient characteristics at baseline that were associated with increased risk of visual acuity loss after adjustment (presence of CMV retinitis, current or past retinal detachment, zone 1 involvement, visual acuity, visual field, trial enrollment, and stage of retinitis) were lower CD4+ T cell counts, lower hemoglobin levels, and the absence of antiretroviral treatment. The same set of risk factors was selected when the risk set was restricted to eyes with CMV retinitis involvement at baseline (data not shown).

Patients with CD4+ T cell counts less than 10/µL were at about twice the risk of visual acuity loss than those with counts of 20 or more. Similarly, patients with low hemoglobin levels (less than 10 g/dL) had a 40% increase in the risk of visual acuity loss. Patients who were receiving antiretroviral treatment at baseline had a 30% reduction in the risk of visual acuity loss during follow-up (Table 5). Baseline characteristics not independently associated with risk of visual acuity loss included initial drug treatment for CMV retinitis, stage of retinitis (newly diagnosed or relapsed), time since initial CMV diagnosis, diagnosis of extracocular CMV infection, initial anti-CMV therapy, filgrastim use, time since AIDS diagnosis, Karnofsky score, number of opportunistic infections, age, sex, racial/ethnic origin, or HIV risk group. A blood culture positive for CMV at baseline was predictive of subsequent visual acuity loss (adjusted relative risk, 1.7; P < .001) in the FGCRT and CRRT; a positive urine culture was not. Blood culture results were not included in the overall model because the procedure was not done in the MACRT.

The rate of visual acuity loss in the MACRT was reduced compared with the FGCRT; the difference remained after adjustment for other factors predictive of visual acuity loss (Table 5). This suggests a temporal trend toward improved visual outcomes despite longer survival in the last trial.8-10 In the unadjusted analysis, no increase in risk of loss of visual acuity was noted between the eyes of patients enrolled in the FGCRT compared with the risk for eyes of patients enrolled in the CRRT. However, in the adjusted analyses, in which extent and location of retinitis was taken into account, the risk of visual acuity loss was substantially reduced in the CRRT. This result demonstrated that the temporal trend toward decreasing rates of loss of visual acuity began before the MACRT.

Patients diagnosed with AIDS-related CMV retinitis before the widespread use of HAART experienced substantial visual loss despite ongoing anti-CMV treatment. In the earlier trials, the principal cause of severe visual acuity loss (to 20/200 or worse) was involvement of the
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macula or optic nerve. In the last trial, the principal cause of severe visual acuity loss was retinal detachment.

The data from these 3 SOCA trials have several strengths as a resource to examine the rates and causes of visual loss among treated patients. Data on characteristics of CMV retinitis and its sequelae as well as visual function were collected prospectively during 7 years with standardized procedures performed by trained personnel. Photographic data were available to document the location and extent of retinitis. However, there are limitations to the interpretations drawn from these data. Only a select group of patients were included, ie, those who enrolled in the 3 SOCA clinical trials. These patient were probably not a representative sample of all patients with CMV retinitis but did encompass a heterogenous mix of primary care and referral patients. The determination of ocular findings causing visual acuity loss was based on the judgment of the clinician as to the cause of vision loss. Finally, several comparisons were made, and some were likely to be significant due to chance alone.

We found substantial rates of visual morbidity, measured as loss of visual acuity and loss of visual field. Among eyes with CMV retinitis at baseline, there were 18.9 to 49.1 events of visual acuity loss to 20/200 or worse per 100 eye-years among the 3 trials. The rates of legal blindness (based on visual acuity loss to 20/200 or worse in their better eye) were 6.6 to 14.8 per 100 patient-years. Greater numbers of patients, 17.2 to 39.8 per 100 patient-years, experienced less severe but important loss of visual acuity to worse than 20/40 in their better eye.

The most common finding associated with visual loss in an involved eye was, as expected, retinitis involvement in zone 1, which includes the fovea and the optic nerve. The second most common cause was retinal detachment. In the third trial (MACRT), retinal detachment was the most common cause of visual acuity loss to 20/200 or worse. Better control of retinitis in the third trial may have reduced visual loss owing to zone 1 involvement, making retinal detachment a relatively more important cause of visual loss. This finding emphasizes the importance of early identification of risk factors for retinal detachment, such as retinitis in the periphery and extent of retinitis.20 Among the nonocular baseline variables examined, antiretroviral treatment and higher CD4+ T cell counts and hemoglobin levels, which are indicative of good response to antiretroviral treatment, were associated with better visual outcome.

After adjustment for baseline variables, both the CRRT and the MACRT showed significantly improved visual outcomes compared with the earlier FGCRT. New antiretroviral therapies and more aggressive use of these therapies does not completely explain the improved outcomes over time. Fewer patients in the CRRT were receiving any antiretroviral therapy than in FGCRT, yet the adjusted risk of visual loss was significantly less in the CRRT. Further, the improved visual outcomes in the second 2 trials persisted after statistical adjustment for antiretroviral therapy and CD4+ T cell count. Multiple factors may be responsible for this improvement. The availability of hematopoietic factors, such as filgrastim, allowed many patients to continue anti-CMV and antiretroviral therapy despite drug-induced bone marrow suppression. Simultaneously, new and changing treatment options for CMV retinitis became available, allowing physicians to customize therapies and to combine treatments. Among the new treatments, the ganciclovir implant extended the relapse-free interval21; however, that effect may not translate into better visual outcomes. Changing drugs in patients with resistant CMV22 and combination therapies in patients with relapsed disease9 can improve control of retinitis and decrease rates of retinal destruction. These new options were particularly helpful for the treatment of patients with relapsed retinitis and those with adverse or toxic reactions to 1 or more agents.

Patients developing CMV retinitis after the introduction of HAART have similar clinical characteristics and immunologic function as these patients.23 Hence, the risk factors for and causes of vision loss identified in this report are likely to be applicable to patients diagnosed with CMV retinitis now. However, patients diagnosed now are also faced with new threats to vision such as the vision-threatening inflammatory response occurring in some patients with CMV retinitis after institution of HAART, known as immune recovery uveitis.25-27 Immune recovery uveitis can lead to reduced vision by causing cystoid macular edema, vitreitis, or epiretinal membrane formation, all rare causes of vision loss in these series. These results provide a context in which to evaluate our progress in the treatment of CMV retinitis. Future analyses of HIV-positive patients will assess how changes in the management of both CMV and HIV will influence visual outcomes.

Submitted for publication March 19, 2002; final revision received July 15, 2002; accepted September 23, 2002.

This study was supported by the National Eye Institute, National Institutes of Health (Bethesda, Md) through cooperative agreements U10 EY 08057, 1 R03 EY 10731-01, and NRSA EY 07127 (Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Md); U10 EY 08052 (School of Medicine, Johns Hopkins University); and U10 EY 08067 (University of Wisconsin School of Medicine). Additional support was provided by the National Center for Research Resources, National Institutes of Health, through General Clinical Research Center grants 5M01 RR 00350 (Baylor College of Medicine, Houston, Tex); 5M01 RR 00035 and 5M01 RR 00722 (John Hopkins University); 5M01 RR 05096 (Louisiana State University/Tulane University, New Orleans, La); 5M01 RR 00071 (Mount Sinai Medical Center, New York, NY); 5M01 RR 00047 (New York Hospital–Cornell Medical Center, New York); 5M01 RR 00096 (New York University, New York); 5M01 RR 00048 (Northwestern University, Evanston, Ill); 5M01 RR 00865 (University of California, Los Angeles); 5M01 RR 00083 (University of California, San Francisco); 5M01 RR 05280 (University of Miami, Miami, Fla); and 5M01 RR 00046 (University of North Carolina, Chapel Hill). Support was also provided by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, through cooperative agreements U01 AI 27668 (Johns Hopkins University); U01 AI 27674 (Louisiana State University/Tulane University); U01 AI 27669 (Memorial Sloan-Kettering Cancer Center, New York) and U01 AI 25917 (New York Hospital–Cornell Medical Center); U01 AI 27667
(Mount Sinai Medical Center); U01 AI 27665 (New York University); U01 AI 25915 (Northwestern University); U01 AI 27660 (University of California, Los Angeles); U01 AI 27670 (University of California, San Diego); U01 AI 27663 (University of California, San Francisco); and U01 AI 25868 (University of North Carolina). Funding was also provided by Astra Pharmaceutical Products, Inc (Westborough, Mass), and Protein Design Laboratories, Inc (Fremont, Calif). Drugs were provided by Amgen Inc (Thousand Oaks, Calif), Astra Pharmaceutical Products, Inc, Bristol-Myers Squibb Co (New York), Burroughs Wellcome Co (Research Triangle Park, NC), Syntex Research (Palo Alto, Calif), and Protein Design Laboratories, Inc. Dr Jabs is a recipient of a Senior Scientific Investigator Award from Research to Prevent Blindness, Inc, New York.

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