Risk Factors for Advancement of Cytomegalovirus Retinitis in Patients With Acquired Immunodeficiency Syndrome

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Objective: To identify ocular and systemic factors that predict advancement of cytomegalovirus (CMV) retinitis during treatment.

Methods: Patients with acquired immunodeficiency syndrome were enrolled in a multicenter clinical trial designed to evaluate foscarnet sodium and ganciclovir sodium as therapy for newly diagnosed CMV retinitis. Ocular characteristics at baseline and measurements of retinitis were assessed from fundus photographs by graders at a fundus photograph reading center. The following measures of advancement were assessed: (1) lesion border movement of at least 750 µm or development of a new lesion in involved eyes; (2) rate of increase in retinal area with CMV in involved eyes; and (3) development of retinitis in uninvolved eyes of patients with unilateral disease at baseline.

Results: In eyes with retinitis, risk factors at baseline for advancement while receiving treatment included smaller area involved, active margins of retinitis, and posterior location. Risk factors for development of retinitis in uninvolved fellow eyes included blood and urine cultures positive for CMV and lower CD8⁺ T-lymphocyte count.

Conclusions: Lesion characteristics can be used to predict advancement of preexisting disease, whereas only systemic factors are associated with development of bilateral disease. These analyses describe retinitis activity before the introduction of potent antiretroviral therapies but provide an important reference point for patients in whom CMV retinitis develops after failure or intolerance of antiretroviral agents.

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Beneficial effects of therapy for cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) have been identified in several clinical trials. However, little information has been published on factors that might predict early progression or more rapid spread of retinitis during therapy. Identification of risk factors for early enlargement of existing lesions or development of a new lesion in uninvolved eyes might assist in planning examination schedules and treatment regimens for individual patients.

The Foscarnet-Ganciclovir CMV Retinitis Trial (FGCRT) was designed to compare the safety and efficacy of intravenous foscarnet sodium and ganciclovir sodium for treatment of newly diagnosed retinitis. The protocol for the trial was suspended in 1991 due to excess mortality among patients assigned to ganciclovir, but no difference in retinitis progression or visual outcomes was noted between patients assigned to foscarnet and those assigned to ganciclovir. Previously reported patient characteristics associated with greater risk of retinitis progression in this study included lower CD4⁺ T-lymphocyte counts, blood cultures positive for CMV, and bilateral disease.

For our report, data from the FGCRT were analyzed to identify ocular characteristics present at diagnosis of CMV retinitis that were associated with earlier progression or more rapid spread of retinitis in involved eyes. In addition, we attempted to identify ocular and systemic risk factors specific for development of retinitis in fellow eyes of patients with unilateral disease at initial diagnosis. The information presented herein applies to patients in whom potent antiretroviral therapies fail or who are intolerant of them and to patients in whom CMV retinitis develops as a result of renewed or persistent immune dysfunction.

RESULTS

Of the 234 patients randomized to treatment in the FGCRT, 224 had baseline and follow-up photographic data available for analysis. Baseline and follow-up data were...
PATIENTS AND METHODS

Patients at 11 clinical centers with newly diagnosed, untreated CMV retinitis were eligible for the FGCRT. Descriptions of the design, procedures, and findings from the FGCRT are published elsewhere. To evaluate changes in the manifestation of retinitis over time, baseline data from patients with newly diagnosed, untreated retinitis enrolled in the later Studies of Ocular Complications of AIDS Research Group trial, the Monoclonal CMV Retinitis Trial (MACRT) at 15 clinical centers also underwent analysis. The protocols for the trials and the consent forms were reviewed and approved by institutional review boards at the coordinating center and at the clinical centers.

For evaluations of retinitis, the retina was divided into 3 zones. Zone 1 included the area within 1500 µm of the margin of the optic disc or within 3000 µm of the center of the macula; zone 2 extended from the limits of zone 1 to a circle passing through the ampullae of the vortex veins; and zone 3 extended peripherally from zone 2 to the ora serrata. For our analyses, the macula was defined as the area within 1000 µm of the margin of the fovea.

Patients were assigned randomly to treatment with intravenous ganciclovir or foscarnet (allocation ratio, 1:1). Study visits were scheduled at enrollment, every 2 weeks for the first 8 weeks, then every month for up to 6 months, and every 2 months after that. For all patients who required multiple courses of induction therapy, additional follow-up visits were scheduled at the beginning of each course of induction therapy. Indirect ophthalmoscopic examinations and fundus photography were required at every study visit.

The fundus photography protocol specified that photographs of 9 fields be taken with a wide-angle fundus camera, ie, stereoscopic photographs of the disc and macula surrounded by nonstereoscopic photographs of 8 peripheral fields. Fundus photographs were evaluated at the fundus photograph reading center (FPRC) by graders unaware of treatment assignment. The photograph grading protocol included assessments of various features of CMV retinitis, principally, location of lesions and appearance of their borders, degree of activity, extent of satellites (small foci of retinitis surrounded by normal-appearing retina), prominence of hemorrhage, and, for follow-up photographs, progression of retinitis.

RETINITIS MEASURES

The extent of retinitis in each eye was determined by FPRC graders with planimetric measurements of a digitized mosaic of the retina created from fundus photographs. This measure was defined as the percentage of total retinal area in zones 1 and 2 with retinitis, ie, area with retinitis divided by the total area of zones 1 and 2 of the retina. Zone 3 was not evaluated because it could not be depicted completely in the fundus photographs. Measurements of percentage of retina with retinitis were made at trial enrollment (baseline) and at 3 and 6 months of follow-up. Data on area with retinitis in zones 1 and 2 were included if baseline and follow-up photograph sets were available in which 85% or more of the area within these zones could be evaluated. For 18 patients who participated in a substudy examining deferral of anti-CMV therapy, measurements of retinal area with retinitis were determined at the time of enrollment rather than at the start of treatment (median length of deferral was 21 days). The FPRC graders assessed progression or occurrence of a new lesion by comparison of photographs taken at follow-up visits with those taken during the 5 days before randomization. The FPRC graders were not informed of clinician assessments of retinitis, but were aware when patients underwent additional courses of induction therapy (by the visit identification code). Laterality of retinitis at baseline and during follow-up was determined by evaluation of the FPRC and clinician assessment of retinitis. In discrepant cases, baseline and follow-up data from ophthalmologic examinations and photographic evaluations were reviewed to determine whether discrepancies were due to false-positive or false-negative observations.

The following retinitis outcomes were defined: (1) progression in an involved eye, defined as the movement of a lesion border by >2000 µm. (2) New lesion (at least 2000 µm) in the involved eye. (3) New lesion (at least 2000 µm) in the noninvolved eye. (4) Complete resolution of retinitis in the involved eye. (5) Complete resolution of retinitis in the involved eye, not followed by new lesion. (6) Disappearance of lesions and return to baseline characteristics of the retina.

CHARACTERISTICS OF EYES WITH RETINITIS

Selected characteristics of the 318 eyes with retinitis at baseline are presented in Table 1. Overall, 77.7% of eyes had retinal hemorrhage at the lesion borders. Perivascular cuffing, present in 20.8% of all involved eyes, was more frequent when lesion borders were wide and hemorrhagic.

To evaluate secular trends in the characteristics of retinitis at diagnosis, ocular characteristics of involved eyes were compared with those of 73 patients (100 involved eyes) with newly diagnosed retinitis who enrolled in the MACRT from September 14, 1995, through July 30, 1996. Both sets of eyes had similar characteristic profiles except that eyes of patients enrolled in the MACRT were less likely to have zone 1 involvement (41.4% vs 52.8%; P = .05), and to exhibit perivascular cuffing (8.0% vs 20.8%; P = .004). In eyes with retinitis at baseline, the median percentage of zones 1 and 2 with retinitis was similar to that for patients enrolled in the FGCR (9% vs 10%; P = .93).

PROGRESSION IN INVOLVED EYES

Progression, while receiving treatment, in involved eyes before first reinduction was observed by the FPRC in 232...
border at least 750 µm along a front 750 µm or greater in length, or the occurrence of a new lesion at least 750 µm in diameter and separated from a previous lesion by 750 µm or more; (2) rate of increase in the area of retina with retinitis (ie, spread) in the same eye, defined as the difference between the total percentage of retinal area with retinitis at the previous measurement time and the percentage at the current visit divided by the number of months between measurements; and (3) development of CMV retinitis in the uninvolved fellow eye.

For observations with an apparent decrease of 5% or less in the area of retina with retinitis (40 observations from 39 eyes of 35 patients), the rate of increase was assigned a value of 0% per month. In cases where there was an apparent decrease of more than 5% in retinal area involved at 3 or 6 months of follow-up (15 observations from 14 eyes of 14 patients), photographic mosaics were reviewed again. In all of these cases, there were errors in the evaluation of the baseline or follow-up photographs that resulted in the apparent decrease in retinal area. These errors were corrected.

Analysis

For most analyses, data from eyes with retinitis at baseline as determined by FPRC graders were used. Categorical and ordinal baseline variables were collapsed and combined according to their meaning and their frequency distributions. Missing data were imputed to the median or most common category if less than 10 observations had missing data; otherwise, a dummy variable was created to represent a separate category for missing data. Percentage area of retina with retinitis at baseline was logarithm-transformed for analysis. Associations between ocular characteristics at baseline were examined with linear regression models, Kruskal-Wallis tests, and χ² tests.

Baseline characteristics were examined for association with progression. In univariate analyses, smaller area involved (as measured by total percentage of zones 1 and 2 with retinitis), absence of zone 3 involvement, and more active borders (defined as activity along ≥90% of the border surrounding the lesion) were associated with earlier first progression. The association between area involved and time to first progression is shown in Figure 1. Based on the results from multivariate models, retinitis characteristics independently associated with earlier progression were smaller area involved and activity along at least 90% of lesion borders (Table 3). On average, eyes with more than 15% of zones 1 and 2 involved were at half the risk of progression, as were eyes with less than 5% involved. Eyes with at least 90% of lesion borders graded as active were 1.5 times as likely to have progression than were eyes with less active borders. Among the systemic variables included in the multivariate model, higher CD4⁺ T-lymphocyte counts and CMV blood culture status at baseline were included because these characteristics were shown in previous analyses to be related to time to first progression.

Risk Factors for First Progression in Involved Eyes

All the characteristics of involved eyes listed in Table 2 were examined for association with progression. In univariate analyses, smaller area involved (as measured by total percentage of zones 1 and 2 with retinitis), absence of zone 3 involvement, and more active borders (defined as activity along ≥90% of the border surrounding the lesion) were associated with earlier first progression. The association between area involved and time to first progression was based on the results from multivariate models, retinitis characteristics independently associated with earlier progression were smaller area involved and activity along at least 90% of lesion borders (Table 3). On average, eyes with more than 15% of zones 1 and 2 involved were at half the risk of progression, as were eyes with less than 5% involved. Eyes with at least 90% of lesion borders graded as active were 1.5 times as likely to have progression than were eyes with less active borders. Among the systemic variables included in the multivariate model, higher CD4⁺ T-lymphocyte counts and CMV blood culture negative for CMV at baseline were associated with a lower risk of progression. Exclusion from the data set of 10 observations with large residuals (≥2) did not change the results of the model selection procedures. We checked for evidence that unmeasured area with retinitis in zone 3, the presence of retinitis satel-
lites, or bilateral disease status might explain the relative risk of progression associated with area involved. There was no evidence that the presence or absence of retinitis in zone 3, the presence or absence of satellites, or bilateral disease status influenced the relative risk of progression associated with area of retina with retinitis (P = .72, P = .13, and P = .20, respectively).

**RATE OF INCREASE IN RETINAL AREA WITH RETINITIS**

Baseline and follow-up data to estimate rates of increase in area of retina involved for eyes with retinitis at baseline were available for 225 eyes of 164 patients, which was 70.8% of eyes and 73.2% of patients with baseline and follow-up fundus photographs. Eyes from patients with longer follow-up times were more likely to have these data available, because follow-up assessments of area were made after 3 and 6 months of follow-up.

The median percentage of retinal area (zones 1 and 2) with retinitis was 10% at baseline (95% CI, 8%-13% [n=225]), 21% at 3 months (95% CI, 16%-25% [n=197]), and 30% at 6 months (95% CI, 21%-39% [n=159]). The median rate of increase per month in the percentage of retina with retinitis during all follow-up was 2.5% per month (95% CI, 2.3%-2.6% per month). At 3 months, the median rate of increase was 2.6% per month (95% CI, 2.3%-2.8% per month), and at 6 months, it was 2.3% per month (95% CI, 2.0%-2.6% per month), and these rates were not significantly different (P = .23).

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**RISK FACTORS FOR RATE OF INCREASE IN RETINAL AREA INVOLVED**

All the photographic and systemic characteristics examined for an association with first progression also were examined for an association with rate of increase in area in involved eyes. Results of univariate analyses were similar to those for time to first progression, except that the presence of satellites and border hemorrhage were significant risk factors and extent of border activity was not.

Based on multivariate models, retinitis characteristics independently associated with a more rapid rate of increase in retinal area involved while receiving treatment were smaller area involved, shorter distance between the optic disc and the closest lesion border, and the presence of satellites along the retinitis borders (Table 3). The β coefficient associated with each characteristic is the average adjusted difference in rate of increase in retinal area involved (percentage per month) between the indicated category and the reference category. For example, the average rate of increase for eyes with greater than 15% of retinal area with retinitis at baseline was 1.8% per month less than the average rate in eyes with less than 5% involved (Table 3). The rate of increase in eyes in which the closest lesion to the optic disc was more than 4300 µm away was, on average, 2.0% per month less than in eyes with lesions adjacent...
to the disc. The presence of border satellites was associated with an average increase in that rate of 2.1% per month.

The association of retinal area with the rate of increase was not different in eyes with zone 3 involvement vs those without ($P=.18$), nor was it different in eyes with satellites vs those without ($P=.38$). However, there was weak evidence that the negative association between area involved and rate of increase was stronger in eyes of patients with unilateral disease at baseline than in those of patients with bilateral disease ($P=.05$).

After adjustment for ocular characteristics found to be associated with rate of increase, patients with higher CD4$^+$ T-lymphocyte counts at baseline had, on average, lower rates of increase. Treatment assignment (foscarnet or ganciclovir) and CMV blood culture status at baseline were not associated with the rate of retinitis increase during follow-up.

We assessed the stability of the final model by deleting outliers for the outcome, observations with high leverage, and observations for which the rate of increase was zero. Exclusion of 2 observations with outlier values for rate of increase from the data set did not change the results of the model selection procedures. Exclusion of the 13 observations with outlier values for leverage resulted in the selection of optic disc involvement in addition to the previously selected covariates. Exclusion of the 40 observations (25 at 3 months and 15 at 6 months) from 39 eyes (35 patients) in which no retinitis advancement was observed resulted in the omission of area in-
volved and distance from the optic disc from the selected covariate set and the selection of optic disc involvement. The median percentage of retinal area involved at baseline was larger for the omitted 39 eyes than for the other 214 eyes (17% vs 10%; \(P = .02\)).

**DEVELOPMENT OF RETINITIS IN AN UNINVOLVED FELLOW EYE**

Of the 224 patients included in these analyses, 120 had unilateral disease at randomization to treatment. Excluded from this analysis were 7 patients with unilateral disease based on FPRC assessment but bilateral disease based on clinician assessment, 1 patient in whom bilateral disease developed during deferral of treatment, and 1 patient for whom the FPRC was uncertain as to the disease status at baseline. Cytomegalovirus retinitis developed in 31 (25.8%) of the 120 uninvolved eyes during follow-up (Figure 2). The median time to development of a lesion in the uninvolved eye was 23 months (95% CI, 13 months to \(\infty\)). There was a suggestion that patients in whom bilateral disease developed during follow-up had a substantially longer median survival than patients in whom it did not (16 vs 9 months; \(P = .13\)). New lesions in eyes not involved at baseline involved zone 1 in 4 eyes (12.9%); zone 2, but not zone 1, in 16 eyes (51.6%); and zone 3 only in 11 eyes (35.5%).

**RISK FACTORS FOR DEVELOPMENT OF A LESION IN AN UNINVOLVED FELLOW EYE**

Characteristics examined for an association with more rapid retinitis spread in an involved eye also were examined for an association with development of retinitis in an uninvolved eye while receiving treatment. In addition, the following systemic characteristics were examined: months since the diagnosis of AIDS, number of opportunistic infections diagnosed before retinitis diagnosis, CD4+ and CD8+ T-lymphocyte counts and other hematologic measures, predicted creatinine clearance, and blood and urine CMV culture status at baseline. Karnofsky score was not included in this analysis because the variable appeared to violate the proportional hazards assumption (\(P = .009\)). Those patients with higher Karnofsky scores at baseline (\(\geq 90\)) were at higher risk for development of retinitis in an uninvolved eye than were patients with lower Karnofsky scores in the first 7 months of follow-up but at lower risk after that time.

In univariate analyses, blood and urine cultures both positive for CMV, urine cultures positive for CMV with negative or missing results for blood culture, lower CD8+ T-lymphocyte counts, and presence of satellites at retinitis borders were associated with a greater risk of development of bilateral disease. The CD4+ T-lymphocyte counts were not associated with development of bilateral disease (\(P = .72\)). In the multivariate model, no ocular characteristics of involved eyes of patients with unilateral retinitis were associated with the development of retinitis in previously uninvolved fellow eyes. Systemic characteristics at baseline identified as independent risk factors for development of bilateral disease were blood and urine cultures positive for CMV, lower CD8+ T-lymphocyte count, and no previous AIDS-related opportunistic infections at diagnosis of retinitis (Table 4).

In the final model that included these variables and treatment assignment, patients with the highest CD8+ T-lymphocyte counts (\(> 0.38 \times 10^9/L\)) were at lowest risk for development of retinitis in the other eye; their risk was one fifth that of patients with the lowest CD8+ counts (\(\leq 0.20 \times 10^9/L\)). Patients with blood and urine cultures both positive for CMV at baseline were almost 5 times as likely to have development of retinitis in the other eye as were patients with negative results of cultures. Patients with urine cultures positive for CMV and a negative or missing result of blood culture at diagnosis were more than 3 times as likely to have development of retinitis in the other eye as were patients with negative re-

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**Figure 1.** Kaplan-Meier estimates for time to first progression of cytomegalovirus retinitis in involved eyes, stratified by area in zones 1 and 2 with retinitis at baseline (small, \(< 5\%\); medium, 5%-15%; and large, \(> 15\%\)).

**Figure 2.** Kaplan-Meier estimates of time to development of cytomegalovirus retinitis in fellow eyes not involved at baseline (fundus photograph reading center and clinician assessments). Bottom, Number of eyes, number with new retinitis (events), and the number of events per person-year (rate) for 6-month intervals.
The objectives of these analyses were (1) to identify characteristics of patients with newly diagnosed CMV retinitis that were predictive of retinitis progression or spread in involved eyes, and (2) to identify characteristics predictive of development of retinitis in uninvolved eyes in patients being treated for CMV retinitis.

The baseline risk factors identified for both measures of retinitis advancement in involved eyes while receiving treatment, progression and the rate of increase in area affected by retinitis initially seems counterintuitive. The apparent effect of the size of the area involved may be related to the disruption of retinal circulation caused by the full-thickness retinal necrosis characteristic of CMV retinitis. Larger lesions may enhance drug delivery because of more extensive circulatory disruption. Hence, replication of virus may be inhibited more quickly in these eyes. It is also possible that smaller area of involvement also may be a marker for new disease, which may spread more rapidly because an immune response, albeit small, has just begun. The evidence of this hypothesis was limited; some evidence (P = .05) suggested that the association between smaller area of involvement and faster rate of increase in area was greater for eyes of patients with unilateral disease, which we used as a marker for new disease, than for eyes of patients with bilateral disease. However, there was less evidence to suggest that the association of area of involvement and time to first progression were influenced by laterality of disease (P = .20).

The association of smaller area involved at baseline with faster retinitis progression or more rapid rates of spread could be an artifact of measurement procedures. An identical amount of border movement may be easier to detect for a smaller lesion. Observations in which no increase in area was noted during follow-up tended to be from eyes with a larger area of involvement at baseline. Eyes with larger areas of retina involved were more likely to have zone 3 involvement, where border advancement could not be measured reliably, but we found little evidence that retinitis progression rate or rates of increase in area differed in eyes with retinitis that extended into zone 3 than in eyes with similar areas of involvement without zone 3 involvement.

A faster rate of increase inretinal area with retinitis was weakly associated with each of the (highly correlated) measures of posterior location (involvement of zone 1, involvement of the macula or disc, and shorter distance from the disc); shorter distance from the disc was selected for inclusion in the multivariate model (Table 3). Posterior location also was associated with clinician-assessed progression (data not shown). The association of closer proximity to the optic disc with faster rates of increase in retinal area with retinitis may have been affected by the poorer quality of peripheral photographs. Alternatively, faster spread of retinitis located near the disc in treated patients might be related to greater thickness and vascularity of the retina here, which might provide more opportunity for spread along vessels.

A retrospective study of patients with untreated retinitis or active retinitis despite treatment with intravenous ganciclovir suggested that border advancement toward the anterior retina was more rapid than advancement toward the posterior retina. Our study did not analyze the direction of border advancement. Both studies found that the location of the retinitis lesions at baseline was

### Table 4. Risk Factors for Development of Bilateral CMV Retinitis in Patients With Unilateral Disease at Baseline

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No. of Events/No. of Patients</th>
<th>Rate†</th>
<th>RR‡</th>
<th>P §</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>31/120</td>
<td>0.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CD4+ T-lymphocyte count ≤0.20 x 10⁹/L</td>
<td>15/36</td>
<td>0.8</td>
<td>1.0</td>
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<tr>
<td>&gt;0.20 x 10⁹/L to 0.38 x 10⁹/L</td>
<td>9/31</td>
<td>0.5</td>
<td>0.91</td>
<td>.88</td>
</tr>
<tr>
<td>&gt;0.38 x 10⁹/L</td>
<td>6/35</td>
<td>0.2</td>
<td>0.2</td>
<td>.51</td>
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<td>1/18</td>
<td>0.1</td>
<td>0.1</td>
<td>.93</td>
</tr>
<tr>
<td>CD8+ T-lymphocyte count ≤0.014 x 10⁹/L</td>
<td>18/55</td>
<td>0.6</td>
<td>1.0</td>
<td>. . .</td>
</tr>
<tr>
<td>&gt;0.014 x 10⁹/L</td>
<td>13/50</td>
<td>0.3</td>
<td>0.7</td>
<td>.43</td>
</tr>
<tr>
<td>Missing</td>
<td>0/15</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and urine CMV culture results Both negative†</td>
<td>6/33</td>
<td>0.2</td>
<td>1.0</td>
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</tr>
<tr>
<td>Blood and urine positive</td>
<td>11/28</td>
<td>0.7</td>
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<td>.006</td>
</tr>
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<td>0.2</td>
<td>2.0</td>
<td>.55</td>
</tr>
<tr>
<td>Urine positive</td>
<td>9/35</td>
<td>0.4</td>
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<td>4/17</td>
<td>0.4</td>
<td>2.7</td>
<td>.16</td>
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<tr>
<td>No. of opportunistic infections None§</td>
<td>21/65</td>
<td>0.5</td>
<td>1.0</td>
<td>. . .</td>
</tr>
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<td>≥1</td>
<td>10/55</td>
<td>0.3</td>
<td>0.3</td>
<td>.002</td>
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<tr>
<td>Treatment assignment Foscarnet sodium¶ 14/51</td>
<td>0.4</td>
<td>1.0</td>
<td>. . .</td>
<td></td>
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<td>Ganciclovir</td>
<td>17/69</td>
<td>0.4</td>
<td>1.4</td>
<td>.38</td>
</tr>
</tbody>
</table>

*CMV indicates cytomegalovirus; FPRC, fundus photograph reading center; and RR, relative risk. Assessments were performed by FPRC graders or clinicians.
†Rates were calculated as events per person-year.
‡Estimated with proportional hazards regression procedures and were adjusted for all listed covariates.
§P values were based on Wald tests.
||Reference group; RR for reference group is 1.0 by definition and no P value was calculated.

The risk of bilateral retinitis in patients with a diagnosis of at least 1 opportunistic infection before the diagnosis of CMV retinitis was about one third that of patients with no other opportunistic infections at diagnosis. Treatment assignment was not associated with development of bilateral disease.

COMMENT

The baseline risk factors identified for both measures of retinitis advancement in involved eyes while receiving treatment, progression and the rate of increase in area affected by retinitis, were smaller area of retina with retinitis and signs of greater border activity, as well as lower CD4+ T-lymphocyte counts. More posterior location of retinitis was only associated with rate of increase in area involved. Inclusion of these baseline risk factors in the models with treatment assignment did not alter the overall conclusion of the trial that intravenous foscarnet and ganciclovir were equally efficacious for treatment of CMV retinitis (Tables 3 and 4).

The associations of border activity, posterior location, and CD4+ T-lymphocyte counts were not surprising, but the association of smaller area of retinitis with more rapid advancement of retinitis initially seems counterintuitive. The apparent effect of the size of the area involved may be related to the disruption of retinal circulation caused by the full-thickness retinal necrosis characteristic of CMV retinitis. Larger lesions may enhance drug delivery because of more extensive circulatory disruption. Hence, replication of virus may be inhibited more quickly in these eyes. It is also possible that smaller area of involvement also may be a marker for new disease, which may spread more rapidly because an immune response, albeit small, has just begun. The evidence of this hypothesis was limited; some evidence (P = .05) suggested that the association between smaller area of involvement and faster rate of increase in area was greater for eyes of patients with unilateral disease, which we used as a marker for new disease, than for eyes of patients with bilateral disease. However, there was less evidence to suggest that the association of area of involvement and time to first progression were influenced by laterality of disease (P = .20).

The association of smaller area involved at baseline with faster retinitis progression or more rapid rates of spread could be an artifact of measurement procedures. An identical amount of border movement may be easier to detect for a smaller lesion. Observations in which no increase in area was noted during follow-up tended to be from eyes with a larger area of involvement at baseline. Eyes with larger areas of retina involved were more likely to have zone 3 involvement, where border advancement could not be measured reliably, but we found little evidence that retinitis progression rate or rates of increase in area differed in eyes with retinitis that extended into zone 3 than in eyes with similar areas of involvement without zone 3 involvement.

A faster rate of increase in retinal area with retinitis was weakly associated with each of the (highly correlated) measures of posterior location (involvement of zone 1, involvement of the macula or disc, and shorter distance from the disc); shorter distance from the disc was selected for inclusion in the multivariate model (Table 3). Posterior location also was associated with clinician-assessed progression (data not shown). The association of closer proximity to the optic disc with faster rates of increase in retinal area with retinitis may have been affected by the poorer quality of peripheral photographs. Alternatively, faster spread of retinitis located near the disc in treated patients might be related to greater thickness and vascularity of the retina here, which might provide more opportunity for spread along vessels.

A retrospective study of patients with untreated retinitis or active retinitis despite treatment with intravenous ganciclovir suggested that border advancement toward the anterior retina was more rapid than advancement toward the posterior retina. Our study did not analyze the direction of border advancement. Both studies found that the location of the retinitis lesions at baseline was
not associated with retinitis progression and that border activity was associated.19

Development of new lesions in a previously uninvolved eye was an infrequent and late-stage event (median time to event, 23 months) occurring in about a quarter of the patients with unilateral CMV retinitis. The overall median survival of patients with unilateral disease was substantially shorter (10.3 months), so the 23-month estimate is likely to be influenced by a survival bias. Regardless, longevity is probably an important risk factor for development of bilateral disease. Other risk factors independently associated with development of bilateral disease were blood and urine CMV cultures both positive for CMV, urine culture only positive for CMV, lower CD8+ T-lymphocyte counts, and fewer AIDS-related opportunistic infections (Table 4). These risk factors were not related to development of bilateral disease via an association with longer survival. Cultures positive for CMV and lower CD8+ T-lymphocyte counts at baseline were associated with shorter survival, and the number of AIDS-related opportunistic infections was not associated with survival.2,4

Blood cultures that are positive for CMV have been shown to be associated with poorer prognosis for CMV retinitis.20 Positive cultures may indicate higher viral load in the blood and more severe immune suppression, which may increase the likelihood of hematogenous spread of virus to an uninvolved eye. Decrease in CD8+ T-lymphocyte counts is a marker for immunosuppression, as indicated by the increased risk of CMV retinitis and shorter survival.21-23 The finding that fewer AIDS-related opportunistic infections is a risk factor for bilateral disease is paradoxical. In view of the small number of patients included in these analyses and the many statistical tests performed, this could be a chance finding.

The rate of increase in retinal area in zones 1 and 2 with retinitis was constant during the first 6 months of follow-up; the median was 2.6% of retinal area per month. This finding seems to conflict with a previous report from this trial that indicated a trend toward shorter times to progression from the first to the second progression (48 to 41 days) and from the second to the third progression (41 to 35 days).3 Those findings indicate that the rate of increase in retinitis area might be expected to accelerate during follow-up. The conflict may, in part, be due to different data sets, analysis approaches, and measures. The previously reported retinitis progression results were based on analysis of patients’ time to progression in either eye. The current analyses used eyes involved at baseline as the unit of analysis. Progression is a binary outcome based on a relatively small amount of linear movement along a segment of a lesion border and can be due to irregular border advancement that does not correlate with overall border movement, whereas rate of increase in area is a continuous outcome that integrates the border movement along the entire visible circumference of lesions during longer periods of follow-up.

There are limitations to our study that should be kept in mind when interpreting these results. Data were collected as part of a clinical trial comparing treatments for patients with previously untreated CMV retinitis, ie, data collection was not designed with these analyses in mind. The current analyses were limited to factors for which data were available and assumed that there were no unknown confounders such as viral strain heterogeneity or host immunologic factors. The analyses were exploratory in nature with few a priori hypotheses. There was low statistical power to detect associations for some variables, such as optic disc involvement. These patients experienced a high mortality rate, reducing the number who could be observed for longer-term retinitis outcomes; the results therefore may be influenced by a survival bias. These data were collected before the availability of potent antiretroviral agents and combination antiretroviral therapies in 1996. Therefore, they may not reflect the course of retinitis in patients receiving these medications. However, the ocular and retinitis characteristics were quite similar to those of patients with newly diagnosed retinitis in 1995 and 1996, some of whom received potent antiretroviral therapy, and severe immunodeficiency is still required for the development of CMV retinitis.

Despite these limitations, these analyses identified the following baseline risk factors for faster progression or spread of retinitis in involved eyes in patients being treated for CMV retinitis: smaller area of involvement, more posterior involvement, and greater border activity. Our findings support more aggressive treatment of such eyes, and we have no reason to think that this suggestion should not be applied to patients in whom CMV retinitis develops before potent antiretroviral treatment is initiated or after it fails. Aggressive treatment of small early lesions remains important. With increased survival, if patients develop CMV retinitis before immune reconstitution or early during antiretroviral treatment, aggressive treatment of CMV retinitis will limit the area with retinitis and thereby decrease the risk of vision-limiting complications, eg, foveal destruction or retinal detachment, in long-term survivors.

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References


From the Archives of the Archives

A look at the past . . .

Wood is of the opinion that in our kindergarten systems we should eliminate as much as possible all that part which demands a close application of the eyes for near work, such as drawing, sewing, embossing, perforated cardwork, etc. The eyes of the kindergartners should be tested by a competent person regularly.