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Abstract

Aim—To describe the risk of developing cytomegalovirus (CMV) retinitis after a first episode of extraocular CMV disease in AIDS patients.

Methods—A review of the clinical records of 20 AIDS patients, without CMV retinitis, with histologically confirmed extraocular CMV disease, was performed. The main outcome measures were occurrence of CMV retinitis, time to development of CMV retinitis, relation to maintenance therapy, and survival.

Results—A CMV retinitis was diagnosed in 17 of 20 (85%) patients with an immunohistologically confirmed diagnosis of extraocular CMV disease after a mean follow up of 6.4 months. Four patients received maintenance therapy. Three of them developed retinitis after a mean of 9.6 months (range 2–16 months). Sixteen did not receive maintenance and retinitis was diagnosed in 14 of them after a mean of 5.7 months (range 2–11 months). Mean survival was 9.9 months after the diagnosis of extraocular disease, and 4.5 months after the diagnosis of retinitis. In the four patients receiving maintenance therapy, mean survival was 11.5 months, and in the 16 other patients mean survival was 9.5 months. Patients did not receive protease inhibitors.

Conclusion—In the preprotease inhibitor era extraocular CMV disease strongly predisposes to the subsequent development of CMV retinitis. Although maintenance therapy did not prevent the occurrence of retinitis, the time period between both events seems to lengthen considerably. In patients receiving maintenance survival is also longer.

(Br J Ophthalmol 1998;82:748–750)

Clinically manifest cytomegalovirus (CMV) disease is the most often diagnosed opportunistic viral infection in HIV positive patients. The annual incidence in patients with CD4+ lymphocyte counts below 100 cells $\times 10^7/l$ is 14%; and if CD4+ cell counts fall below 50 the incidence rises to 24% per year. The most debilitating, clinically significant CMV disease affects the eye, and CMV retinitis is present in approximately 90% of all cases with CMV disease.1-3

Extraocular CMV disease has been considered to predispose for developing CMV retini-
For statistical analysis, comparing the time period between the first non-ocular CMV disease and the occurrence of CMV retinitis, in the patients receiving maintenance therapy versus the patients not receiving maintenance, the Kaplan–Meier method and the log rank test were used.

**Results**

In 17 of 20 (85%) patients with an immunohistologically proved non-ocular clinically manifest CMV infection a CMV retinitis occurred after a mean follow up of 6.4 months (range 2–16 months, see Table 1). Four patients (patients 1–4, Table 1) received maintenance therapy, 5 mg ganciclovir/kg/day or 90 mg foscavir/kg/day, and in three of them CMV retinitis was diagnosed after 2, 11, and 16 months (mean 9.6 months). The fourth patient (patient 3) died after a follow up of 4 months without the occurrence of retinitis. In one patient (patient 4) maintenance therapy was stopped after 1 month because of drug toxicity, but no retinitis occurred. Twelve patients (mean 9.5 months) died after a mean follow up of 9 months (range 2–11 months). Two patients (patients 19 and 20) died without the occurrence of retinitis. In one patient (patient 3) died after a follow up of 4 months without the occurrence of retinitis. The other patient (patient 3) died after a follow up of 4 months without the occurrence of retinitis. The fourth patient received maintenance therapy after a diagnosis of CMV retinitis was diagnosed after 2, 11, and 16 months. Owing to the relatively short time after diagnosis of CMV retinitis in months, the survival analysis was performed, comparing the time between the diagnosis of extraocular CMV disease and CMV retinitis in months. The mean survival after a diagnosis of CMV retinitis was 4 months in the maintenance group and 9.5 months in the non-maintenance group of patients.

**Discussion**

This study shows that extraocular CMV disease is a major risk factor for developing CMV retinitis. Seventeen out of 20 (85%) AIDS patients with a biopsy proved extraocular CMV disease developed CMV retinitis after a mean follow up of 6.4 months.

Although numbers are small, maintenance therapy seems to postpone the development of CMV retinitis after an extraocular CMV disease. Without maintenance therapy retinitis occurred after a mean follow up of 5.7 months, whereas with maintenance therapy the mean retinitis-free interval became 9.6 months (2, 11, and 16 months). Owing to the relatively small numbers of patients, the survival analysis was performed, comparing the time between the diagnosis of extraocular CMV disease and CMV retinitis in months.

**Table 1** Characteristics of 20 AIDS patients with a histopathologically confirmed first episode of extraocular CMV disease, but not yet suffering from retinitis

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Date</th>
<th>Localisation</th>
<th>CD4+</th>
<th>Induction therapy</th>
<th>Maintenance</th>
<th>Interval E-Oc/Ret</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>01-06-91</td>
<td>Upper GI</td>
<td>20</td>
<td>GCV(2)/Fosc(1)/GCV+Fosc(2)</td>
<td>GCV</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>01-03-90</td>
<td>Poly rad</td>
<td>10</td>
<td>GCV(1)/GCV+Fosc(2)</td>
<td>GCV</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>10-07-91</td>
<td>Upper GI</td>
<td>40</td>
<td>GCV(4)</td>
<td>GCV</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>07-04-89</td>
<td>Upper GI</td>
<td>10</td>
<td>GCV(2)/Fosc(2)</td>
<td>Fosc</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>01-05-89</td>
<td>Lower GI</td>
<td>10</td>
<td>GCV(3)</td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
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<td>Lungs</td>
<td>10</td>
<td>GCV(3)</td>
<td></td>
<td>3</td>
<td>2</td>
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<tr>
<td>7</td>
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<td>Upper GI</td>
<td>10</td>
<td>GCV(2)</td>
<td></td>
<td>4</td>
<td>1</td>
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<td>Upper GI</td>
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<td>GCV(4)</td>
<td></td>
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<tr>
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<td>GCV(2)</td>
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<td>2</td>
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<tr>
<td>10</td>
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<td>GCV(2)/Fosc(2)</td>
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<td>2</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
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<td>10</td>
<td>GCV(2)/Fosc(2)</td>
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<td>2</td>
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<tr>
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<td>40</td>
<td>GCV(3)</td>
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<tr>
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<td>14</td>
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<td>Lower GI</td>
<td>20</td>
<td>Fosc(3)</td>
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<td>2</td>
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<tr>
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<tr>
<td>16</td>
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<td>GCV(3)/Fosc(1)</td>
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<td>12</td>
</tr>
<tr>
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<td>8</td>
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<td>GCV(2)</td>
<td></td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>19</td>
<td>05-03-92</td>
<td>Lungs</td>
<td>10</td>
<td>GCV(1)/Fosc(2)</td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
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<td>20-09-90</td>
<td>Upper GI</td>
<td>80</td>
<td>GCV(2)</td>
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<td>11</td>
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</tr>
</tbody>
</table>
small number of patients this difference did not reach statistical significance.

One recent study reported CMV retinitis to occur in 22% of 239 HIV positive patients within 1 year of follow up. CD4+ lymphocyte count was less than 50 cells × 10^9/l in over 90% of these patients. In another prospective study of 367 HIV positive patients, with a CD4+ count below 100 cells × 10^9/l, and a mean follow up of 2.9 years, 32% of the patients developed a CMV retinitis.

Both patient groups described are comparable with the patients included in this study. All patients have the same disease stage and equal CD4 positive lymphocyte counts. Comparing the incidence of CMV retinitis in the patients included in this study, 85% in 2 years, with the reported incidence in the literature, 22% in 1 year and 35% in 2.9 years, proves extraocular CMV disease to be a major risk factor for developing subsequent retinitis.

To the best of our knowledge there are no reports that systematically look for retinitis as a secondary event after a first episode of extraocular CMV disease or the effect of maintenance therapy in these cases. The overall conclusion out of those studies at least mentioning the occurrence of CMV retinitis after a first episode of extraocular CMV disease is that the association between both events is very high.1, 9-13

In a study describing the natural history and necropsy findings in a cohort of 1227 HIV positive patients, seen between 1984 and 1994, the risk of a relapse of CMV disease was significantly higher in patients not receiving maintenance therapy.14 Moreover, relapses occurred later in patients given maintenance therapy compared with those without maintenance treatment (20% of patients, median time of 17 months, versus 62%, median time of 5.5 months). Maintenance therapy however did not improve survival, with a mean of 8 months in both groups. Relapse was defined in this study as a new CMV organ disease at the same or different site after a complete resolution of the first episode. No details were provided concerning the occurrence of CMV retinitis after a diagnosis of extraocular CMV disease. A previous study however claims no effect of maintenance therapy after a successful treatment of gastrointestinal CMV disease. Neither the number of relapses of gastrointestinal CMV disease, nor the number of CMV retinitis developing, nor the median time to occurrence of this second event differed between patients receiving maintenance therapy or patients without maintenance therapy. In the latter study, the decision to embark on further treatment was left to the clinical investigator unless there was concurrent retinitis; in such cases, maintenance therapy was started routinely. The maintenance receiving group must have included patients with retinitis from the start and this must have influenced the recurrence rate in a negative way, in light of the high rate of recurrence of CMV retinitis despite maintenance therapy.

Protease inhibitors were not generally prescribed during the time period the patients included in this study were seen, and in fact there were no patients included who received protease inhibitors.

Considering the 85% of patients with a diagnosis of CMV retinitis, following a first episode of extraocular CMV disease, after a mean follow up of 6.4 months, found in this study, it seems obvious that extraocular CMV disease strongly predisposes to the subsequent development of CMV retinitis. CMV retinitis occurred despite the fact that extraocular CMV disease seemed to be completely healed after 3–5 weeks of antiviral treatment. Although maintenance treatment did not prevent the occurrence of CMV retinitis the time interval between both events was considerably longer in patients receiving maintenance therapy. One patient receiving maintenance therapy with foscavir, 90 mg/kg/day, had to stop, owing to drug toxicity. This patient developed CMV retinitis within 1 month after stopping the maintenance therapy. This patient is a good example of both the desirability of an effective maintenance therapy and the unwanted toxic side effects of the drugs available today.

Although our study does not provide conclusive evidence in favour of maintenance therapy after an initial extraocular CMV disease, frequent ophthalmic examinations are definitely warranted in such patients. The introduction of protease inhibitors and the use of anti-HIV multidrug combination therapy may alter the treatment strategies against CMV drastically in the near future.

We would like to thank Professor Marc D de Smet for critically reading the manuscript.

7 Centers for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR Suppl 1987;36:18–38.