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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 be lengthened considerably. In patients receiving maintenance survival is also longer.

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 × 10⁹/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.

Extraocular CMV disease has been considered to predispose for developing CMV retinitis, but exact data are not well known. Although maintenance therapy in case of CMV retinitis is mandatory, it is more questionable after other end organ disease. Most authors advise maintenance therapy only after a relapse of CMV disease. One study reported an equal number of newly diagnosed CMV retinitis with or without maintenance therapy after a first episode of gastrointestinal CMV disease. Even though new treatment modalities, such as oral ganciclovir, are now available, secondary prophylaxis is not routinely prescribed.

To answer the question, how often CMV retinitis occurs after an extraocular CMV disease, and whether there is a rationale for maintenance treatment after CMV end organ disease outside the eye, we carried out a retrospective analysis in all HIV positive patients seen in the AIDS department, who had a biopsy proved non-ocular CMV disease between March 1989 and March 1995. The incidence of CMV retinitis after a non-ocular CMV end organ disease and the time period between both events was registered, as was the survival after the occurrence of CMV disease. Additionally, the influence of maintenance therapy on these events was analysed.

Patients and methods

Medical records of patients admitted to the AIDS unit of the Academic Medical Centre between March 1989 and March 1995 with a biopsy proved first episode of extraocular CMV disease were reviewed.

For histopathology, biopsies were fixed in 10% buffered formalin (pH 7.4) and embedded in paraffin, processed, and routinely stained with haematoxylin and eosin. Sections 4 µm thick were used for immunohistochemical detection of CMV, using a monoclonal antibody against the immediate early antigen of CMV (E13, Biosoft Lab) with the streptavidin method. Before incubation, the slides were deparaffinised and pretreated with pepsin 0.25% in 0.01 HCl for 10 minutes. Slides were read positive when nuclei of epithelial, endothelial, or stromal cells stained brightly with the antibody, whether or not nuclear inclusions were seen on the haematoxylin and eosin slides.

According to standard practice of the Academic Medical Centre all these patients were seen by an ophthalmologist at the time of diagnosis of extraocular CMV disease. Patients were included in this study if no retinitis was diagnosed at that time. All patients had to
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Patients 1–4, Table 1) received maintenance therapy for a mean of 2 years (range 0.5–8 years). AIDS defining diagnosis was pneumonia in 14 patients, Kaposi’s sarcoma in five, cryptosporidial diarrhoea, Pneumocystis carinii pneumonitis, and twice pneumococcal pneumonia. Induction therapy: GCV=ganciclovir 5 mg/kg/day; Fosc=foscavir 90 mg/kg/day; GCV+Fosc=combination of both therapies. (n)= number of weeks treated. Maintenance: GCV=ganciclovir 5 mg/kg/day; Fosc=foscavir 90 mg/kg/day. Interval E-Oc/Ret=time between extraocular CMV disease and CMV retinitis in months; (—)= no CMV retinitis occurred. Survival=survival time after diagnosis of 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>
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<tbody>
<tr>
<td>1</td>
<td>01-06-91</td>
<td>Upper GI</td>
<td>20</td>
<td>GCV(2)</td>
<td>GCV</td>
<td>16</td>
<td>8</td>
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<tr>
<td>2</td>
<td>01-03-90</td>
<td>Poly rad</td>
<td>10</td>
<td>GCV(1)</td>
<td>GCV</td>
<td>11</td>
<td>8</td>
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<tr>
<td>3</td>
<td>10-07-91</td>
<td>Upper GI</td>
<td>40</td>
<td>GCV(4)</td>
<td>GCV</td>
<td>16</td>
<td>8</td>
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<tr>
<td>4</td>
<td>07-04-89</td>
<td>Upper GI</td>
<td>10</td>
<td>GCV(2)</td>
<td>Fosc</td>
<td>2</td>
<td>3</td>
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<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>2</td>
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<tr>
<td>6</td>
<td>01-07-92</td>
<td>Lungs</td>
<td>10</td>
<td>GCV(3)</td>
<td>—</td>
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<td>2</td>
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<td>7</td>
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<td>Upper GI</td>
<td>10</td>
<td>GCV(2)</td>
<td>—</td>
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<td>GCV(4)</td>
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<tr>
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<td>Upper GI</td>
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<td>GCV(2)</td>
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<tr>
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<td>GCV(2)</td>
<td>—</td>
<td>6</td>
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<tr>
<td>11</td>
<td>10-03-93</td>
<td>Upper GI</td>
<td>40</td>
<td>GCV(4)</td>
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<td>12</td>
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<td>GCV(3)</td>
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<td>13</td>
<td>01-04-93</td>
<td>Lower GI</td>
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<td>GCV(5)</td>
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<td>14</td>
<td>08-05-95</td>
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<td>20</td>
<td>Fosc(3)</td>
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<td>GCV(2)</td>
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<tr>
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<td>20-08-92</td>
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<td>GCV(3)</td>
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<tr>
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<td>01-08-92</td>
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<td>GCV(3)</td>
<td>—</td>
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<td>3</td>
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<td>GCV(2)</td>
<td>—</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>19</td>
<td>05-03-92</td>
<td>Lungs</td>
<td>10</td>
<td>GCV(1)/Fosc(1)</td>
<td>—</td>
<td>2</td>
<td>2</td>
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<tr>
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<td>20-09-90</td>
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<td>80</td>
<td>GCV(2)</td>
<td>—</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Date= date of diagnosis of extraocular CMV disease. Localisation: upper GI= upper gastrointestinal tract; lower GI= lower gastrointestinal tract; Lungs= CMV pneumonitis; Poly rad= CMV polyradiculopathy; CD4+= CD4 positive lymphocyte count, cells x10\(^{-1}\). Induction therapy: GCV=ganciclovir 5 mg/kg/twice daily; Fosc=foscavir 90 mg/kg/twice daily; GCV+Fosc= combination of both therapies. (n) = number of weeks treated. Maintenance: GCV=ganciclovir 5 mg/kg/day; Fosc=foscavir 90 mg/kg/day. Interval E-Oc/Ret=time between extraocular CMV disease and CMV retinitis in months; (—)= no CMV retinitis occurred. Survival=survival time after diagnosis of CMV retinitis in months.

Results

In 17 of 20 (85%) patients with an immunohistologically proved non-ocular 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, 1 month before a diagnosis of retinitis. Sixteen patients did not receive maintenance. In 14 of these patients (87.5%) a CMV retinitis was diagnosed after a mean follow up of 5.7 months, range 2–11 months. Two patients (patients 19 and 20) died without the occurrence of retinitis, after 2 and 11 months respectively. Statistical analysis showed that the difference in the time between both events was not statistically significant ($\chi^2 = 1.8545$, p=0.17).

Mean survival after a diagnosis of non-ocular CMV disease was 11.5 months in the four patients with maintenance and 9.5 months in the 16 patients without maintenance. Mean survival after a diagnosis of CMV retinitis was 4 months in the maintenance group and 4.5 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
Protease inhibitors were not generally prescribed during the time period the patients included in this study were seen, and in fact none were used in 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.