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Risk of developing CMV retinitis following non-ocular CMV end organ disease in AIDS patients

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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.

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 after a mean follow up of 6.4 months (range fest CMV infection a CMV retinitis occurred

Results

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>
</thead>
<tbody>
<tr>
<td>1</td>
<td>01-06-91</td>
<td>Upper GI</td>
<td>20</td>
<td>GCV(2)/Fosc(1)</td>
<td>GCV</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>01-03-90</td>
<td>Upper GI</td>
<td>10</td>
<td>GCV</td>
<td>11</td>
<td>4</td>
<td></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>2</td>
<td></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></td>
</tr>
<tr>
<td>5</td>
<td>01-05-89</td>
<td>Lower GI</td>
<td>10</td>
<td>GCV(3)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>01-07-92</td>
<td>Lungs</td>
<td>10</td>
<td>GCV(3)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>15-03-95</td>
<td>Upper GI</td>
<td>10</td>
<td>GCV(2)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>01-06-92</td>
<td>Upper GI</td>
<td>10</td>
<td>GCV(4)</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>15-09-92</td>
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<td>10</td>
<td>GCV(2)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>09-10-92</td>
<td>Upper GI</td>
<td>10</td>
<td>GCV(2)/Fosc(2)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>01-06-90</td>
<td>Upper GI</td>
<td>10</td>
<td>GCV(3)</td>
<td>—</td>
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<td></td>
</tr>
<tr>
<td>12</td>
<td>01-04-93</td>
<td>Lower GI</td>
<td>10</td>
<td>GCV(3)</td>
<td>9</td>
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<td></td>
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<tr>
<td>13</td>
<td>08-05-95</td>
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<td>20</td>
<td>Fosc(3)</td>
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<td></td>
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<td>14</td>
<td>09-12-93</td>
<td>Lower GI</td>
<td>10</td>
<td>GCV(2)</td>
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<td></td>
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<tr>
<td>15</td>
<td>20-08-92</td>
<td>Lower GI</td>
<td>10</td>
<td>GCV(3)/Fosc(1)</td>
<td>—</td>
<td></td>
<td></td>
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<tr>
<td>16</td>
<td>01-08-92</td>
<td>Lower GI</td>
<td>20</td>
<td>GCV(3)</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>17</td>
<td>01-02-91</td>
<td>Lower GI</td>
<td>20</td>
<td>GCV(2)</td>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td>18</td>
<td>05-03-92</td>
<td>Lungs</td>
<td>10</td>
<td>GCV(1)/Fosc(2)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>20-09-90</td>
<td>Upper GI</td>
<td>80</td>
<td>GCV(2)</td>
<td>—</td>
<td></td>
<td></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 × 10⁹/l. Induction therapy: GCV= ganciclovir 5 mg/kg/day twice daily; Fosc= foscavir 90 mg/kg/day 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.

respond favourably to induction therapy with either ganciclovir, 5 mg/kg/day twice daily, or foscavir, 90 mg/kg/day twice daily, or a combination of both drugs. Maintenance therapy after extraocular CMV disease is generally not prescribed. All patients included had regular, monthly eye examinations by an ophthalmologist after the occurrence of an extraocular CMV disease. According to the CDC classification, CMV retinitis was diagnosed when a necrotising retinitis with a characteristic “cheese-like” appearance was present with or without haemorrhages. Additionally a favourable response to therapy had to be present.

Entry criteria were fulfilled in 20 patients. Patient characteristics are shown in Table 1. Mean age at diagnosis of extraocular CMV disease was 42 years (range 32–58 years). In two patients the CMV disease was the AIDS defining diagnosis. In the other 18 patients the AIDS diagnosis preceded the diagnosis of CMV disease. According to the CDC classification, CMV retinitis was diagnosed after 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. 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 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 16 patients without 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
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 $\times 10^3$/l in over 90% of these patients.2 In another prospective study of 367 HIV positive patients, with a CD4+ count below 100 cells $\times 10^3$/l, and a mean follow up of 2.9 years, 32% of the patients developed a CMV retinitis.3

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 extracellular 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 extracellular 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 extracellular CMV disease is that the association between both events is very high.3 5 6 10

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 positive patients, seen between 1984 and 1994, necropsy findings in a cohort of 1227 HIV positive patients, with a CD4+ count below 100 cells $\times 10^3$/l, and a mean follow up of 2.9 years, 32% of the patients developed a CMV retinitis.3

Although our study does not provide conclusive evidence in favour of maintenance therapy after an initial extracellular 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.

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 extracellular CMV disease, after a mean follow up of 6.4 months, found in this study, it seems obvious that extracellular CMV disease strongly predisposes to the subsequent development of CMV retinitis. CMV retinitis occurred despite the fact that extracellular 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.

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