Influence of highly active antiretroviral therapy on the development of CMV disease in HIV positive patients at high risk for CMV disease

Verbraak, F.D.; Boom, W.R.; Wertheim-van Dillen, P.M.E.; van den Horn, G.J.; Kijlstra, A.; de Smet, M.D.

Published in: British journal of ophthalmology

DOI: 10.1136/bjo.83.10.1186

Citation for published version (APA):
Influence of highly active antiretroviral therapy on the development of CMV disease in HIV positive patients at high risk for CMV disease

Frank D Verbraak, René Boom, Pauline M E Wertheim-van Dillen, Gerardus J van den Horn, Aize Kijlstra and Marc D de Smet

Br. J. Ophthalmol. 1999;83;1186-1189

Updated information and services can be found at:
http://bjo.bmj.com/cgi/content/full/83/10/1186

These include:

References
This article cites 13 articles, 5 of which can be accessed free at:
http://bjo.bmj.com/cgi/content/full/83/10/1186#BIBL

1 online articles that cite this article can be accessed at:
http://bjo.bmj.com/cgi/content/full/83/10/1186#otherarticles

Rapid responses
You can respond to this article at:
http://bjo.bmj.com/cgi/eletter-submit/83/10/1186

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections
Articles on similar topics can be found in the following collections

- HIV Infection/AIDS (1314 articles)
- Ophthalmology (1579 articles)

Notes

To order reprints of this article go to:
http://www.bmjournals.com/cgi/reprintform

To subscribe to British Journal of Ophthalmology go to:
http://www.bmjournals.com/subscriptions/
Influence of highly active antiretroviral therapy on the development of CMV disease in HIV positive patients at high risk for CMV disease

Frank D Verbraak, René Boom, Pauline M E Wertheim-van Dillen, Gerardus J van den Horn, Aize Kijlstra, Marc D de Smet

Abstract

Background/aims—In the pre-HAART era, HIV positive patients with CD4+ cell counts below 50 cells ×10^6/l, and those with detectable cytomegalovirus (CMV) DNA in their peripheral blood, were considered to be at high risk for the development of CMV disease. With the start of highly active antiretroviral therapy (HAART), a restoration of immune function occurred in these patients, and as a consequence patients became less vulnerable to CMV disease. Since it is not exactly known how HAART influences CMV viral load in peripheral blood and the incidence of CMV disease in high risk HIV positive patients a group of patients was followed before and after initiation of HAART.

Methods—29 HIV positive patients, seen in the first 3 months of 1996 at the AIDS clinic of the Academic Medical Centre, at high risk for development of CMV disease (positive CMV DNA assay in blood and/or CD4+ cell count below 50 cells ×10^6/l), not receiving anti-CMV maintenance therapy, were included in a prospective cohort study. HAART was started in the second trimester of 1996. Patients were evaluated for the occurrence of CMV retinitis, or CMV disease elsewhere, comparing the incidence of CMV events before and after the start of HAART. Following the introduction of HAART, CD4+ cell counts and quantitative polymerase chain reaction (PCR) for CMV DNA in blood were monitored in all patients who remained alive and were not receiving anti-CMV maintenance therapy (n=22). Follow up was performed until August 1998; the mean follow up after the start of HAART was 14.9 months (range 8–22 months).

Results—In the pre-HAART period four patients developed CMV disease, and four died (without clinically manifest CMV disease). After the start of HAART no patient developed CMV disease or died. With HAART, the mean CD4+ cell counts increased from 34 cells ×10^6/l to 194 cells ×10^6/l at the end of follow up, CMV DNA could be detected in the blood of 11 patients. Quantification showed a decline in the amount of detectable DNA during follow up. At the last examination only one patient showed a positive PCR assay. This was the only patient with a CD4+ cell count remaining below 100 cells ×10^6/l.

Conclusion—In HIV positive patients at high risk of CMV retinitis, either with a positive CMV PCR assay in blood and/or with CD4+ cell counts below 50 cells ×10^6/l, HAART causes a dramatic decrease in the occurrence of CMV disease. This decrease is paralleled by an increase in CD4+ cell count, and a decrease in the amount of CMV DNA in the blood, which was below detection levels in all patients with CD4+ cell counts above 100 cells ×10^6/l.

The presence of cytomegalovirus (CMV) DNA either in whole blood or in cell free samples has been recognised as an important risk factor, in addition to low CD4+ cell counts, for the development of clinical manifest CMV disease in HIV positive patients. Studies on serum or plasma samples reported useful statistical variables for CMV DNA polymerase chain reaction (PCR) assays in predicting CMV disease (sensitivity between 75% and 90%; specificity between 60% and 85%; positive predictive value between 60 and 70%; negative predictive value between 80 and 98%). The overall incidence of CMV retinitis in these studies during a follow up period of 12 months was between 25% and 35%. Spector et al reported a 12 month Kaplan–Meier CMV disease event rate of 14% in PCR CMV negative patients and of 43% in the PCR positive patients, corresponding to a 3.4-fold increased risk of developing CMV disease. In over 90% of cases CMV disease manifested itself as retinitis.

The use of antiretroviral combination therapy—for example, triple therapy consisting of two reverse transcriptase inhibitors and one protease inhibitor, often called highly active antiretroviral therapy (HAART), has resulted in a dramatic change in the morbidity associated with HIV. A significant decline in the incidence of CMV disease has been reported in patients receiving this combination antiretroviral therapy. Van den Horn et al reported that patients with CMV retinitis treated with HAART showed no recurrences during a follow up period of 42–52 weeks provided the CD4+ cell counts remained above 100 cells ×10^6/l. HAART induces a rapid redistribution and eventually a restoration of the immune system, and as a result, patients, normally expected to be at high risk for developing CMV retinitis or recurrences of already
Influence of HAART on the development of CMV disease in HIV positive patients

Table 1: Effect of HAART on occurrence of CMV events and survival in HIV positive patients at high risk for developing CMV disease

<table>
<thead>
<tr>
<th>CMV events (n)</th>
<th>Before HAART (n=29)</th>
<th>After HAART (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR+</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>PCR−</td>
<td>(n=16)</td>
<td>(n=13)</td>
</tr>
<tr>
<td>Time to event or death (months)*</td>
<td>0.5, 2, 2, 3</td>
<td>—</td>
</tr>
<tr>
<td>Mean follow up (months)‡</td>
<td>14.9†</td>
<td>11</td>
</tr>
<tr>
<td>Death (n)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Living, without anti-CMV maintenance therapy (n)</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Mean follow up (months)‡</td>
<td>5.0†</td>
<td>14.9†</td>
</tr>
</tbody>
</table>

HAART = highly active antiretroviral therapy; PCR = polymerase chain reaction; + = positive result, − = negative result; *time between start of study and occurrence of event/death; †mean follow up between start of study and start of HAART; ‡mean follow up following start of HAART.

neuropathy. Additionally at each visit, the treating physician from the department of internal medicine received a questionnaire and was explicitly asked for any signs of extracocular CMV disease. CD4+ cell counts were performed every third month.

PCR ANALYSIS

CMV DNA was purified from 50 μl EDTA blood specimens together with 70 molecules of internal control (IC) DNA as described previously, using 20 μl of size fractionated silica particles.10 DNA was eluted in 100 μl TE buffer (10 mM TRIS, 1 mM EDTA, pH 8.0). CMV DNA levels in blood were determined by electrochemical luminescence (ECL) as described previously (Boom R, Sol C, Wiel J, et al. A highly sensitive assay for detection and quantification of human cytomegalovirus DNA in serum and plasma by PCR and electrochemiluminescence, submitted). In short, purified DNA (25 μl) was subjected to a 35 cycle PCR with a single primer pair which amplifies a 578 bp DNA fragment from exon 4 of the major immediate early gene of CMV and a fragment of identical size and GC content from IC DNA. The amounts of CMV and IC PCR products were subsequently determined by electrochemiluminescence (ECL) in the QPCR System 5000 (Perkin Elmer) after hybridisation with (TRIS (2,2’-bipyridine) ruthenium (II) chelate) (TBR) labelled probes specific for either CMV or IC amplimers. The viral load (expressed as copies CMV/ml blood) was calculated from the ratio (R) of CMV over IC ECL signals (after background correction) by the algorithm “copies CMV/ml blood = R × 1400”.

STATISTICAL ANALYSIS

For statistical analysis we compared the CMV event rate, during follow up before the start of HAART, with CMV event rate following the start of HAART, using the Kaplan–Meier method and the log rank test.11

Results

Four patients, all belonging to the CMV PCR positive patient group, developed a clinically manifest CMV disease in the pre-HAART period, after 1, 7, 9, and 12 weeks. Three patients were diagnosed with a CMV retinitis and all were put on maintenance therapy after successful induction therapy. One patient developed a CMV colitis and only received a 3 week induction therapy. Additionally, four patients died before the start of HAART, without clinically manifest CMV disease, after 4, 7, 8, and 17 weeks respectively (Table 1).
Following the start of HAART none of the 22 patients not receiving anti-CMV maintenance treatment developed clinically manifest CMV disease during a mean follow up of 14.9 months (range 8–22 months), and none of these patients died.

Statistical analysis comparing the incidence of CMV disease in patients before and after the start of HAART using the Kaplan–Meier method and the log rank test resulted in a p value of 0.05. Most patients responded to HAART with a steady increase in their CD4+ cell counts (Table 2). The mean CD4 positive count increased from 32 cells × 10^6/l (range 10–150) at the start of follow up, through 144 cells × 10^6/l (range 40 to 260) halfway, to 250 cells × 10^6/l (range 60–500) at the last examination. With the exception of one patient (patient number 13), all CD4+ cell counts were over 100 cells × 10^6/l at the last examination.

In eight patients a positive CMV PCR test was obtained during follow up after the start of HAART (Table 2). Quantification of the PCR test showed a decrease of the amount of CMV DNA detectable in the peripheral blood of all these patients. At the seventh examination, longest follow up 10 months after the start of HAART, none of the tested patients had detectable CMV DNA in their blood. However, in patient 7, 12 months following start of HAART, 280 CMV copies/ml could be measured, and in patient 14, 14 months following the start of HAART, 98 CMV copies/ml could be detected (not shown in Table 2). At the last examination, after a mean follow up of 14.9 months, only one patient (number 13) tested positive, with a CMV viral load of 727 copies/ml. This was also the only patient with a CD4+ cell count less than 100 cells × 10^6/l.

Discussion

In this study we present data showing that in 22 patients, previously considered to be at extremely high risk for developing CMV disease, not one new case of CMV disease manifested itself during a mean follow up of 14.9 months (range 8–22 months).

HAART resulted in a gradual rise in CD4+ lymphocyte counts and a gradual drop in CMV viral load in the peripheral blood. At the last examination CMV DNA became undetectable, with the exception of one patient whose CD4+ cell count remained less than 100 cells × 10^6/l. No patient died during follow up.

Comparing the incidence of CMV disease in the patients before and after the start of HAART, using the Kaplan–Meier method with the log rank test, we found a statistically significant, albeit weak, difference between both observation periods (p = 0.05). A placebo controlled trial (withholding HAART to these patients) was considered to be unethical.

Patients with a history of extraocular CMV disease have been reported to be especially prone to the subsequent development of CMV retinitis. Over 85% of these patients developed a CMV retinitis after a mean follow up of 6.4 months.2 Not one of the three patients (patient nos 9, 10, and 22, Table 2) in this study with gastrointestinal CMV disease developed CMV retinitis during follow up after the start of HAART.

The fact that no clinically manifest CMV disease occurred in our group of HIV positive patients can only be explained by the success of the HAART treatment. Others have also reported the decreased incidence of CMV disease in HIV positive patients with favourable responses to HAART treatment.4 The decrease of CMV viral load found in this study confirms the restoration of the immune system.
Influence of HAART on the development of CMV disease in HIV positive patients

This decrease is paralleled by an increase in CD4+ lymphocyte count, and a decrease in the amount of CMV DNA in the blood, which becomes undetectable in all patients with CD4+ cell counts above 100 cells ×10^6/l.