Cytomegalovirus retinitis after the initiation of highly active antiretroviral therapy: a 2 year prospective study

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Abstract

Background/aims—There have been several recent reports suggesting that the natural history of cytomegalovirus retinitis (CMVR) has been significantly modified with the development of highly active antiretroviral therapy (HAART). This 2 year prospective cohort study assesses the effect of HAART on the incidence and progression of CMVR in patients with CD4 cell counts below 50 cells $\times 10^6/l$. Methods—63 patients, with CD4 cell counts below 50 cells $\times 10^6/l$, who were recruited to a 2 year prospective cohort study at the commencement of combination antiretroviral therapy including the use of the protease inhibitor, indinavir, were reported. The response to HAART was assessed in terms of a rise in the CD4 cell count and fall in HIV viral load. An experienced ophthalmologist performed dilated fundoscopy at the time of recruitment and thereafter at 2 weekly intervals and retinal photography was performed at monthly intervals in patients with CMVR. The activity and progression of CMVR was assessed on the basis of the characteristic clinical and photographic findings.

Results—34 patients achieved at least 50 CD4 cells $\times 10^6/l$ at 3 months after initiation of therapy. New diagnoses of CMVR were seen only in the non-responder group (p=0.085). Overall, the relative risk of a new retinitis event in this group was 3.52 (95% CI 1.16, 10.68) at 3 months compared with those patients who were responsive to HAART. 12 of the 63 patients had previous CMVR. Disease progression was associated with non-response to therapy (p=0.182 exact). In patients with CMVR the median time to first progression was 18 days (95% CI 8, 91) in non-responders and 121 days (95% CI 0.59, 3.65) in responders. By the end of the 2 year follow up period all surviving patients had $>$50 CD4 cells $\times 10^6/l$. No CMV events were seen after 8 months of therapy in either group of patients.

Conclusions—These findings suggest that significant clinical immunorestitution to CMV occurs in response to HAART in patients with CMVR after a lag time of 3–8 months. Initially, a rise in CD4 count is predictive of CMVR response but after the lag period all survivors appear to have developed a clinical immunorestitution to CMV. If HAART is commenced in at risk patients before the development of CMVR the incidence of new disease falls significantly.

Cytomegalovirus retinitis (CMVR) remains the commonest opportunistic infection in patients with AIDS, occurring with increasing frequency as the CD4 count falls below 100 cells $\times 10^6/l$. Before the use of highly active antiretroviral therapy (HAART), consisting of antinucleoside analogues and protease inhibitors, the lifetime risk of developing CMVR was reported to be 44.9%. Although in recent years the number of therapeutic options for the treatment of CMVR has increased, treatment remains suboptimal. Despite a good response in the first instance to anti-CMV therapy, CMVR tends to progress. Before the use of HAART the median time to first progression of CMVR with no anti-CMV maintenance therapy was less than 21 days and with oral ganciclovir maintenance therapy is reported as 57 days. Most patients with CMVR have good vision at presentation. In a series of 287 patients the median time to vision of 6/60 or worse in an eye with retinitis was 13.4 months.

The HIV protease inhibitor indinavir, in combination with nucleoside analogues, has been shown to produce a fall in serum HIV viral load and a sustained rise in CD4+ T cell count. The effect of this partial immunorestitution on the incidence of opportunistic diseases in patients with AIDS is still being evaluated but mortality decreases significantly in patients with CMVR treated with HAART.

Early reports by Whitcup and colleagues report on several patients who continued to develop progression of CMVR in the first 2 months of HAART despite rises in CD4 cell count. However, over-all these patients also had delayed progression of their CMVR.

The aim of this 2 year prospective study was to assess the effect of starting indinavir (as part of antiretroviral combination therapy) on the incidence and progression of CMVR in a larger cohort of late stage HIV patients.

Patients and methods

Patients with CD4 cell counts below 50 cells $\times 10^6/l$ were recruited to the study between November 1995 and November 1996. All
Table 1 Summary of new CMV retinitis and progression of CMV retinitis measuring response to therapy as a rise of 50 cells $\times 10^6$ over 3 months.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>63</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>No with previous CMVR</td>
<td>12</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>No with progression of CMVR</td>
<td>51</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>No with new CMVR</td>
<td>3 (6%)</td>
<td>0</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>No with progression or new CMVR</td>
<td>12 (19%)</td>
<td>3 (9%)</td>
<td>9 (31%)</td>
</tr>
</tbody>
</table>

Discussion
CMVR progression is stopped by HAART within 100 days in subjects whose CD4 counts rise above 50 cells $\times 10^6$ in the first 3 months of therapy. We show that even in the group of patients who initially do not respond to HAART with a rise in the CD4 cell count no further CMV events are seen after 8 months. This indicates that a significant clinical immunorestoration to CMV also occurs in these patients.

The observed decrease in CMV events in these patients is probably associated with a heightened CMV specific T cells response occurring after initiation of HAART.
could result from an increase in T cell activity, an expansion of a pre-existing (but low frequency) CMV specific T cell pool, or by the generation of new T cell clones from the thymus.

Recent studies have shown that it is possible to quantitate specific CMV responses by antigen specific CD4+ lymphocyte responses (upregulation of lymphocyte activation marker CD69+ and production of effector cytokine TNFα) by flow cytometry. 13-15 Komanduri and co-authors have shown that the loss of CMV specific CD4+ lymphocyte responses can be restored after ganciclovir therapy and HAART and that there is strong correlation between the presence of active end organ disease and reduced specific CD4+ lymphocyte frequencies. 14 It is important to note that progression of CMVR post HAART, can occur with higher than expected CD4 cell counts suggesting that the absolute CD4 T cell number increases before T cell function, or T cell repertoire, has been restored.

An increased thymic activity has been suggested to occur during HAART which could cause the observed rise in the “naive” (CD45RA+) T cells. 13 Such a rise in thymically derived T cell clones might provide the best hope of true immunorestoration. The repertoire of T cell specificities, which is decreased during HIV disease, could be broadened providing the immune system with the capability to recognise more potential pathogens. The CD45RA+ increase is seen at 4-6 months, however, implying that the heightened CMV specific activity, suggested in this study, probably occurs too early to be explained by renewed thymic activity. It may, however, contribute to the later reduction in CMV events seen in the survivors of the non-responder group. Indeed it may be more accurate to call this group late responders to therapy rather than non-responders. In this group no correlation was found between CMVR, HIV viral load, and CD4 count. Other authors have noted this discordance between these factors and it is clear that more clinically applicable measures of CMV specific immunorestoration are still required. 16

In this study an absolute rise of CD4 cell count to >50 cells x 10^6/l in the first 3 months of HAART, which was sustained for a further 3 months, was a useful indication of those patients who would develop a significant clinical immunorestoration to CMV and hence may well be a useful predictive marker of those patients who could safely stop anti-CMV therapy. Successful discontinuation of anti-CMV therapy using the CD4 cell count as a marker of immunorestoration has already been reported. 17–19 This study also shows that even in surviving patients who are non-responders sufficient immunological reconstitution has occurred by 8 months to prevent further CMV events. Hence, with time, they too may be considered candidates for the discontinuation of therapy. The survival issues surrounding discontinuation of anti-CMV therapy in this group of patients are still unclear but the potential improvement in quality of life and reduction in drug associated side effects ensure that studies looking at the discontinuation of anti-CMV therapy will continue.

In the 28 patients without previous CMVR who responded to therapy none developed new disease. In clinical studies the probability of developing CMVR has been shown to be 24.6% by 4 years after the first CD4 count <0.1 x 10^6/l. 20 The expected incidence of new CMVR was not seen in patients receiving HAART in this study.

In the pre-HAART era molecular techniques based on quantitative CMV polymerase chain reaction (PCR) made it possible to associate CMV replication with clinical disease. Perterson et al showed that in patients CMV counts <50 cells x 10^6/l the risk of developing CMV end organ disease was associated with an increased CMV viral load. 21 In PCR positive patients, each 0.25 log increase in viral load increased the risk of CMV disease (relative hazard 1.37). The value of this technique together with those measuring CMV specific lymphocyte responses needs further analysis if pre-emptive therapy is to be appropriately targeted to at risk patients in the HAART era.

In summary, this study demonstrates the immunological benefit of HAART on the natural history of CMVR. It not only demonstrates the value of CD4 cell count in predicting a subgroup of patients where new CMV or CMV progression will cease to occur, but also highlights a second subgroup where CMV events cease at a later date. It may well be that CD4 count alone is a useful predictive marker for the safe discontinuation of anti-CMV therapy in the first group, but highlights the fact that in the second subgroup further evaluation of sensitive microbiological and immunological assays are required. In all patients the long term benefit of HAART and the safety of withdrawal of anti-CMV therapy remains unknown.

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