

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

Suzanne M Mitchell, William L Membrey, Michael S Youle, Adanna Obi, Simon Worrell, Brian G Gazzard

Abstract

Background/claims—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 CMV retinitis 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 proteinase 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 funduscopy 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 CMV retinitis 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.

(Br J Ophthalmol 1999;83:652–655)

Cytomegalovirus retinitis (CMVR) remains the commonest opportunistic infection in patients with AIDS, occurring with increasing frequency as the CD4 count falls below 100 cells $\times 10^6/l$.^{1,2} Before the use of highly active antiretroviral therapy (HAART), consisting of antinucleoside analogues and proteinase inhibitors, the lifetime risk of developing CMVR was reported to be 44.9%.³ 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 days⁴ and with oral ganciclovir maintenance therapy is reported as 57 days.⁵ 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.⁶

The HIV proteinase 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.⁷ 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.⁸ Early reports by Whitcup *et al* describe the beneficial effect of HAART on CMVR.⁹ Jacobson 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, overall these patients also had delayed progression of their CMVR.¹⁰

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

Department of Ophthalmology, St Stephen's Centre, Chelsea and Westminster Hospital, London
S M Mitchell
W L Membrey
M S Youle
A Obi
S Worrell
B G Gazzard

Correspondence to: Miss Suzanne Mitchell, Department of Ophthalmology, St Stephen's Centre, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 5HT.

Accepted for publication 18 December 1998

Table 1 Summary of new CMV retinitis and progression of CMV retinitis measuring response to therapy as a rise of 50 cells $\times 10^6/l$ over 3 months

| | All patients | Responders | Non-responders |
|---------------------------------|--------------|------------|----------------|
| No of patients | 63 | 34 | 29 |
| No with previous CMVR | 12 | 6 | 6 |
| No with progression of CMVR | 9 (75%) | 3 (50%) | 6 (100%) |
| No with no previous CMVR | 51 | 28 | 23 |
| No with new CMVR | 3 (6%) | 0 | 3 (11%) |
| No with progression or new CMVR | 12 (19%) | 3 (9%) | 9 (31%) |

patients were CMV antibody positive and were proteinase naive. Combination antiretroviral therapy was commenced with 800 mg indinavir three times a day, together with a change of nucleoside analogues where possible. The patients were followed prospectively and CD4 cell counts were monitored monthly. Dilated funduscopy was performed at the time of entry into the trial and at 2 weekly intervals thereafter in patients with CMVR. Fundal photography was performed monthly in these patients. All ophthalmological examinations were performed by an experienced ophthalmologist. CMVR was diagnosed on the basis of the typical clinical findings and reactivation and progression monitored in the standard way.¹¹ Anti-CMV therapy available during the course of the study included intravenous ganciclovir, foscarnet, and cidofovir, intravitreal ganciclovir, foscarnet, ISIS 2922, and oral ganciclovir, and was assumed to have remained optimal throughout the study.

Examining the change in the patients' CD4 count was used to assess the response to indinavir therapy. Subjects with an increase to 50 cells $\times 10^6/l$ or more, following 3 months of HAART, were classified as "responders". HIV viral load measurements showed significant decreases in the great majority of subjects and was therefore not used to discriminate between patients. Of the 63 patients in this study, there were 34 responders (median increase of 108 cells $\times 10^6/l$, quartiles 72, 144), and 29 non-responders (median increase of 20 cells $\times 10^6/l$, quartiles 1 and 33). There was no difference in duration of follow up between the responders and non-responders ($p=0.92$, Wilcoxon rank sum test).

When frequencies were small, comparison was made by the Fisher's exact two tail test. Otherwise the Cochran-Mantel-Haenszel χ^2 test (CMH) was used to construct a test based confidence interval on relative risk estimates. The log rank test was used to assess the time to progression of disease in those patients with CMV retinitis.

Results

Sixty three patients were recruited into the study, which included 12 patients with previous CMV retinitis. At 3 months, 29 of the patients had achieved greater than 50 CD4 cells $\times 10^6/l$ (responders). Overall, 12 (19%) patients had a new CMV retinitis event or a progression: three (9%) of the responders, and nine (31%) of the non-responders ($p=0.026$, CMH: relative risk 3.52, 95% CI 1.16, 10.68).

In the group with previous CMV retinitis, all of the six non-responders had a disease progression whereas only three of the six

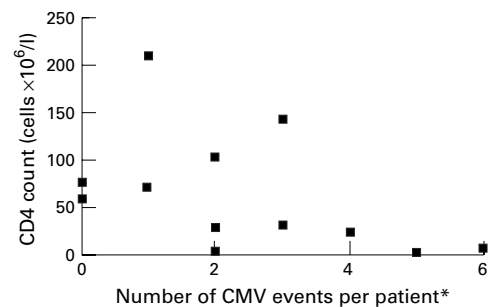


Figure 1 Number of CMV events against CD4 count at 3 months. *There were no CMV events after 8 months.

responders had further retinitis ($p=0.182$, exact). Three patients (6%) with no previous retinitis developed new CMV disease: all were non-responders ($p=0.085$, exact).

In patients with CMVR, the median time to first progression of CMVR after the start of therapy was 18 days for the non-responders (95% CI 8, 91) and 121 days for the responders (95% CI 51, 181) ($p=0.03$, log rank test).

In the follow up period after the initial 3 months, none of the responders developed further progressions or new CMV retinitis. In the non-responder group, however, disease progression continued until 8 months, after which time no further CMV episode occurred throughout the 2 year follow up (Table 1). Indeed, in all the surviving patients, the CD4 count had risen to at least 50 cells $\times 10^6/l$ by the end of the study. Analysis of the HIV viral load in this group of patients at 2 years showed no correlation of viraemia with CD4 count or CMV events.

The number of CMV progressions per year was used to define the event density. A reduction in the CMV retinitis event density was seen in those patients who responded to HAART ($p=0.0036$). In Figure 1 the total number of CMV events per patient is plotted against their CD4 count at 3 months.

There were six deaths in the original cohort of 63 patients. All were non-responders and died within 6 months of commencing HAART ($p < 0.001$ exact).

In this series, response to HAART was not found to be related to the fall in the CD4 count preceding therapy, duration of low CD4 count, previous antiretroviral therapy, or to the presence of CMVR before the commencement of therapy.

Discussion

CMVR progression is stopped by HAART within 100 days in subjects whose CD4 counts rise above 50 cells $\times 10^6/l$ 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 immunorestitution 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. This

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 TNF α) by flow cytometry.^{12,13} 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.¹⁵ Such a rise in thymically derived T cell clones might provide the best hope of true immune reconstitution. 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 immunorestitution are still required.¹⁶

In this study an absolute rise of CD4 cell count to >50 cells $\times 10^6/l$ 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 immunorestitution 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 immunorestitution 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 $\times 10^9/l$.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. Pertel *et al* showed that in patients with CD4 counts <50 cells $\times 10^6/l$ the risk of developing CMV end organ disease was associated with an increased CMV viral load.²¹ In PCR positive patients, each 0.25 log₁₀ 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 and pathogenesis of CMVR. It not only demonstrates the value of CD4 cell count in predicting a subgroup of patients where new CMVR 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.

We thank A W Sawyer for statistical advice.

- Gallant JE, Moore RD, Richman DD, *et al*. Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group. *J Infect Dis* 1992;166:1223–7.
- Kuppermann BD, Petty JG, Richman DD, *et al*. Correlation between CD4+ counts and prevalence of cytomegalovirus retinitis and human immunodeficiency virus-related non-infectious retinal vasculopathy in patients with acquired immunodeficiency syndrome. *Am J Ophthalmol* 1993;115:575–82.
- Hoover DR, Saah AJ, Bacellar H, *et al*. Clinical manifestations of AIDS in the era of pneumocystis prophylaxis. Multicenter AIDS Cohort Study. *N Engl J Med* 1993;329:1922–6.
- Studies of Ocular Complications of AIDS Research Group. Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. *N Engl J Med* 1992;326:213–20.
- Drew WL, Ives D, Lalezari JP, *et al*. Oral ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS. *N Engl J Med* 1995;333:615–20.
- Jabs DA. Ocular manifestations of HIV infection. *Trans Am Ophthalmol Soc* 1995;93:623–83.
- Hammer SM, Squires KE, Hughes MD, *et al*. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* 1997;337:725–33.
- Walsh J, Jones C, Barnes E, *et al*. Increasing survival in AIDS patients with cytomegalovirus retinitis treated with combination antiretroviral therapy including HIV protease inhibitors. *AIDS* 1998;12:613–18.
- Whitcup SM, Fortin E, Nussenblatt RB, *et al*. Therapeutic effect of combination antiretroviral therapy on cytomegalovirus retinitis [letter]. *JAMA* 1997;277:1519–20.

- 10 Jacobson MA, Zegans M, Pavan PR, *et al*. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. *Lancet* 1997;**349**:1443–5.
- 11 Holland GN, Buhles WC Jr, Mastre B, *et al*. A controlled retrospective study of ganciclovir treatment for cytomegalovirus retinopathy. Use of a standardized system for the assessment of disease outcome. *Arch Ophthalmol* 1989;**107**:1759–66.
- 12 Waldrop SL, Pitcher CJ, Peterson DM, *et al*. Determination of antigen-specific memory effector CD4+ T cell frequencies by flow cytometry: evidence for a novel, antigen specific homeostatic mechanism in HIV-associated immunodeficiency. *J Clin Invest* 1997;**99**:1739–50.
- 13 Prussin C, Metcalfe DD. Detection of intracytoplasmic cytokine using flow cytometry and directly conjugated anti-cytokine antibodies. *J Immunol Methods* 1995;**188**:117–28.
- 14 Komanduri KV, Viswanathan MH, Wieder ED, *et al*. Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. *Nat Med* 1998;**4**:953–6.
- 15 Kelleher A, Carr A, Zaunders J, *et al*. Alterations in the immune response of human immunodeficiency virus (HIV)-infected subjects treated with an HIV-specific protease inhibitor, ritonavir. *J Infect Dis* 1996;**173**:321–9.
- 16 Kaufmann D, Pantaleo G, Sudre P, *et al*. CD-4 cell count in HIV-1 infected individuals remaining viraemic with highly active antiretroviral therapy (HAART). *Lancet* 1998;**351**:723–4.
- 17 Tural C, Romeu G, Sirera D, *et al*. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. *J Infect Dis* 1998;**177**:1080–3.
- 18 Macdonald JC, Torriani FJ, Morse LS, *et al*. Lack of reactivation of cytomegalovirus (CMV) retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4 T cells in response to highly active antiretroviral therapy. *J Infect Dis* 1998;**177**:1182–7.
- 19 Vrabec TR, Badassano VF, Whitcup SM. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated CD4+ counts. *Ophthalmology* 1998;**105**:1259–64.
- 20 Bowen E, Sabin C, Wilson P, *et al*. Cytomegalovirus (CMV) viraemia detected by polymerase chain reaction identifies a group of HIV-positive patients at high risk of CMV disease. *AIDS* 1998;**11**:889–93.
- 21 Pertel P, Hirschtick RE, Phair J, *et al*. Risk of developing cytomegalovirus retinitis in persons infected with the human immunodeficiency virus. *J Acquir Immune Defic Syndr* 1992;**5**:1069–74.



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

Suzanne M Mitchell, William L Membrey, Michael S Youle, et al.

Br J Ophthalmol 1999 83: 652-655

doi: 10.1136/bjo.83.6.652

Updated information and services can be found at:

<http://bjo.bmj.com/content/83/6/652.full.html>

References

These include:

This article cites 20 articles, 6 of which can be accessed free at:

<http://bjo.bmj.com/content/83/6/652.full.html#ref-list-1>

Article cited in:

<http://bjo.bmj.com/content/83/6/652.full.html#related-urls>

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 online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Eye \(globe\)](#) (543 articles)

[Retina](#) (1217 articles)

[Epidemiology](#) (766 articles)

Notes

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>