Discontinuation of Anticytomegalovirus Therapy in Patients With HIV Infection and Cytomegalovirus Retinitis

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Context  Persons with cytomegalovirus (CMV) retinitis and acquired immunodeficiency syndrome (AIDS) have required lifelong anti-CMV therapy to prevent the progression of retinal disease and subsequent loss of vision.

Objective  To determine whether patients who were taking highly active antiretroviral therapy (HAART) and who had stable CMV retinitis could safely discontinue anti-CMV therapy without reactivation of their retinitis or increase in human immunodeficiency virus (HIV) viral load.

Design  Prospective nonrandomized interventional trial performed from July 1997 to August 1999.

Setting  Clinical Center of the National Institutes of Health, Bethesda, Md.

Patients  Fourteen patients with stable CMV retinitis and HIV infection and CD4+ cell counts higher than 0.15 × 10^9/L and being treated with systemic anti-CMV medications and HAART.

Interventions  Discontinuation of specific anti-CMV therapy.

Main Outcome Measures  Reactivation of CMV retinitis, development of extraocular CMV infection, detection of CMV in blood and urine, HIV burden, immunologic function, quality of life, morbidity, and mortality.

Results  Twelve (89.7%) of 14 patients had evidence of immune recovery uveitis before anti-CMV drugs were discontinued. No patient had reactivation of CMV retinitis or development of extraocular CMV disease during mean follow-up of 16.4 months (range, 8.3-22.0 months) without anti-CMV therapy. Human immunodeficiency viral load remained stable following cessation of anti-CMV medications. Blood and urine assays for CMV were briefly positive in 9 patients but did not predict reactivation of CMV disease. Worsening immune recovery uveitis was associated with a substantial (>3 lines) vision loss in 3 patients.

Conclusions  Maintenance anti-CMV medications were safely stopped in those patients who had stable CMV retinitis and elevated CD4+ cell counts and who were taking HAART. The study demonstrates that immune recovery following potent antiretroviral therapy is effective in controlling a major opportunistic infection, even in patients with a history of severe immunosuppression.

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0.10 × 10⁹/L. Without therapy, CMV retinitis leads to diffuse retinal necrosis and blindness, with a median time from detection of active CMV retinitis to progression of disease of 2 to 3 weeks. Systemic therapy slows the progression of retinitis only moderately to a median time to progression with 2 months with intravenous ganciclovir a median time to progression with 2 progression of retinitis only moderately to a median time to progression with 2 months with intravenous ganciclovir.

Systemic therapy slows the progression of retinitis only moderately to a median time to progression of 2 to 3 months with intravenous ganciclovir or foscarnet sodium2 and is associated with considerable toxic effects, inconvenience, and financial cost. Several case series have suggested that CMV might not reactivate after stopping maintenance anti-CMV therapy in some patients with AIDS who had elevated CD4+ cell counts and were taking combination antiretroviral therapy.4-10 The purpose of this clinical trial was to investigate prospectively whether anti-CMV therapy could be safely discontinued in patients who have some degree of immune recovery while receiving highly active antiretroviral therapy (HAART). The effect of discontinuing anti-CMV therapy on plasma human immunodeficiency virus (HIV) viral load, the ability to detect CMV in the urine or blood, and intraocular inflammation was also evaluated.

METHODS

Study Design

The study protocol complied with the principles of the Declaration of Helsinki and was approved by the National Eye Institute Data and Safety Monitoring Committee and the National Eye Institute Institutional Review Board. Informed consent was obtained from all study participants. All patients continue to be followed up until progression of CMV retinitis or death.

Patients

Eligible patients included women and men at least 18 years of age with a diagnosis of CMV retinitis and HIV infection with a CD4+ cell count higher than 0.15 × 10⁹/L.11 Patients had inactive CMV retinitis that was not immediately sight-threatening based on examination by 2 ophthalmologists and confirmed by centralized grading of retinal photographs by an independent reading center. Retinitis was defined as not immediately sight-threatening if located at least 1000 µm away from the optic disc or more (periphery of zone 1) or if the visual acuity in the affected eye was already severely reduced from any cause (fewer than 19 letters as measured on an Early Treatment of Diabetic Retinopathy Study [ETDRS] chart).12 Patients had to be receiving systemic anti-CMV therapy with ganciclovir, foscarnet, or cidofovir at maintenance doses. Patients receiving immunotherapy for AIDS, such as interleukin 2, were assessed for eligibility at least 1 month after the last infusion. Patients were excluded from the study if they had received a sustained-release ganciclovir intravitreal implant.

Study Procedure

Systemic anti-CMV medications were discontinued in enrolled patients. Study visits were performed at baseline, every 2 weeks for the first 3 months of the study, every 3 weeks from 3 to 6 months after baseline, and at least every 4 weeks thereafter.

Data Collection

All study visits included a complete ophthalmologic examination, including slit lamp biomicroscopy and dilated retinal examination, and 60° retinal photographs graded at a centralized reading center (Fundus Photograph Reading Center, University of Wisconsin, Madison). Best corrected visual acuity was measured using logarithmic charts and a standardized protocol. Immune recovery uveitis was defined as the presence of 2+4 vitritis associated with greater than a 2-line loss in visual acuity or clinically documented macular edema. A medical history and physical examination were performed at each visit. Human immunodeficiency virus antibody using enzyme-linked immunosorbent assay and Western blot were obtained at baseline. A quality of life assessment using the National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25, Copyright 1996, RAND, Santa Monica, Calif) was performed at baseline and every 3 months thereafter. CD4+ cell counts on whole blood and HIV load obtained on plasma were taken at baseline and every 1 to 2 months thereafter using a branched DNA (bDNA) assay (Chiron, Emeryville, Calif). Cytomegalovirus shell vial and standard cultures on blood were performed at each study visit.13 The presence of CMV in whole blood was detected and quantified using non-nested polymerase chain reaction (PCR) to amplify 149 base pairs of the human cytomegalovirus glycoprotein B gene (gpUL55). Positive samples from the qualitative assay were quantitated from 5 µL of DNA extracted from 200 µL of whole blood as previously evaluated in clinical studies.14

End Points

The primary end point for the study was reactivation of CMV retinitis determined by centralized grading of retinal photographs by an independent reading center. Reactivation of CMV retinitis was defined as the time from baseline when (1) a new retinal CMV lesion developed, (2) the border of an existing CMV lesion reactivated as evidenced by opacification and whitening, or (3) the border of any CMV lesion advanced by 750 µm over a 750-µm front into previously normal-appearing retina. Secondary end points included the development of extraocular CMV disease, detection of CMV by culture and PCR, HIV burden, adverse events, quality of life measures, and mortality.

RESULTS

Fourteen patients were enrolled in this study between July 1997 and August 1998 and were seen at more than 95% of the expected patient visits. Patient demographics, duration of and treatment for HIV disease and CMV retinitis, length of follow-up, and CD4+ cell counts and maximal HIV viral loads are listed in the Table. Duration of HIV infection prior to study enrollment ranged from 1.8 years to 13.2 years with a median of 6.3 years. All patients were taking at least
Table. Patient Characteristics*  

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<th>Therapy</th>
<th>CMV Date of Diagnosis</th>
<th>Therapy</th>
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<th>CD4* Cell Count, ×10^3/L</th>
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*HIV indicates human immunodeficiency virus; CMV, cytomegalovirus; 3TC, lamivudine; D4T, stavudine; DDI, didanosine; AZT, zidovudine; DDC, zalcitabine; GOPO, ganciclovir sodium; IL-2, interleukin 2; PO, oral; and IV, intravenous.
†Receiving at time of enrollment.

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3 antiretroviral agents with at least 1 protease inhibitor. The length of time between first CMV retinitis diagnosis and enrollment ranged from 1.1 years to 3.3 years (mean 1.9 years). The median CD4+ cell count at the time of diagnosis of CMV retinitis was 0.025 × 10^9/L (range, 0.0-0.11 cells × 10^9/L). All patients had CD4+ cell counts in excess of 0.15 × 10^9/L at screening for eligibility. The CD4+ cell counts at the time of discontinuation of anti-CMV medications ranged from 0.08 to 1.3 × 10^9/L (median, 0.032 × 10^9/L). The CMV retinitis was unicocular in 8 patients; 3 patients had retinitis less than 1500 µm from the optic disc or less than 3000 µm from the fovea. Twelve (85.7%) of 14 patients had evidence of immune recovery uveitis in an eye with CMV retinitis prior to discontinuation of anti-CMV medications, based on a decline in visual acuity in 10 patients and macular edema in 2 patients.

Cytomegalovirus retinitis did not progress in any patient after a mean of 16.4 months (range, 8.3-22.0 months) after stopping anti-CMV therapy. During the study, 1 patient had an improvement in visual acuity of at least 15 letters. Four patients had a decrease in visual acuity of at least 15 letters from baseline in at least 1 eye on at least 2 consecutive visits. Three of these 4 patients had an increase in immune recovery uveitis characterized by worse vitritis and/or macular edema; all had intraocular inflammation at the time of entry into the study. Vision loss in the fourth patient followed removal of silicone oil that was placed prior to study enrollment for a retinal detachment. None of the visual loss was attributed to progression or reactivation of CMV.

There were no new retinal detachments in any patient. There was no significant difference in the National Eye Institute’s Visual Function Questionnaire composite score at baseline (79) and at 12 months (73) (P > .25). The score ranges from 0-100. The CD4+ cell counts significantly increased over time (P < .001).

Nine patients were culture positive for CMV in their urine by both conventional and shell vial specimens at various times during the study. Qualitative PCR was intermittently positive in 10 patients, but the viral load was too low for formal quantification in 9 of these 10 patients. The 10th patient had a qualitatively positive CMV PCR at week 2 that persisted through week 32. Quantitatively increasing CMV viral load was detected by PCR beginning at week 8 with 3200 copies/mL and increased to 15 600 copies/mL by week 12 but then decreased to levels below detection at weeks 15 through 21.

COMMENT

Standard therapy for CMV retinitis in persons with HIV infection has required lifelong treatment with systemic ganciclovir, foscarnet, or cidofovir or with an intravitreal ganciclovir implant. In this prospective cohort study, all 14 patients with AIDS, inactive CMV retinitis, and CD4+ cell counts higher than 0.15 × 10^9/L were able to discontinue maintenance anti-CMV therapy without progression of retinitis after a mean follow-up of 16.4 months and a minimum follow-up of 8.3 months. Benefits of stopping anti-CMV medications include avoiding toxic effects associated with treatment and decreasing the cost of treatment.

Previous studies have shown that activation of the immune response in patients with AIDS caused by opportunistic infections such as CMV could lead to increased HIV replication. In this study, discontinuation of maintenance anti-CMV therapy causes no significant changes in plasma HIV.

Potent combination antiretroviral therapy has decreased the incidence of CMV retinitis and altered its clinical presentation. Although mild vitreous inflammation (vitritis) was reported in patients with severe immunosuppression and with CMV retinitis, more profound inflammation is now occurring in patients with inactive CMV retinitis receiving HAART. This immune recovery uveitis is characterized by significant vitritis, increased permeability and leakage of the central retinal blood vessels causing retinal edema (cystoid macular edema), fibrotic tissue adherent to the retina (epiretinal membranes), and swelling of the optic nerve head (disc edema). Immune recovery uveitis was documented in 12 of 14 patients at baseline, and substantially increased in 3 patients during the course of the trial. Although there is variability in the occurrence of immune recovery uveitis reported in the literature, other investigators have reported immune recovery uveitis in about 90% of patients with CMV retinitis on HAART. The reason for the high prevalence of immune recovery uveitis in this study remains unclear, but it may be related to the strict adherence and a strong response to antiretroviral therapy. The median CD4+ cell count was above 0.30 × 10^9/L at baseline. Since immune recovery uveitis has been reported in patients with increasing CD4+ cell counts who continue to receive anti-CMV medications, larger studies will be needed to determine if stopping anti-CMV medications exacerbates the uveitis.

No new retinal detachments occurred during the study, although the risk in a similar population before the use of combination antiretroviral therapy was 19% at 6 months. Intraocular inflammation and hypertrophy of the retinal pigment epithelium may be associated with increased adherence of the retina and a decreased risk of retinal detachment.

In this study, maintenance anti-CMV therapy was stopped in patients with CD4+ cell counts higher than 0.15 × 10^9/L receiving HAART and with CMV retinitis that was not immediately sight threatening. Stopping anti-CMV medications in patients with immediate sight-threatening retinitis should only be considered in patients who can have frequent examinations. All patients in this trial were receiving HAART for at least 4 months prior to stopping anti-CMV medications. Since patients may not have adequate immunologic protection during the first several weeks while receiving HAART as CD4+ cell counts are rising, we cannot make recommendations on stop-
ping anti-CMV medications in patients who have recently started HAART.

Although this study lacks a control group, absence of progression of retinitis in any of the 14 patients is significant since other well-controlled randomized clinical trials prior to the use of HAART report a median time to CMV retinitis progression of 3 weeks in patients without specific anti-CMV therapy and 2-27 and 2 months in patients taking specific anti-CMV therapy and with CD4+ cell counts lower than 0.050 \times 10^9/L.\textsuperscript{28} The lack of reactivation of retinitis or development of extraocular CMV disease in our patients is likely due to improved immunologic control of CMV infection.

Because of the clonal nature of the antigen-specific immune response, there was concern that increased T-cell numbers following potent antiretroviral therapy may not restore adequate protection against opportunistic pathogens such as CMV. This study provides clinical proof that immune recovery in patients receiving HAART is effective in controlling a major opportunistic infection, even among those with a history of severe immunosuppression.

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REFERENCES


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