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Evaluation of the United States Public Health Service guidelines for discontinuation of anti-CMV therapy after immune recovery in patients with CMV retinitis

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Abstract

Purpose—To evaluate US Public Health Service (USPHS) guidelines for discontinuing anti-CMV therapy in patients with AIDS who have immune recovery and quiescent retinitis after initiating highly active anti-retroviral therapy (HAART).

Design—Cohort study of patients with CMV retinitis (Longitudinal Study of Ocular Complications of AIDS).

Methods—Participants had CMV retinitis and CD4+ T-cell counts of 50 cells/uL or fewer enrolled from 1998 to 2009 who demonstrated sustained immune recovery (two consecutive

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CD4+ T-cell counts of 100 cells/uL or more at least 6 months apart) and inactive retinitis. Participants were classified into 2 groups according to anti-CMV treatment after immune recovery: (1) continued anti-CMV therapy and (2) discontinued therapy. We evaluated survival, visual acuity, and CMV retinitis activity; we employed propensity scores to adjust for confounding factors for these analyses.

Results—Of 152 participants reviewed, 71 demonstrated immune recovery; 37 of whom discontinued therapy and 34 who continued therapy. At immune recovery, participants continuing therapy tended to be older (44 vs 40 years, $P=0.09$), have bilateral retinitis (53% vs 32%, $P=0.10$), and have lower CD4+ T-cell counts (148 vs 207 cells/ μ L, $P<0.001$). There were no statistical differences in any of the clinical outcomes (death, retinitis progress, visual acuity or incidence of bilateral retinitis). Both groups lost visual acuity during follow-up, on average 1.2 letters per year ($P<0.01$).

Conclusion—Discontinuation of anti-CMV therapy after immune recovery did not increase the risk of poor outcomes. These results support the current guidelines for discontinuation of anti-CMV therapy after achievement of sustained immune recovery.

Keywords

CMV retinitis; immune recovery; maintenance therapy; USPHS guidelines

Introduction

Cytomegalovirus (CMV) retinitis is typically a late-stage opportunistic infection in patients with acquired immune deficiency syndrome (AIDS) and severe immunodeficiency, CD4+ T-cell counts fewer than 50 cells/uL. Before the introduction of highly active antiretroviral therapy (HAART) up to 30% of patients with AIDS developed cytomegalovirus (CMV) retinitis.¹ Chronic maintenance therapy with an anti-CMV agent was required to prevent reactivation of the disease; time to retinitis progression after stopping therapy was typically 6 to 8 weeks.^{2,3} After the introduction of highly active anti-retroviral therapy (HAART), the incidence of CMV retinitis declined dramatically because of the preservation or restoration of immune function in many patients with AIDS associated with use of HAART.⁴ There have been several case-reports of patients with AIDS-related CMV retinitis who experience immune recovery, as evidenced by a sustained increase in CD4+ T cell counts to more than 100 cells/uL, reporting that they can discontinue maintenance therapy without reactivation of CMV retinitis.^{5–11} There have not been long-term studies comparing survival and vision loss in patients discontinuing treatment to those continuing treatment after immune recovery.

Based on the case reports of successful discontinuation of treatment without disease reactivation, the United States Public Health Service (USPHS) guidelines for secondary prophylaxis were revised in 1999 to suggest discontinuing anti-CMV therapy once patients with quiescent retinitis achieve sustained immune recovery.¹² Continued close follow-up by an ophthalmologist is recommended since reactivation of retinitis and vision loss due CMV retinitis may occur among patients with CD4+ T-cell counts higher than 200 cells/uL, albeit at much reduced rates.^{10,12–14} The purpose of this analysis was to evaluate and compare clinical outcomes (retinitis activity, visual acuity loss, and survival) between patients who continued on maintenance anti-CMV therapy after immune restoration compared to those who discontinued therapy according to the USPHS treatment guidelines. Participants with CMV retinitis enrolled and followed in the multicenter Longitudinal Study of Ocular Complications of AIDS (LSOCA) between 1998 and 2009 were evaluated.

Methods

LSOCA is a prospective, observational study designed to collect data on the incidence, prevalence, and complications due to AIDS-related ocular morbidities during the era of HAART.^{15,16} Recruitment began in 1998 at 19 clinical centers across the United States, most located in urban areas with large HIV-infected populations. The study is an open-cohort design, and recruitment is continuing to at least 2011. The protocol and consent statements were approved by Institutional Review Boards at all participating centers. Eligible patients were diagnosed with AIDS as defined by the 1993 Center for Disease Control diagnostic criteria for AIDS.¹⁷ Participants eligible for this analysis were enrolled from September 1998 to January 2009; the data base was frozen for this analysis as of 31 July 2009.

Participants with CMV retinitis were seen every 3 months for the first 10 years of the study (September 1998 – July 2008) after which they were seen every 6 months (August 2008 – July 2009). At each follow-up visit participants underwent an eye exam that included slit lamp exam and dilated indirect ophthalmoscopy, a medical history interview, and assessment of best-corrected visual acuity using logarithmic visual acuity charts according to a standard protocol.¹⁸ The location of the CMV retinitis lesion in each eye was categorized into three zones based on a standard classification system.¹⁹ Zone 1 is defined as the area within 1500 μm of the optic nerve or within 3000 μm of the center of the macula. Zone 2 extends from Zone 1 to the vortex veins and Zone 3 lies anterior to the vortex veins. Immune recovery uveitis was diagnosed clinically as the presence of intraocular inflammation in a patient who had undergone immune recovery. Laboratory tests obtained at each follow-up visit included hematology, lymphocyte subset analysis and HIV viral load determinations. Participants meeting the eligibility requirements described below were included in this analysis.

Eligible participants were those with a diagnosis of CMV retinitis at enrollment or during follow-up receiving anti-CMV treatment who had a CD4+ T-cell count of 50 cells/uL or fewer that were observed to have immune recovery during follow-up. Immune recovery was defined as having CD4+ T-cell counts of 100 cells/uL or greater at two or more consecutive visits at least 6 months apart. The date of immune recovery was set at the date of the second CD4+ T-cell count equal or greater than 100 cells/uL. We classified these participants according to the initial management strategy for maintenance therapy after immune recovery, i.e., was the USPHS recommendation initiated six months after immune recovery or not.¹¹ Participants with CMV retinitis whose CD4+ T-cell counts were never observed to be fewer than 50 cells/uL were excluded since an approximate date of immune recovery could not be determined.

Characteristics at immune recovery were compared via Chi-square or Wilcoxon rank sum tests for categorical or continuous variable, respectively. We also evaluated mortality, retinitis progression, and changes in visual acuity, and compared these outcomes between the groups. Survival outcomes (mortality and retinitis progression) were evaluated with Kaplan-Meier curves and proportional hazards regression models with staggered-entry; the entry anchor time (time=0) was the date of immune recovery (the second consecutive CD4+ T-cell count greater than or equal to 100 cells/ μL).²⁰ Analyses needed to be adjusted for confounders since the allocation of patients to discontinue vs. continue therapy was not randomized and therefore prone to selection bias. Because the number of confounders was large relative to the number of observations, we chose to use propensity scores for covariate adjustment.²¹ Hazard ratios were adjusted for the following characteristics measured at the time of immune recovery: gender, CD4+ T-cell counts, age, bilateral disease status and time since CMV diagnosis; for eye-specific outcomes the percentage of retina involved with

CMV retinitis was also included in the model and P-values were adjusted for patient-level clustering.²² For visual acuity, we defined time zero as the date of immune recovery and used general linear models with patient-level clustering to evaluate change in visual acuity over time.²²

Results

We identified 152 participants with CMV retinitis at study enrollment or incident retinitis that occurred during follow-up that had CD4+ T-cell counts less than 50 cells/uL and were receiving anti-CMV therapy. Sixty-nine participants were diagnosed with CMV retinitis prior to study enrollment, 64 were diagnosed with CMV retinitis at enrollment and 19 were diagnosed during follow-up. Of these 152 participants, 71 (47%) had evidence of immune recovery during follow-up: 38 (55%) with CMV retinitis diagnosed prior to enrollment, 31 (48%) of those with a new diagnosis at enrollment, and 2 (11%) with incident disease during follow-up. Most of these 71 participants were observed to achieve immune recovery after January 2000 (Table 1). We followed these participants for a median time of 5 years (interquartile range: 3 to 7 years) after immune recovery.

Thirty-seven of the eligible participants (52%) discontinued anti-CMV treatment within 6 months of achieving immune recovery, the remaining 34 patients continued on anti-CMV therapy for more than 6 months after immune recovery (Table 1); the median length of continuous therapy was 2.1 years (95% confidence interval 1.5, 2.7 years). Participants who continued anti-CMV therapy tended to be older and had lower CD4 counts at the time of immune recovery. Over 80% of participants in both groups were receiving HAART at the time of immune recovery and continued during follow-up (data not shown).

Participants who continued treatment tended to have a higher rate of bilateral disease, despite the fact that they tended to have a shorter duration from their diagnosis of CMV retinitis to immune recovery (Table 1). The median percentage of retinal area involved with retinitis was the same in both groups and the proportion with involvement of the posterior areas of the retina (zone 1 disease) was similar (Table 2). None of the eyes with CMV retinitis in either group had evidence of CMV lesion border activity at the time of immune recovery. The median visual acuity at immune recovery in eyes with CMV retinitis was less in the eyes of patient's who discontinued treatment, but the difference was not statistically significant and both groups had similar levels of visual acuity impairment in involved eyes (Table 2).

There were no statistically significant differences in the development of bilateral retinitis, mortality, retinitis progression or visual acuity loss between the groups (Table 3, Figures 1: Kaplan-Meier curve for mortality). All cases of retinitis progression were associated with decline in CD4+ T-cell counts to fewer than 100 cells/ μ L, ranging from 3 to 66 cells/ μ L.

Both groups experienced similar losses of visual acuity overtime at similar rates ($P=0.94$, Figure 2). The overall average rate of loss was 1.2 standard letter per year, which was significantly different from zero ($p<0.01$). The rates of visual loss to standard thresholds²³, i.e., worse than 20/40 or 20/200 or worse, were high in both groups (Table 2) with nominally higher rates in the participants discontinuing anti-CMV treatment. However, that group tended to have a lower visual acuity at immune recovery, which may account for this trend.

The most common reason cited for a drop in visual acuity to worse than 20/40 was cataract (10 cases), uveitis with or without macular edema (4 cases, 2 of which were classified as immune recovery uveitis), CMV retinitis (4 cases), epiretinal membrane (3 cases), and optic nerve atrophy (1 case); in some cases more than 1 reason was cited and no reason was cited

for 3 cases. Most of these eyes (11 of 14 in the discontinued group and 6 of 10 in the continued group) recovered vision to 20/40 or greater after the initial drop below 20/40 was noted. However, not all affected eyes returned to the level of vision measured at the time of immune recovery nor did all remain better than 20/40 after regaining visual acuity to that level.

We evaluated the influence of other factors on clinical outcomes. Women had a higher rate of death rate and higher rates of progression of CMV retinitis than men (data not shown). Higher viral loads at immune recovery were associated with higher risk of progression of CMV retinitis (data not shown). These variables were included as covariates in the adjusted analysis of risk (Table 3).

Discussion

Prior to introduction of HAART and other effective therapies for AIDS, HIV-related CMV retinitis was an end-stage opportunistic infection with a median life expectancy of less than a year after diagnosis.² Patients with CMV retinitis now are likely to live much longer after diagnosis with substantially lower rates of retinitis progression generally with better clinical and visual acuity outcomes.^{4, 24} In 1999, the USPHS treatment guidelines for management of opportunistic disease were modified to recommend discontinuation of secondary prophylaxis for CMV retinitis in patient with sustained immune recovery after receiving HAART based on a few case-series that followed patients for retinitis activity.^{6–8} The recommendation in the most recent version of these guidelines is the same²⁵, and also relies on case-series data focusing on CMV retinitis activity. We evaluated data from participants with CMV retinitis followed prospectively in LSOCA from 1998 to 2009. We identified patient who achieved immune recovery and compared clinical outcome for patients who discontinued therapy after immune recovery to those who continued therapy. Our evaluation is unique in that we included data on individuals who continued therapy after immune recovery for comparison, have a longer period of follow-up time (median follow-up of 5 years), and included outcomes not previously reported, i.e., mortality and visual acuity.

Our results show that after adjusting for potentially confounding factors, e.g., CD4+ T cell count, HIV load, bilateral lateral disease status, time since CMV retinitis diagnosis and age, participants who discontinue therapy did at least as well as participants who continued on therapy in terms of retinitis activity, visual acuity and survival. The characteristics of patients at immune recovery (Table 1) and the propensity score analysis indicate the factors that were most associated with the decision to continue treatment were lower CD4+ T-cell count, shorter time since CMV diagnosis, and female gender. The fact that CMV retinitis progression was uniformly associated with low CD4+ T-cell counts indicates that the primary reason for re-activation is immune compromise regardless of the treatment strategy. Furthermore, these results suggest that the phenomenon of immune system lacunae²⁶, i.e., deficiencies in restoration of specific types of T-cells, after immune recovery is rare even in patients that have experienced severe immunodeficiency (all of our patients had a nadir CD4+ of 50 cells/ μ L or fewer).

Visual acuity outcomes were similar in both groups; overall the average loss of visual acuity was 1.2 letters per year. The steady loss of acuity may indicate that despite control of CMV retinitis, these patients maybe at higher risk than other AIDS patients or the general public for significant vision loss over their lifetimes. Furthermore, patients with HIV and AIDS may develop visual function loss in the absence of CMV retinitis.^{27,28} There were relatively high rates of vision of declining to worse than 20/40 in eyes with retinitis, which is consistent with the steady decline in visual acuity observed.

Our results are strengthened by the fact they are from a multicenter prospective study with standard procedures for follow-up. The case-series addressing this question did not include patients whose treatment was not discontinued, nor did they evaluate longer-term clinical outcomes such as visual acuity or survival. Nonetheless, ours was a relatively small group of patients enrolled in an observational study and thus do not provide definitive evidence for the safety of discontinuing anti-CMV therapy in patients with AIDS and quiescent CMV retinitis after immune recovery. In fact, they illustrate well the difficulties of selection bias when using observational data to address the comparative effectiveness of different treatment strategies even with the use of statistical adjustment procedures to control for confounding by indication. Regardless, these results are the strongest evidence thus far in support of the USPHS guideline because they show that there is no evidence of shortened survival or worsened course of retinitis in patients discontinuing anti-CMV treatment after sustained immune recovery.

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Biography

Janet Holbrook, PhD, MPH is an associate professor of epidemiology at the Johns Hopkins University Bloomberg School of Public Health in Baltimore, Maryland. She is member of the Center for Clinical Trials, which is a multidisciplinary group focused on research and scholarship in the areas of clinical trials evidence-base healthcare. She graduated from the Universities of Maryland and California and received her doctoral degree from The Johns Hopkins University.

Figure 1.

Kaplan-Meier Curve of time to death in years after immune recovery by CMV treatment status. Cont CMV Rx = continued CMV treatment is represented by the solid line; D/C CMV Rx = discontinued CMV treatment is represented by the dashed line.

Figure 2. Boxplots of visual acuity (standard letters) in eyes with CMV retinitis at 6 month intervals starting at immune recovery. Circle and triangle represent outliers for the discontinued and continued treatment groups, respectively. Cont CMV Rx = continued CMV treatment is represented by the open boxes; D/C CMV Rx = discontinued CMV treatment is represented by the shaded boxes.

Table 1

Characteristics of patients with CMV retinitis at immune recovery by treatment strategy (discontinuing vs continuing CMV Rx)

	D/C CMV Rx	Cont. CMV Rx	P-value *
N	37	34	
Demographics			
Age, yrs, median (IQR)	40 (35, 44)	44 (37, 49)	0.09
Male gender, N (%)	29 (78%)	24 (71%)	0.59
Race, N (%)			0.69
White, non-Hispanic	14 (38%)	11 (32%)	
Black, non-Hispanic	15 (40%)	11 (32%)	
Hispanic	6 (16%)	9 (26%)	
Other	2 (5%)	3 (9%)	
HIV characteristics			
HIV exposure, N (%)			0.50
Male to male sexual contact	19 (51%)	12 (32%)	
Injection drug use	1 (3%)	2 (6%)	
Heterosexual contact	12 (32%)	12 (35%)	
Other	5 (14%)	8 (23%)	
HIV viral load: ≤ 400 copies/mL, N (%)	20 (54%)	18 (53%)	0.78
CD4 count, cells/uL, median (IQR)	207 (157, 295)	148 (129, 170)	0.001
HAART exposure, N (%)	31 (84%)	28 (82%)	1.00
Anti-retroviral treatment category, N (%)			1.00
None	1 (3%)	0 (0%)	
1-2 therapies	2 (5%)	2 (6%)	
HAART without protease inhibitor	27 (73%)	25 (74%)	
HAART with protease inhibitor	4 (11%)	3 (9%)	
Date achieved immune recovery			0.29
Before January 2000	6 (16%)	2 (6%)	
January 2000 and December 2004	24 (65%)	22 (65%)	
January 2005 or later	7 (19%)	10 (29%)	
CMV retinitis characteristics			
Bilateral involvement, N (%)	12 (32%)	18 (53%)	0.10
Years from CMVR dx to CD4 recovery, median (IQR)	2.4 (1.1, 4.3)	1.5 (0.9, 3.7)	0.15
Follow-up time [†] , yrs, median (IQR)	6.4 (3.3, 8.1)	4.5 (3.0, 6.4)	0.16

Abbreviations: D/C CMV Rx= discontinued CMV treatment; Cont. CMV Rx = continued CMV treatment; HAART = highly active anti-retroviral therapy; IQR = inter-quartile range

* Based on Fishers exact test for categorical variables and Wilcoxon rank sum test for measured variables

[†] Follow up times for CMV retinitis progression analysis

Table 2

Characteristics of eyes with CMV retinitis at immune recovery by treatment strategy (discontinuing vs continuing CMV Rx)

	D/C CMV Rx	Cont. CMV Rx	P-value*
Eyes with retinitis	49	52	
CMV retinitis			
Percent of retina involved, median (IQR)	20 (15, 50)	20 (10, 50)	0.43
Eyes with zone 1 involvement, N (%)	17 (35%)	21 (40%)	0.68
Eyes with zone 2 involvement, N (%)	40 (82%)	38 (73%)	0.35
Eyes with zone 3 involvement, N (%)	42 (86%)	36 (69%)	0.06
Visual Acuity			
Standard letters, median (IQR)	75 (46, 86)	82 (57, 90)	0.31
Worse than 20/40, N (%)	19 (39%)	18 (35%)	0.66
20/200 or worse N (%)	10 (20%)	11 (21%)	0.93

Abbreviations: D/C CMV Rx= discontinued CMV treatment; Cont. CMV Rx = continued CMV treatment; IQR = inter-quartile range

* Based on Fishers exact test for categorical variables and Wilcoxon rank sum test for measured variables

Table 3

Clinical outcomes among immune recovered CMV retinitis patients by treatment strategy (discontinuing vs continuing CMV Rx)

	D/C CMV Rx		Cont. CMV Rx	HR	Adjusted [†]	
	N (evts/100yr) [*]				95% CI	P-value
Participants	37		34			
Death	5 (2.2)		8 (4.8)	1.71	0.41, 7.22	0.46
Participants [‡]	25		16			
Incident bilateral retinitis	3 (1.1)		4 (1.5)	2.12	0.44, 10.09	0.35
Eyes with retinitis	49		52			
CMV retinitis progression	2 (0.7)		4 (1.5)	0.62	0.16, 2.50	0.50
Eyes with retinitis [‡]	30		34			
worse than 20/40	14 (11.6)		10 (7.6)	0.82	0.26, 2.61	0.74
Eyes with retinitis [‡]	39		41			
20/200 or worse	9 (4.3)		5 (2.7)	0.49	0.12, 2.95	0.53

Abbreviations: D/C CMV Rx= discontinued CMV treatment; Cont. CMV Rx = continued CMV treatment; CI=confidence interval; HR=hazard ratio

^{*} Rate per 100 person-years of follow-up for death and incidence of bilateral disease; rate per 100 eye-years of follow-up in eyes with retinitis at IR for retinitis progression and visual acuity events

[†] Hazard ratio (HR) and 95% confidence intervals calculated using Cox models comparing continued CMV treatment to discontinued treatment at immune recovery; confidence intervals and P-values corrected for within patient clustering for visual acuity outcomes. HR's are adjusted for the following characteristics measured at immune recovery: CD4 count, log of HIV load, age, gender, bilateral disease status and years since CMV diagnosis. Eye-specific outcomes were also adjusted for percentage of retinal involvement and P-values were corrected for within patient clustering. All adjustments were made using propensity scores.

[‡] Number of patients (or eyes) who did not have event of interest at immune recovery.