Incidence of Immune Recovery Vitritis in Cytomegalovirus Retinitis Patients following Institution of Successful Highly Active Antiretroviral Therapy


This study was conducted to determine the likelihood of the development of a new ocular inflammatory syndrome (immune recovery vitritis, IRV), which causes vision loss in AIDS patients with cytomegalovirus (CMV) retinitis, who respond to highly active antiretroviral therapy (HAART). We followed 30 HAART-responders with CD4 cell counts of ≥60 cells/mm³. Patients were diagnosed with IRV if they developed symptomatic vitritis of ≥1+ severity associated with inactive CMV retinitis. Symptomatic IRV developed in 19 (63%) of 30 patients and in 26 (59%) of 44 eyes over a median follow-up from HAART response of 13.5 months. The annual incidence of IRV was 83/100 person-years. Excluding patients with previous cidofovir therapy did not significantly alter the time course of IRV (P = .79). These data suggest that IRV develops in a significant number of HAART-responders with CMV retinitis and is unrelated to previous cidofovir therapy.

Following the introduction of combination antiretroviral treatment including protease inhibitors, many patients with human immunodeficiency virus disease have shown laboratory and clinical evidence of improved immune function [1–3]. Cytomegalovirus (CMV) retinitis is the most common ocular opportunistic infection associated with AIDS and the leading cause of blindness among this patient population. It is a necrotizing retinitis that develops in severely immunocompromised patients with CD4 T lymphocyte levels usually ≤50 cells/mm³ [4].

Highly active antiretroviral treatment (HAART) has affected the incidence, severity, and clinical course of CMV retinitis. Reports show a decrease in the incidence of CMV retinitis since the introduction of HAART [3, 5]. Others have suggested that CMV retinitis is more easily controlled with anti-CMV therapy in patients who respond to HAART [6]. Tural et al. [7] and Macdonald et al. [8] demonstrated that some patients who respond to HAART regain the ability to suppress CMV retinitis without anti-CMV therapy.

HAART has also affected the clinical manifestations of ocular CMV. Prior to the use of protease inhibitors, CMV retinitis was typically characterized by minimal intraocular inflammation [9], possibly because of the severe immunodeficiency involved. Since the advent of HAART, inflammatory complications have been described in the setting of inactive CMV retinitis.

We described a new ocular inflammatory syndrome that develops in patients with inactive CMV retinitis who have experienced an increase in CD4 T lymphocyte levels in response to HAART [10]. This immune recovery vitritis (IRV) manifests symptomatically with vision decrease and floaters and is characterized by posterior segment inflammation, including vitritis, papillitis, and macular changes. Subsequently, Zegans et al. [11] described similar inflammation associated with CMV retinitis in patients who responded to HAART. These initial reports suggest that the clinical significance of this inflammatory syndrome is 2-fold: It is a cause of visual morbidity in patients with CMV retinitis, and it may reflect partial immune recovery.

In our initial report [10], 4.2% of patients with CMV retinitis developed IRV, suggesting that IRV is relatively rare. The initial reports, however, were limited by small groups of affected patients and relatively short follow-up. Since these initial publications, we have seen an increasing number of patients with symptomatic intraocular inflammation associated with HAART and inactive CMV retinitis. To determine the likelihood of developing IRV and to evaluate the effect of time on the development of this new syndrome, we conducted a cohort study of 30 patients with CMV retinitis who responded to HAART over a 13.5-month (range, 3–24) follow-up period.

Methods

Study cohort. We prospectively reviewed the database records of all patients with CMV retinitis from December 1996 through April 1998 at the AIDS Ocular Research Unit (AORU) of the
University of California, San Diego, to identify HAART responders. HAART responders were defined as patients who demonstrated CD4 cell counts of $\geq 60$ cells/mm$^3$ as a result of HAART and maintained these counts for $\geq 2$ months. This definition was based on a previously published report from our group in which patients who fulfilled these criteria successfully maintained inactivity of CMV retinitis without anti-CMV therapy. Diagnosis of CMV retinitis and assessment of activity was based on the typical ophthalmoscopic appearance [4]. The rationale for this choice of study cohort comes from previously published reports [10, 11] as well as from our experience with IRV, from which it has become evident that IRV develops in eyes of patients with a history of CMV retinitis and a HAART-mediated increase in CD4 T lymphocyte levels.

Determination of IRV. Full ophthalmoscopic examination was performed on all CMV retinitis patients. Visual acuity was assessed with the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart. Vitritis was evaluated according to the grading system proposed by Nussenblatt et al. [12]. All patients were examined consecutively by the same examiners (M.P.K., J.C.M., W.R.F.) and reexamined in the event of disagreement, to reduce interobserver variability. Fluorescein angiography was performed on all patients with clinically apparent macular changes, as well as in patients with vitritis and vision decrease, in whom macular changes were not evident on examination. The levels of CD4 T lymphocytes and human immunodeficiency virus mRNA were monitored every 2–3 months. All patients’ medications were reviewed to exclude from the IRV cohort patients who had received rifabutin or cidofovir within 2 months of the onset of inflammation.

Patients were diagnosed with IRV if they developed clinically significant inflammation in the setting of inactive CMV retinitis in one or both eyes. IRV was defined as vitritis of $\geq 1$ severity which caused visually significant floaters and/or decrease in vision of $\geq 1$ lines with or without associated papillitis and macular changes. Patients were diagnosed with more-severe IRV if they had macular fluorescein leakage on fluorescein angiography and/or a $\geq 2$-line decrease in visual acuity.

Statistical methods. For each eye with IRV, we calculated the time to development of IRV from the time of response to HAART (i.e., the date of increase of CD4 cell count $\geq 60$ cells/mm$^3$). For eyes that did not develop IRV, we calculated the time from response to HAART to the final examination date. For each eye with more-severe IRV, we calculated the time to development of more-severe IRV from the date of response to HAART. For eyes that did not develop more-severe IRV (including eyes diagnosed with less severe IRV), we calculated the time to the final examination date from the date of response to HAART.

The incidence of IRV (and more-severe IRV) was calculated as the ratio of the number of patients with IRV in at least one eye divided by the patient-years of study. The probability of developing IRV in at least one eye over time was estimated using Kaplan-Meier methods. To accommodate patients with IRV in both eyes, we used the time to the first diagnosis of IRV. When IRV occurred in only one eye, the time to diagnosis of IRV was used in the analysis. For a patient in whom neither eye had IRV, the time to last examination was used for the analysis. Similar methods were used for estimating the probability of developing more-severe IRV. In situations in which more-severe IRV developed in one eye but not the other, the eye with more-severe IRV was used in the analysis.

Finally, to investigate a possible proinflammatory effect of prior cidofovir therapy, analyses were repeated, excluding eyes in patients with a history of local or systemic cidofovir treatment. Statistical comparisons were made using the log-rank test for comparing survival curves.

Results

At the AORU, 54 patients with AIDS-related CMV retinitis were examined from December 1996 through April 1998. Of these, 52 patients received HAART, and 30 patients were characterized as HAART responders. HAART responders were followed for a median of 21.5 months (range, 6–46) from the first examination date and for a median of 13.5 months (range, 3–24) following increase in CD4 cell count. During the follow-up period, of the 30 patients (44 eyes) who had responded to HAART, 19 patients (63%) developed IRV in 26 eyes (59%). Fifteen IRV patients (50%) had more-severe IRV in 16 eyes (36%). Thirteen (33%) of the 30 patients and 18 of the 44 eyes (41%) had a history of cidofovir therapy. Symptomatic vitreous inflammation did not develop either in any of the 24 patients who did not fulfill the HAART responder criteria or in the cohort of HAART responders prior to increase in CD4 cell count.

Likelihood and time to IRV. The annual incidence of IRV for HAART responders was 83/100 person-years (19/22.9 person-years). The annual incidence for more-severe IRV for HAART responders was 60/100 person-years (15/25.0 person-years).

Figure 1 presents the Kaplan-Meier curve for the time to IRV for all patients in the cohort. The median time to IRV was 43 weeks (95% confidence interval [CI], 35–47). Also shown in figure 1 is the time to IRV for the 17 patients who had never received cidofovir. The median event time was also 43 weeks (95% CI, 26–87). For the 13 patients with prior cidofovir, the median event time was 44 weeks (not shown). There were no significant differences between the event patterns for patients with and without cidofovir treatment ($P = .79$, log-rank).

Figure 2 presents the Kaplan-Meier curve for more-severe IRV for all cohort patients. The median time to more-severe IRV was 45 weeks (95% CI, 40–107). Included in figure 2 is the time to more-severe IRV for patients who had never received cidofovir. The median event time was also 45 weeks (95% CI, 26–107). For patients who had received cidofovir, the median event time was 57 weeks (not shown). There were no significant differences between the event patterns for patients with and without cidofovir treatment ($P = .74$, log-rank).

Characteristics of IRV. All patients with IRV complained of visually significant floaters. Seventeen of the 19 patients had vision decrease of $1–6$ lines, as follows: 5 with 1-line vision loss, 5 with 2-line loss, 3 with 3-line loss, 1 with 4-line loss, 2 with 5-line loss, and 1 with 6-line loss. Visual acuity did not improve in any case over 2–64 weeks (median, 20). All of the 26 affected
Figure 1. Kaplan-Meier curves for time to IRV for all patients and patients who were not treated with cidofovir. There was no significant difference between event patterns for patients with and without prior cidofovir treatment ($P = .79$, log-rank).

Figure 2. Kaplan-Meier curves for time to more-severe IRV for all patients and patients who were not treated with cidofovir. There was no significant difference between event patterns for patients with and without cidofovir treatment ($P = .74$, log-rank).

Eyes had vitritis of 1–3+ severity. Nine eyes of 9 patients developed clinically apparent macular edema, while 8 eyes of 7 patients developed epiretinal membrane changes.

All IRV patients had inactive CMV retinitis in the affected eye(s) at the time of diagnosis of vitritis and were undergoing HAART with one or two reverse-transcriptase inhibitors (lamivudine, stavudine, zidovudine) and one or two protease inhibitors (indinavir, ritonavir, nelfinavir, saquinavir). Consequently, all patients had experienced an increase in CD4 cell count (range of absolute increase, 51–707/mm$^3$; median increase, 113/mm$^3$; range of percent increase, 182%–2618%). The increase in CD4 cell count preceded the onset of vitritis by 2–84 weeks (median, 20).

Discussion

IRV is a cause of visual morbidity in patients with CMV retinitis in the era of HAART. The clinical spectrum of inflammation includes vitritis, papillitis, macular edema, and epiretinal membranes and causes vision decrease and visually significant floaters in the affected patients [10].

IRV seems to be associated with CMV retinitis and an increase in CD4 T lymphocyte levels following HAART. The pathogenesis of this inflammation is unknown. CMV-related vitritis has been reported before the advent of HAART but was associated with active retinitis [13]. In our previous report, we did not find any cases of symptomatic vitritis associated with inactive CMV retinitis prior to use of HAART in 509 patients over 9 years [10]. Similarly, evaluation of a contemporaneous group of 24 non–HAART responders in the current study revealed no such inflammation. In addition, in our initial report, IRV did not develop in CMV retinitis patients who had not responded to HAART with an increase in CD4 cell count or in the eyes of HAART-responders without CMV retinitis [10]. This suggests that IRV may be caused by an immunologic reaction to CMV and may reflect increased immunocompetence.

Inflammatory manifestations associated with CMV retinitis have been described in iatrogenically suppressed patients, after the reduction of immunosuppressive medication [14]. There have been reports of necrotizing lymphadenitis related to latent Mycobacterium avium-intracellulare infection in HAART responders [15]. IRV may represent a similar inflammatory reaction to latent CMV in the eye that is made possible by HAART-mediated improved immune status.

Currently available reports on HAART-related intraocular inflammation describe small groups of patients [10, 11] and report a low probability of development of IRV among patients with CMV retinitis. However, these studies are limited by relatively short follow-up. In the current study, we report on the probability of developing IRV in a cohort of CMV retinitis patients responding to HAART and followed for 13.5 months. Symptomatic IRV developed in 19 (63%) of 30 HAART responders and 26 (59%) of 44 eyes. The annual incidence of IRV for HAART responders was 83/100 person-years, and the median time to IRV was 43 weeks.

All IRV patients had inactive CMV retinitis and presented with symptoms of floaters and/or vision decrease and vitritis that was not present on previous examinations. Our definition of IRV was symptomatic vitritis of $\geqslant 1+$ severity. This included some cases of mild but symptomatic vitritis without macular changes. We included these cases because mild vitritis was the
initial manifestation of IRV in many patients who eventually developed more-severe inflammation with macular changes. Early identification of these patients is significant, as it will allow early treatment of inflammation. It is possible that in other clinical settings IRV may be detected only when it is more severe. For this reason, to estimate the prevalence of more-severe inflammation, we set more-stringent criteria and included only eyes with fluorescein angiographically proven macular changes and/or ≥2 lines of vision loss. We found that 15 (50%) of 30 patients developed more-severe IRV in 16 (36%) of 44 eyes. The annual incidence for more-severe IRV for HAART responders was 60/100 person-years, and the median time to IRV was 45 weeks.

Finally, we performed the above analyses excluding all patients who had previously received cidofovir, to investigate a possible proinflammatory effect of this drug. There were no significant differences between the event patterns for patients with and without cidofovir treatment, thereby suggesting that prior cidofovir use was not a causative factor of inflammation in this cohort of patients.

References