SCIENTIFIC REPORT

Long term visual outcome of patients with cytomegalovirus retinitis treated with highly active antiretroviral therapy

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Background: Healed cytomegalovirus (CMV) retinitis in the setting of highly active antiretroviral therapy (HAART) is complicated by inflammatory sequelae and vision loss.

Aim: To determine the long term visual outcome of AIDS patients with CMV retinitis who received HAART.

Methods: 90 eyes of 63 consecutive AIDS patients with extramacular CMV retinitis were studied prospectively.

Results: Immune recovery status was related to time to onset of epiretinal membrane ($p=0.05$) and cystoid macular oedema ($p=0.06$) as well as to the incidence of cataract ($p=0.001$) and moderate vision loss ($p<0.0001$). Severe vision loss was associated with retinal detachment ($p<0.001$).

Conclusion: AIDS patients with extramacular CMV retinitis lose vision while on HAART. HAART related immune recovery is associated with increased frequencies of epiretinal membrane, cystoid macular oedema, cataract, and retinal detachment with resultant vision loss in AIDS patients with healed CMV retinitis.

Since the introduction of highly active antiretroviral therapy (HAART), patients with AIDS have benefited from profound and sustained elevations in CD4 counts and depression of HIV viral loads. Concurrent with the improved immune response secondary to HAART and immune recovery, researchers in ocular disease have also described a new syndrome called immune recovery uveitis (IRU).¹

IRU may represent an immune reaction to cytomegalovirus (CMV) antigens in the eye made possible by augmentation of immune function causing vitritis with or without cystoid macular oedema (CMO), epiretinal membrane (ERM), or retinal neovascularisation.^{2–4} The use of intravitreal as well as systemic cidofovir in many of these patients are additional cofactors that may contribute to the development of IRU.^{4,5}

The purpose of this study was to determine the long term visual outcome of a large cohort of eyes with good visual acuity (VA) potential, extramacular CMV retinitis and HAART therapy in relation to post-treatment outcomes, including immune failure (IF) or immune recovery (IR), with or without IRU.

METHODS

Study cohort

The study cohort consisted of HIV patients examined at the AIDS Ocular Research Unit of the University of California, San Diego Medical Center between 1986 and 2000. Inclusion criteria included a history of CMV retinitis, history of treatment with HAART, and ETDRS VA of 20/40 or better. Exclusion criteria included CMV retinitis involving the fovea or optic nerve

at time of diagnosis, absence of or incomplete HAART regimen, and VA worse than 20/40 before initiation of HAART. The study cohort combined eyes diagnosed with CMV retinitis before treatment with HAART, subsequent to initiation to HAART, and eyes diagnosed with CMV retinitis concurrently with the initiation of HAART.

Study variables

Study variables included patient age and sex; date of CMV diagnosis and retinal location of CMV lesions; date of initiation of HAART; HAART drugs; occurrence and date of immune recovery (defined as elevation of absolute CD4 count ≥ 50 cells $\times 10^6/l$ for a period of at least 3 months)^{6–12}; pretreatment and post-treatment best corrected ETDRS visual acuity; date of clinically observed and photographic documentation of ERM and/or angiographically demonstrable CMO; visually significant cataract, glaucoma; date and occurrence of retinal detachment (RD); date of intraocular surgery; date and duration of intravenous or intravitreal cidofovir as well as periocular corticosteroids.

Recovery status IF included eyes of patients with immune failure defined as never having achieved absolute CD4 counts of 50 cells $\times 10^6/l$ for a sustained period of 3 or more months despite treatment with HAART. Recovery status IR included eyes of patients having achieved immune recovery without visual blur, floaters, CMO, or ERM. Recovery status IR+IRU included eyes of patients who achieved IR but were subsequently diagnosed with IRU.

With time, as certain patients responded to HAART, some eyes developed IR and converted to subgroup IR. Similarly, as patients in subgroup IR subsequently developed IRU, they were assigned to subgroup IR+IRU.

Statistical analyses

Because we regarded transitions in the immune recovery status (IF, IR, or IR+IRU) as a time dependent covariate, we used Cox regression analyses with time dependent covariates to test for associations between immune recovery status (independent variable) and time to onset of ERM, CMO, and retinal detachment (RD) (dependent variables). Time zero was defined as the intersection time that both HAART and CMV were present. Assuming independence of ocular outcomes within a patient, we conducted all analyses on a per eye basis. Over time, patients (eyes) could move from one subgroup to the next. If a clinical end point (ERM, CMO or RD) was reached, then the patient (eye) status at the time of reaching the end point was used in calculating the incidence rate.

In addition, Fisher's exact tests were used to test for associations between immune recovery status and the incidence rates (at the end of study) of cataract, moderate (MVL), and severe vision loss (SVL) defined as loss of three or more or six or more ETDRS lines, respectively.

Table 1 Incidence of ocular sequelae post-HAART treatment

Sequelae	Overall (n=90)	IR+IRU (n=26)	IR (n=39)	IF (n=25)	p Value
CMO	22 (24%)	18 (69%)	2 (5%)	2 (8%)	0.06*
ERM	27 (30%)	17 (65%)	6 (15%)	4 (16%)	0.05*
RD	13 (14%)	5 (19%)	3 (8%)	5 (20%)	0.35*
Cataract†	47/84 (52%)	21/25 (84%)	12/37 (33%)	14/22 (64%)	<0.001‡

HAART = highly active antiretroviral therapy; CMO = cystoid macular oedema; ERM = epiretinal membrane; RD = retinal detachment; IR+IRU = immune recovery with immune recovery uveitis; IR = immune recovery without immune recovery uveitis; IF = immune failure.

*p Values obtained from Cox regression analysis with immune recovery status as a time dependent covariate.

†Excluded six eyes with cataracts at the baseline visit.

‡p Values from Fisher's exact test.

Table 2 Distribution of visual acuity outcomes post-HAART treatment

Outcome	IR+IRU (n=90)	IR (n=26)	IF (n=39)	IF (n=25)	p Value*
Overall:					
<3 line loss	57 (63%)	9 (35%)	32 (82%)	16 (64%)	–
3–6 line loss (MVL)	18 (20%)	14 (54%)	2 (5%)	2 (8%)	<0.0001
6+ line loss (SVL)	15 (17%)	3 (11%)	5 (13%)	7 (28%)	0.2
Eyes without retinal detachment:	(n=77)	(n=21)	(n=36)	(n=20)	
<3 line loss	57 (74%)	9 (43%)	32 (88%)	16 (80%)	–
3–6 line loss (MVL)	14 (18%)	11 (52%)	2 (6%)	1 (5%)	<0.0001
6+ line loss (SVL)	6 (8%)	1 (5%)	2 (6%)	3 (15%)	0.5
Eyes with retinal detachment:	(n=13)	(n=5)	(n=3)	(n=5)	
<3 line loss	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
3–6 line loss (MVL)	4 (31%)	3 (60%)	0 (0%)	1 (20%)	N/A
6+ line loss (SVL)	9 (69%)	2 (40%)	3 (100%)	4 (80%)	0.34

HAART = highly active antiretroviral therapy; IR+IRU = immune recovery with immune recovery uveitis; IR = immune recovery without immune recovery uveitis; IF = immune failure.

*p Values obtained from Fisher's exact test comparing 3–6 line loss (MVL) versus less than 3 line loss, and 6+ line loss (SVL) versus less than 6 line loss, respectively.

RESULTS

The study cohort consisted of 63 patients (90 eyes). The average patient age was 32.3 (SD 1.2) years old; five (8%) of the patients were female. Of the 90 eyes, 27 (30%) were diagnosed with CMV before HAART, 54 (60%) developed CMV after treatment with HAART, and nine (10%) received HAART at the time of diagnosis for CMV. The mean follow up time was 31.9 (SD 19.8) months (range 0–66 months).

The incidence of IR was 72.2%, and the median time of developing IR was 7 months (range 0–41 months). Of the 48 patients who achieved IR, 21 patients (26 eyes) developed IRU, the remaining 27 patients (39 eyes) did not develop IRU.

The incidence of ocular sequelae, overall, and stratified by immune recovery status are presented in Table 1. Eyes of patients with IR without ocular IRU had the lowest incidence of ocular sequelae. In contrast, eyes of patients with IR with subsequent ocular IRU had the highest incidence of ocular sequelae. Of 26 eyes with IRU 18 (69%) developed CMO, 17 (65%) developed ERM, and five (19%) developed RD. Eyes with IF demonstrated a high incidence of RD (20%) similar to that of eyes with IRU (19%).

Time to the onset of CMO was related to immune recovery status ($p=0.06$). When compared to IF, the CMO hazard rate for IR+IRU was 4.8 ($p=0.04$). Time to the onset of ERM was also significantly associated with immune recovery status ($p=0.05$). When compared to IF, the ERM hazard rate for IR+IRU was 3.6 ($p=0.03$). Time to onset of RD was not related to immune recovery status ($p=0.35$).

Forty seven of 84 (52%) eyes developed cataract after time at which both criteria of CMV retinitis and HAART were satisfied (Table 1). Post-HAART cataract was statistically associated with immune recovery status ($p<0.001$); eyes with IRU dem-

onstrated the highest rate of cataract formation (84%) while eyes with IR without subsequent IRU demonstrated the lowest incidence of cataract formation (33%).

The incidence rates of moderate and severe vision loss were calculated for each subgroup overall, and stratified by retinal detachment status (Table 2). Moderate vision loss was associated with immune status overall and for eyes without RD ($p<0.0001$). Eyes with IR and subsequent IRU were most likely to develop moderate visual acuity loss (54% overall, and 52% for eyes without RD). No association of severe vision loss with immune status was noted ($p>0.2$). Rather, severe vision loss was significantly associated with the occurrence of RD (9/13 = 69% of the eyes with RD versus 6/77 = 8% of the eyes without RD, $p<0.001$). Four of the six eyes without retinal detachment developed severe vision loss secondary to IF and progression or recurrence of active CMV retinitis in or near the fovea. One of the eyes was classified as IR+IRU but developed severe vision loss from hypotony maculopathy after intravitreal cidofovir treatments.

For moderate and severe vision loss, Fisher's exact test detected no significant effect associated with HAART administration pre-CMV versus post-CMV (data not shown). The differing time sequences of HAART administration also did not affect the relation between cataract and immune status (data not shown). Because of these results and also because the incidence rates of CMO, ERM, and RD, the analyses for CMO, ERM, and RD were not adjusted for differing CMV-HAART sequences.

DISCUSSION

In the setting of immune reconstitution secondary to HAART, anti-CMV therapy can safely be withdrawn from HIV patients

with CMV retinitis.³ Long term follow up, however, has proved that post-immune reconstitution inflammatory sequelae including ERM, CMO, cataract, RD, and glaucoma are common in these patients with attendant visual loss.⁶ Our purpose is to determine long term outcomes in patients with and without IRU in the HAART era.

We found that the highest incidence of ERM, CMO, and cataract occurred in the IR+IRU subgroup and the lowest incidence in the IR without IRU subgroup. The incidence of RD in the IR without IRU subgroup was less than half that of the remaining subgroups ($p=0.35$). Time to the onset of ERM was significantly associated with immune recovery status ($p=0.05$). The ERM hazard ratio for IR+IRU when compared to IF was 3.6 (95% confidence interval: 1.1 to 11.2, $p=0.03$) and the ERM hazard ratio for IR compared to IF was 1.7 (95% confidence interval: 0.3 to 9.3, non-significant). Time to onset of CMO was also related to immune recovery status ($p=0.06$). Although the p value did not reach a significant level, the sample size was small and our power of detecting a significant difference in hazard rate was limited.

We attribute our findings to the high incidence of intraocular inflammation secondary to HAART induced immune recovery uveitis in the setting of healed CMV retinitis.⁷ The incidence of RD was highest in the IF group, presumably because immune failure sets the stage for progression and/or recurrence of active CMV retinitis with resultant full thickness retinal necrosis leading to retinal breaks and detachment.^{8,9} The incidence of RD in the IR+IRU subgroup was similar to that in the IF subgroup but data review revealed that RD in this subgroup was commonly secondary to surgical interventions such as TPPV, ERM peeling and cataract extraction. The IR without IRU subgroup demonstrated the lowest incidence of all sequelae including RD. This may be because immune recovery protected this group against CMV recurrence and progression and may have promoted stronger retinochoroidal adhesions, resulting in a lower incidence of RD, while the absence of uveitis protected these eyes from developing ERM, CMO, and cataract.

We also determined the relation between MVL and SVL and subgroup. We found a significant relation between MVL and immune subgroup with the highest incidence of MVL (14/26 eyes; 54%) occurring in the IR+IRU subgroup ($p<0.0001$). Although the highest incidence of SVL occurred in the IF subgroup (7/25 eyes; 28%), SVL was not associated with subgroup in a statistically significant fashion ($p=0.20$). SVL was, however, significantly associated with incidence of RD ($p<0.001$). Since RD occurred with similar incidence across all subgroups there was no statistical association with subgroup but severe vision loss occurred in 9/13 (69%) eyes with RD compared with only 6/77 (8%) eyes without RD. In five of the six eyes without RD, SVL was attributable to IF complications including recurrence of CMV retinitis in the macula and intraocular lymphoma. In the remaining eye, SVL occurred in the setting of IR+IRU, as a result of hypotony maculopathy after many intravitreal cidofovir treatments.

The best visual prognosis is associated with the IR without IRU subgroup in which the rate of MVL was the lowest (2/39 eyes; 5.1%) because all inflammatory complications occurred with the lowest incidence rates in this subgroup. Although the incidence of SVL in the IR without IRU subgroup was similar to that in the IR+IRU subgroup, the incidence of SVL in both

these subgroups was less than half that in the IF subgroup. This underscores the finding that RD is found in all subgroups for various different reasons but is associated with worse visual outcome in the IF subgroup.

In summary, in the HAART era, vision loss is still common in CMV retinitis patients. Moderate vision loss occurs in 5–54% of eyes with the highest incidence in the subcategory of patients with IR+IRU. Severe vision loss occurs in 12–28% of eyes with the highest incidence in the subcategory of patients with IF. Retinal detachment is the most statistically significant variable related to SVL and occurs with the highest frequency in the IF subgroup. Vision is most preserved in the subcategory of patients with IR without IRU who experience the lowest rates of ERM, CMO, cataract and RD. The eyes in this subcategory do not experience ERM, CMO, and cataract as commonly as the IR+IRU subcategory because they lack the uveitis that causes these inflammatory phenomena, and they do not experience RD as commonly as eyes in the IF subcategory because immune reconstitution protects them from recurrence and progression of CMV retinitis which are directly responsible for retinal necrosis, breaks and detachment.

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