

Treatment of CMV retinitis with intravitreal ganciclovir in the HAART era

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OBJECTIVE: To describe the course and outcome of cytomegalovirus (CMV) retinitis among AIDS patients treated with intravitreal ganciclovir and systemic highly active antiretroviral therapy (HAART). The secondary objective was to compare the course of CMV retinitis between patients receiving HAART and those not receiving this treatment.

DESIGN: A retrospective cohort design consisting of 21 eyes from 16 patients with AIDS and CMV retinitis consecutively enrolled between January 1996 and August 1999. All patients received intravitreal ganciclovir therapy, and half of the patients began HAART as well. Duration of intravitreal therapy and ensuing disease quiescence, as well as CD4+ T cell counts at diagnosis and at cessation of ganciclovir, were calculated. Secondly, instantaneous hazards for outcomes such as CMV retinitis progression, ocular complications and mortality were compared.

SETTING: Tertiary care centre in Ottawa, Ontario.

RESULTS: Five of eight patients receiving HAART discontinued intravitreal ganciclovir after a mean treatment period of 428 days. During this period, their mean CD4+ count rose from 7.5 to 190/ μ L. Subsequently, none of these patients experienced retinitis progression during follow-up periods lasting up to 820 days (mean of 617 days). Progression of CMV retinitis was 11.4 times more likely among those not receiving HAART (P=0.049).

CONCLUSIONS: On initiating HAART, patients with CMV retinitis may enjoy significant recovery in CD4+ counts and sustained retinitis quiescence without specific anti-CMV therapy. Intravitreal ganciclovir injections seem well suited to offer effective CMV control during temporary periods of decreased CD4+ counts while awaiting HAART-mediated immune system reconstitution.

Key Words: *CMV; Cytomegalovirus; Ganciclovir; HAART; Highly active antiretroviral therapy; Intravitreal treatment; Protease inhibitor; Retinitis*

Traitement de la rétinite à CMV par ganciclovir intravitréen à l'ère des HAART

OBJECTIF : Décrire l'évolution et l'issue d'une rétinite à cytomégalovirus (CMV) chez des patients sidéens traités par ganciclovir intravitréen et HAART (pour *highly active antiretroviral therapy*) systémique. L'objectif secondaire était de comparer l'évolution de la rétinite à CMV entre des patients selon qu'ils étaient traités ou non par HAART.

MODÈLE : Une cohorte rétrospective comportant 16 patients sidéens atteints de rétinite à CMV consécutifs (21 yeux), inscrits entre janvier 1996 et août 1999. Tous les patients ont reçu un traitement par ganciclovir intravitréen et la moitié des patients ont commencé également un traitement de type HAART. On a mesuré la durée du traitement intravitréen et la quiescence de la maladie qui en a résulté, de même que les numérations de CD4+ au moment du diagnostic et à l'arrêt du

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ganciclovir. Ensuite, on a comparé les différents risques pronostiques, par exemple la progression de la rétinite à CMV, les complications oculaires et la mortalité.

CONTEXTE : Hôpital de soins tertiaires d'Ottawa, Ontario.

RÉSULTATS : Cinq patients sous HAART sur huit ont cessé leur ganciclovir intravitréen après un traitement d'une durée moyenne de 428 jours. Au cours de cette période, leur numération moyenne des CD4+ est passée de 7,5 à 190/volume. Par la suite, aucun de ces patients n'a présenté une progression de sa rétinite au cours des périodes de suivi qui ont duré jusqu'à 820 jours (moyenne de 617 jours). La progression de la rétinite à CMV a été 11,4 fois plus susceptible de survenir chez les patients qui ne recevaient pas d'HAART ($p = 0,049$).

CONCLUSION : Lorsqu'on débute un traitement de type HAART, les patients atteints de rétinite à CMV peuvent connaître un rétablissement significatif de leur numération de CD4+ et une quiescence soutenue de leur rétinite sans traitement anti-CMV spécifique. Les injections intravitréennes de ganciclovir semblent traiter efficacement le CMV durant les brèves périodes où les numérations des CD4 baissent en attendant le rétablissement du système immunitaire par l'entremise du traitement HAART.

Cytomegalovirus (CMV) retinitis is a frequent cause of Opportunistic ocular infection in patients with AIDS. Historically, the lifetime incidence among these patients has been reported to be approximately 30% (1). However, the development of potent antiretroviral chemotherapeutic agents has led to a significant decrease in the incidence of CMV retinitis (2). Such highly active antiretroviral therapy (HAART) protocols reduce viral load, improve CD4+ T cell counts and reduce mortality (3-5).

Before HAART, treatment of CMV retinitis consisted of lifelong treatment with specific anti-CMV compounds, with relapse of retinitis occurring within two to three weeks after discontinuation of maintenance therapy (6). However, in the HAART era, numerous reports have demonstrated that the improved immune function induced by HAART makes possible the cessation of all specific anti-CMV therapy without reactivation of quiescent CMV retinitis (7-10). Moreover, regression of active CMV retinitis has been reported in patients receiving HAART without specific anti-CMV therapy (11).

Despite such reports, standard initial treatment of active CMV retinitis still involves anti-CMV chemotherapeutics. Three antiviral drugs – ganciclovir, foscarnet and cidofovir – are currently in use (12-14). Ganciclovir, a guanosine analogue, was the first of these proven to be effective in halting the progression of CMV retinitis (15). Initial therapy with this drug generally involves intravenous administration; however, maintenance therapy has been effective via intravenous, oral and intravitreal routes.

Intravitreal drug delivery can be accomplished via an intravitreal implant device or through repeated intravitreal injection (16,17). In Canada, the injection option has been widely employed, because intravitreal implants are not funded by provincial health insurance programs. Therefore, the primary objective of the present study was to describe the course and outcome of CMV retinitis among patients treated with intravitreal ganciclovir injections and HAART. A secondary objective was to evaluate the impact of HAART on such outcomes as CMV retinitis progression, ocular complications of intravitreal treatment and mortality among CMV retinitis patients receiving intravitreal ganciclovir.

PATIENTS AND METHODS

Inclusion and exclusion criteria: Medical records were reviewed from all AIDS patients diagnosed with CMV retinitis at the University of Ottawa Eye Institute (UOEI), Ottawa,

Ontario between January 1996 and August 1999. The UOEI is the only site providing tertiary ophthalmology service for this patient group in the greater Ottawa region, and thus, all patients diagnosed with CMV retinitis in this region were evaluated at the UOEI. Throughout this time, HAART was available to HIV patients at the Ottawa Hospital, Ottawa, Ontario, which provides tertiary care for the same population covered by the UOEI. Patients younger than 18 years of age at the time of diagnosis and those followed for less than two weeks were excluded from the present study. Hence, the study included 21 eyes from 16 patients.

Diagnosis and covariates measured: All ophthalmological data were obtained from detailed ophthalmology clinic notes and drawings, with the additional support of fundus photographs. The diagnosis of CMV retinitis was based on well established clinical criteria (18). The baseline threat to central vision was assessed by determining the invasion of retinitis into three distinct retinal zones as previously delineated (19). Other covariates measured were age at diagnosis, sex, CD4+ T cell count immediately preceding diagnosis of CMV retinitis, CD4+ T cell count at time of cessation of intravitreal ganciclovir, the number of AIDS-related opportunistic infections or malignancies suffered before the onset of CMV retinitis and final visual acuity.

Follow-up and outcomes measured: All patients underwent fundus examination at one-month intervals during intravitreal ganciclovir therapy. If ganciclovir was discontinued after HAART-induced immune recovery, the frequency of fundus evaluation was slowly decreased, with a maximum time between examinations of six months. Subjects were followed until August 1999. The primary outcomes were retinitis progression, ocular complications and death. Subjects were censored at the time of discontinuing intravitreal injections, except in the case of survival measurements, in which all patients were included until the end of the study period.

Disease progression was defined using previously established criteria – specifically, new regions of opacity or hemorrhage, or advancement of the leading edge of necrosis by more than 750 μm (19). Ocular complications consisted of retinal detachment and endophthalmitis. Date of death was established using hospital patient files and records from the infectious diseases clinic at the Ottawa Hospital. Using these resources, all subjects were accounted for at the end of the study period. Because the impact of intravitreal ganciclovir is local, each eye was evaluated independently for the ophthal-

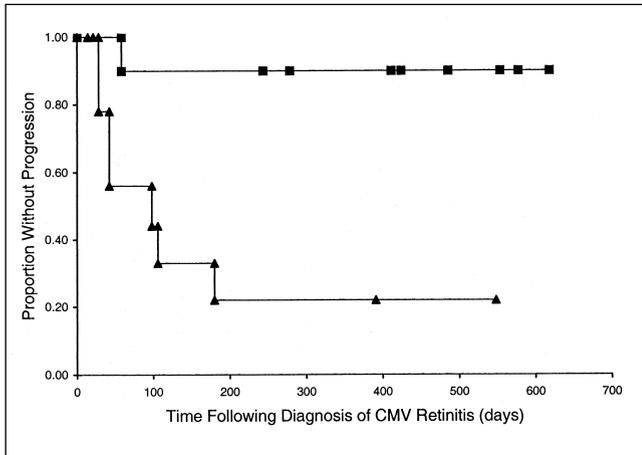


Figure 1 Cytomegalovirus (CMV) retinitis progression during intravitreal ganciclovir therapy; comparison of group receiving highly active antiretroviral therapy (■) and group not receiving highly active antiretroviral therapy (▲)

mological outcomes. However, each subject was counted only once in survival calculations.

Treatment: Immediately after the diagnosis of CMV retinitis, all patients received induction therapy consisting of 14 days of daily intravenous ganciclovir infusions. After this period, patients received maintenance therapy in the form of weekly intravitreal injections of ganciclovir (2 mg in 0.05 mL balanced saline [20]). HAART consisted of the combination of at least one protease inhibitor with at least two reverse transcriptase inhibitors. Patients in the HAART group typically began HAART within 30 days of the diagnosis of CMV retinitis. However, two patients in this group began HAART much later, commencing at 298 and 313 days after the diagnosis. Before the diagnosis of CMV retinitis, some patients in both the group receiving HAART and the group not receiving HAART (NOHAART) groups had received antiretroviral therapy in the form of mono or dual reverse transcriptase inhibitors (none had received protease inhibitors), while others were not receiving any anti-HIV medications at the time of retinitis diagnosis.

Statistical analysis: Using Student's unpaired *t* test, covariates such as age, CD4+ T cell count at the time of CMV retinitis diagnosis, CD4+ T cell count at the time of cessation of intravitreal ganciclovir, number of AIDS-related illnesses before CMV retinitis and final visual acuity were compared between the HAART group and the NOHAART group. Affected retinal zone proportions were compared using a χ^2 test. Finally, progression, ocular complication and mortality rates were compared using a censored Cox proportional hazards analysis. The instantaneous hazard for each outcome was calculated while controlling for age, CD4+ T cell count at the time of diagnosis of CMV retinitis and HIV disease severity, as estimated by the number of AIDS-related illnesses suffered before the onset of CMV retinitis.

RESULTS

In the present study, 12 patients were diagnosed with CMV retinitis in 1996, three in 1997, one in 1998 and none in the first seven months of 1999. Among patients receiving HAART, five of eight subjects discontinued all specific anti-CMV therapy and returned for regular follow-up. These patients underwent intravitreal ganciclovir treatment for a mean period of 428 days, during which time, mean CD4+ T cell count rose from 7.5 to 190/ μ L. Subsequently, after cessation of intravitreal ganciclovir, none of these patients experienced CMV retinitis recurrence during a mean follow-up period of 617 days (range 408 to 820 days). Among the other three individuals in the HAART group, one developed bacterial endophthalmitis and, after resolution, failed to return for ongoing ophthalmic assessment. This complication was felt to be secondary to the intravitreal injections. The other two patients did not experience significant recovery in CD4+ T cell count during the study period. One of these patients was eventually switched to intravitreal foscarnet because of ongoing CMV retinitis progression, which was felt to be secondary to ganciclovir resistance. The other began HAART 298 days after the development of CMV retinitis and then only tolerated HAART for 121 days. This subject continued to receive intravitreal ganciclovir for a further 158 days, during which time no CMV retinitis progression occurred. The patient subsequently entered a palliative care phase and died one month later.

Overall, three patients who originally presented with unioocular disease subsequently developed CMV retinitis in the second eye with a mean time of 175 days between diagnoses. Mean CD4+ count at the time of diagnosis of retinitis in the second eye was 21/ μ L. Two of these patients were not on HAART, while the third had started HAART less than four months before the diagnosis of CMV retinitis in the second eye and had not experienced a measured rise in CD4+ T cell count.

The secondary objective of this study was to compare the course of CMV retinitis in HAART patients and NOHAART patients. CD4+ counts were not different at diagnosis of CMV retinitis, with means of 22.6/ μ L and 16.5/ μ L for the HAART and NOHAART groups, respectively ($P=0.33$). However, there was a wide gap in CD4+ counts at the end of intravitreal ganciclovir therapy, with means of 115/ μ L and 43.3/ μ L for the HAART and NOHAART groups, respectively ($P=0.062$). The proportions of initially affected retinal zones were significantly different, with the HAART group displaying more sight-threatening central lesions ($P=0.023$; χ^2 test). However, final visual acuities were not different ($P=0.66$). While all patients in both groups displayed initial stabilization of CMV retinitis with intravenous ganciclovir induction therapy, subsequent progression during intravitreal ganciclovir therapy was 11.4 times more likely among those not receiving HAART ($P=0.049$). Median time to progression was 98 days for the NOHAART group, while the median progression event in the HAART group did not occur (Figure 1). Ocular complication rates during intravitreal ganciclovir

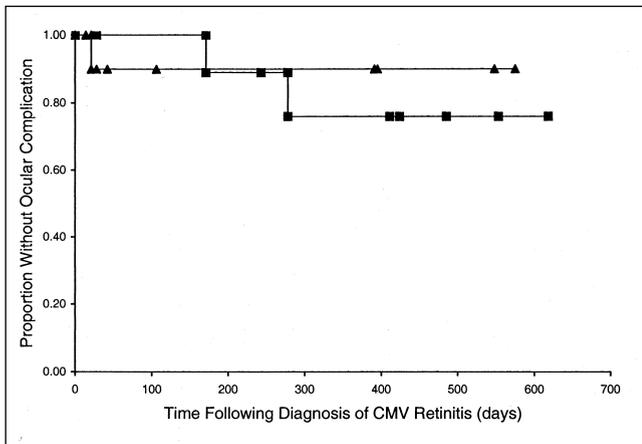


Figure 2) Ocular complications during intravitreal ganciclovir therapy for cytomegalovirus (CMV) retinitis; comparison of group receiving highly active antiretroviral therapy (■) and group not receiving highly active antiretroviral therapy (▲)

therapy were not different in the HAART and NOHAART groups ($P=0.92$; Figure 2). Finally, patients not receiving HAART were 4.9 times more likely to die than those receiving HAART; however, this result was not highly significant ($P=0.22$) (Figure 3).

DISCUSSION

During recent years, HAART has greatly altered the morbidity and mortality associated with AIDS (2,21). Indeed, our data show the marked decrease in the incidence of CMV retinitis among AIDS patients during the HAART era. However, HAART not only helps prevent CMV retinitis, but also influences treatment of this retinitis. Numerous reports have demonstrated that after HAART-mediated immune system reconstitution, specific anti-CMV therapy may be discontinued without reactivation of CMV retinitis during follow-up periods of three to 18 months (7-11). Our data show that the potential duration of disease quiescence after discontinuation of ganciclovir can be as long as 820 days. These results are contributing to the evolution of CMV retinitis therapy. For instance, the frequency of follow-up evaluations is gradually being decreased, and in some patients with stable CD4+ T cell counts, yearly ophthalmic examinations may be appropriate.

One of the risks of local therapy for CMV retinitis is the lack of prophylaxis against second eye involvement. It is interesting to note that second eye involvement occurred in only one of eight patients receiving HAART. In that patient, second eye involvement occurred soon after initiation of HAART and before a significant improvement in CD4+ count, which was only $39/\mu\text{L}$ at the time of diagnosis in the second eye. This is consistent with an earlier report that suggested that for patients responding to HAART, systemic ganciclovir may not provide additional benefit in the prevention of second eye disease (22).

As anticipated, during both the early and later phases of CMV retinitis, those receiving HAART were much less likely

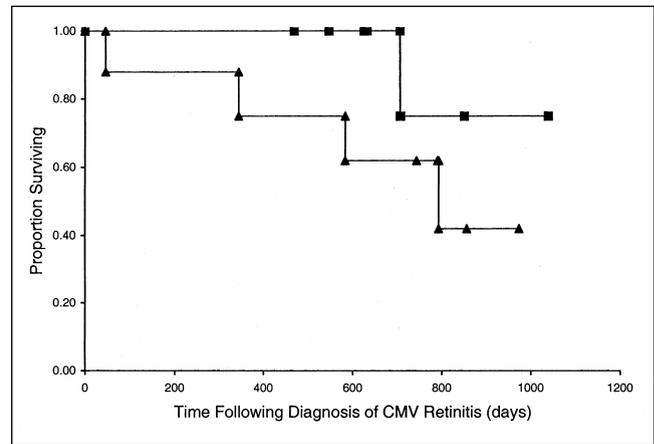


Figure 3) Survival among patients treated with intravitreal ganciclovir injections for cytomegalovirus (CMV) retinitis; comparison of group receiving highly active antiretroviral therapy (■) and group not receiving highly active antiretroviral therapy (▲)

to suffer progression of this disease. This was seen despite the fact that two patients included in the HAART group did not begin HAART until months after diagnosis of CMV retinitis. This leads to an underestimation of the impact of HAART in preventing CMV retinitis progression in the early phases of retinitis. This correlates closely with previous observations in patients with recurrent CMV retinitis treated with ganciclovir implants (23). A recent report showing the elimination of CMV viremia and prevention of retinitis in patients with documented CMV viremia and low initial CD4+ T-cell counts further supports the concept of HAART possessing the capability of halting CMV disease (24).

While a trend was observed indicating a decreased mortality rate among those receiving HAART, our results did not reach a high level of significance. This was likely a consequence of relatively small cohort sizes combined with the 'intent-to-treat' analysis, which resulted in the only death in the HAART group – in a patient who had tolerated HAART for only 121 days.

A potential bias in this study arose from the process of deciding whether a patient would initiate HAART. This clinical decision involved many patient and physician factors, with the ensuing possibility of systematic differences existing between the HAART and NOHAART groups. Moreover, while an effort has been made to adjust statistically for numerous potential confounding variables, the existence of unrecognized confounders cannot be ruled out.

In the HAART era, the incidence of CMV retinitis has declined significantly. However, new or reactivated cases continue to occur among patients who are HAART-naïve or for whom HAART has failed. With the potential development of resistance to HAART, we may witness a rise in CMV retinitis incidence, necessitating temporary or long-lasting reintroduction of intravitreal ganciclovir to control CMV disease. This raises the possibility that intravitreal injections may play an expanding role as a local treatment option for active CMV retinitis.

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