Once-Weekly Intraocular Injections of Ganciclovir for Maintenance Therapy of Cytomegalovirus Retinitis: Clinical and Ocular Outcome

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The clinical course and the outcome of treatment were studied in 40 patients with primary cytomegalovirus (CMV) retinitis in 57 eyes. All had received one 14-day course of intravenous ganciclovir and all were free of other end-organ CMV disease. All afflicted eyes received weekly intravitreal injections of 400 μg of ganciclovir for maintenance therapy. Median survival of patients was at least 13 months. Fifteen patients had new opportunistic infections during the observation period, but none developed new nonocular CMV disease. Active retinitis recurred in 68.4% of the eyes while receiving maintenance therapy, with a median time to progression of 14.7 weeks. CMV retinitis occurred in 30.4% of the previously uninvolved eyes (follow-up, 3.1 years). Bacterial endophthalmitis complicated treatment in 1 eye, and 5 eyes developed a retinal detachment. Thus, the long-term treatment of CMV retinitis with weekly intraocular injections of ganciclovir was associated with survival and ocular outcome similar to those reported with systemic ganciclovir.

Cytomegalovirus (CMV) retinitis occurs in 20%–40% of persons with AIDS [1,2]. Ganciclovir and foscarnet are the only two drugs approved for treatment of this disease. Current guidelines recommend the use of either drug in multiple daily intravenous induction doses for 14–21 days followed by lifelong once-daily intravenous maintenance doses [3,4]. Without maintenance therapy, CMV retinitis relapses in 100% of patients [3]. Both of the anti-CMV drugs have a low therapeutic index and are very costly, and their intravenous administration is logistically complex.

Weekly ganciclovir injections directly into the vitreous cavity may prevent relapses as effectively as daily intravenous injections of either ganciclovir or foscarnet [5]. However, it is believed that systemic maintenance therapy with intravenous anti-CMV drugs protects against CMV disease elsewhere in the body and possibly against the putative CMV enhancement of human immunodeficiency virus (HIV) replication. No published studies support these beliefs.

After ganciclovir became approved for use through the Canadian Emergency Drug Release Program and before the formulation of treatment guidelines, we began a program of maintenance therapy for CMV retinitis using weekly intraocular injections of ganciclovir. We have continued this therapy as an option for CMV retinitis patients who have just completed induction treatment with intravenous ganciclovir. To date, there is no study describing long-term morbidity, mortality, or progression of retinitis in a large cohort of patients treated with this method. We report the clinical course of our patients with AIDS and CMV retinitis who have chosen local maintenance with weekly intraocular injections of 400 μg of ganciclovir.

Methods

Study design. This was a single-arm descriptive study with patient selection based on nonprobability consecutive sampling. Between November 1989 and December 1992, all patients with AIDS referred to our hospital for the treatment of a first episode of CMV retinitis in one or both eyes received a 14-day twice-daily intravenous ganciclovir induction treatment and were then considered for maintenance weekly intraocular ganciclovir if they had no prior or concurrent clinical manifestations of CMV reactivation in other organ systems. Patients who could not be followed regularly were excluded from this study.

For the intraocular injection, patients were first anesthetized with topical proparacaine and subconjunctival lidocaine (2%); then, 400 μg of ganciclovir in 0.05 mL of balanced salt solution (made from an 80 mg/10 mL preparation) was injected with a 3D-gauge needle placed in the vitreous cavity through the pars plana in the superonasal or superotemporal quadrant of the eye. Visual acuity measurements, slit lamp biomicroscopy including intraocular pressure readings, and indirect ophthalmoscopy were done weekly, and visual field tests and fundus photography were done at least monthly. Any clinical evidence of progression was confirmed by photography. Progression of retinitis was defined as a leading edge of retinitis 750 μm from a previously quiescent area of retinitis or a new area of retinitis consistent with CMV. All retinitis outcomes were determined on the basis of photographic assessments. Treatment of retinitis progression consisted of reinduction with intravenous ganciclovir followed by same-dose intraocular maintenance treatment. Patients obtained primary care services within our insti-
tution and were followed continuously even if they abandoned the intraocular injection program.

Study end points. The primary outcome measures were mortality, occurrence of systemic opportunistic infections while receiving maintenance therapy, retinitis progression in the involved eye, occurrence of retinitis in the uninvolved eye, and ocular complications caused by the intraocular injections.

For the outcome measures of mortality, occurrence of systemic infections, and retinitis progression, the dependent variable was the time to the outcome event. These outcomes were described and analyzed using the Kaplan-Meier method for estimating time-to-outcome functions.

Results

Patients. At study entry, CMV retinitis was detected in 57 eyes of 40 patients. All patients were male, with a median age of 37.5 years. In 25 patients, the risk factor for HIV infection was determined: 21 men had homosexual contacts and 4 had used injection drugs. Lymphocyte subset analyses were available for 25 patients. In 21, the CD4 lymphocyte count was determined a mean of 140 days (range, 3–375) before diagnosis of retinitis, and the mean count was 30 ± 71 cells/μL. In 4 patients, the test was done a mean of 111 days (range, 65–158) after diagnosis of CMV retinitis, and the mean CD4 cell count was 9 ± 6/μL. The median time from the beginning of induction therapy to first intraocular injection was 3 weeks (range, 2–6; interquartile interval, 2–3.5). The median follow-up time was 53.1 weeks (range, 6–156). In 20 surviving patients with 22 affected eyes, treatment was temporarily or totally abandoned because of systemic deterioration in 6, end-stage ocular disease in 11, patient choice in 4, and ocular complication in 1.

Mortality. Two patients were lost to follow-up and have been eliminated from the analysis of mortality. Thirteen (34.2%) of 38 patients died during follow-up, with a median time from diagnosis of CMV retinitis to death of 32.1 weeks. Of the 25 survivors, the median survival time from diagnosis of CMV retinitis to the end of the study (May 1993) was 55.4 weeks. The Kaplan-Meier survival function of this cohort is shown in figure 1.

Opportunistic infections. Fifteen patients developed 19 opportunistic infections during maintenance intraocular therapy, with a median time from diagnosis of CMV retinitis to first opportunistic infection of 20.6 weeks. The most common opportunistic infections were Pneumocystis carinii pneumonia (5), cerebral toxoplasmosis (3), cryptococcal meningitis (3), and bacteremia with Mycobacterium avium-intracellulare complex (3).

Retinitis progression and involvement of the other eye. Maintenance ganciclovir was initially injected into 57 CMV-infected eyes of 40 patients. The CMV retinitis progressed in 39 eyes (68.4%) while receiving intraocular maintenance therapy. The median time from diagnosis of CMV retinitis to progression was 14.7 weeks. CMV retinitis was detected in the previously uninvolved eye in 7 patients (30.4%) receiving maintenance intraocular ganciclovir. The median time to occurrence was 10.1 weeks (range, 5.1–16.5) from the diagnosis of CMV retinitis in the first eye.

Complications. Bacterial endophthalmitis due to Staphylococcus epidermidis complicated one intraocular injection of ganciclovir; it was effectively treated with vitrectomy and intraocular injections of vancomycin; visual acuity was restored to the preinjection level. Retinal detachment occurred in 5 eyes receiving maintenance intraocular injections. Three detachments occurred in the superotemporal quadrant and 2 in the inferonasal quadrant of the fundus. All occurred at areas of necrosis, and no other retinal detachment risk factors were present in these eyes. Cataracts and vitreous hemorrhages were not detected in study patients.

Discussion

This is the first report on long-term systemic and ocular outcomes of a large cohort of patients treated with maintenance doses of intraocular ganciclovir for CMV retinitis. In our study, 57 eyes of 40 patients were studied for a median follow-up time of 53.1 weeks.

The median survival time observed in this study was at least 13 months and compared favorably with historical controls maintained with 5 weekly or even daily intravenous injections of anti-CMV drugs [4, 6–8]. In a study comparing the efficacy of long-term daily intravenous ganciclovir or foscarnet, participants survived 8.5 or 12.6 months, respectively [5]. In two other recent studies of long-term intravenous foscarnet maintenance therapy, median survival was 11.0 and 13.5 months [7, 8].

In our study, 15 patients developed 19 opportunistic infections while receiving maintenance therapy. Previous studies on the treatment of CMV retinitis have not clearly documented the occurrence of systemic opportunistic infections, making any comparisons difficult. Interestingly, extraocular CMV end-or-
gan disease was not detected while patients were receiving maintenance therapy, in part because the recruitment process excluded patients with clinical evidence of other CMV syndromes. During the study period, most patients were followed in an immunodeficiency clinic but they were not systematically evaluated for nonocular CMV disease. It is thus possible that some systemic CMV disease escaped detection.

CMV infection occurs frequently in persons with HIV-1 infection, and it disseminates asymptptomatically long before the occurrence of end-organ CMV disease [9]. Thus, intuitively, systemic therapy seems preferable to local therapy as a maintenance treatment for CMV retinitis. However, both systemic ganciclovir and foscarnet are toxic, and both usually ultimately require the insertion of permanent venous accesses with the ensuing risk of bloodstream infections [5]. The hematologic toxicity of ganciclovir precludes the concomitant use of equally myelotoxic zidovudine, but didanosine may be somewhat better tolerated [10]. Finally, the in vitro anti-HIV activity of ganciclovir and didanosine is antagonized by ganciclovir [11]. Thus, new therapies or modified regimens of existing therapies are clearly required for safer and more effective treatment of HIV-infected persons with complicating CMV end-organ disease, such as retinitis. Maintenance therapy with once-weekly intravitreal injections of ganciclovir may provide such a modified regimen, allowing the concomitant use of optimal anti-HIV therapies, obviating the need for a permanent venous access, and considerably reducing the use of health services while providing a survival time without an excess of other opportunistic diseases at least equal to that observed in other studies.

In the absence of maintenance therapy, CMV retinitis reacts and progresses in virtually all patients [3]. Compared to cessation of treatment after the induction phase of treatment with anti-CMV drugs, long-term maintenance treatment with either intravenous ganciclovir or foscarnet clearly delays the time to reactivation and progression of the retinitis [7, 12]. However, intravitreal injections provide a concentration of ganciclovir in the vitreous cavity much higher than that following intravenous treatment [13]. This may explain why in the comparative trial of maintenance with intravenous ganciclovir and foscarnet [5], the median time to recurrence was 8 and 8.4 weeks, respectively, whereas in our study it was 14.7 weeks. Maintenance studies using intravenous administration have reported a wide range of values for mean time to recurrence from 3.3 weeks to 21 weeks [4]. Furthermore, another study showed that in 17% of persons receiving maintenance treatment for CMV retinitis, the previously uninvolved eye became infected [14]. In our study, development of CMV disease in the uninvolved eye occurred in 30.4%. Thus, in our study, disease progression and duration of remission in the diseased eye was similar or better and the occurrence of CMV infection in the uninvolved eye was somewhat higher than in historical controls.

Bacterial endophthalmitis was the only serious treatment complication. Our injection volume was 0.05 mL, probably explaining the absence of retinal artery occlusion. The prevalence of retinal detachment (9%) in our study was similar to that observed in studies of systemic maintenance therapies (19%–24%) [4]. Cataracts and vitreous hemorrhages were not observed in our study. The number of ocular complications due to treatment was far smaller in our study than in a study of the surgical intravitreal implantation of a slow drug-release device [15].

We have reported the long-term results of intravitreal ganciclovir injections in a large cohort of patients. Comparison with other studies must be made cautiously. Nevertheless, the clinical results observed in this study and the probable improvement in quality of life from the absence of indwelling catheters and daily injections suggest that intravitreal ganciclovir injections could be a first-line maintenance treatment for CMV retinitis in patients without other clinically significant CMV syndromes. Testing this hypothesis would require a clinical trial comparing intravitreal ganciclovir with systemic anti-CMV drugs.

References
Measurement of Human Herpesvirus 7 Load in Peripheral Blood and Saliva of Healthy Subjects by Quantitative Polymerase Chain Reaction

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Qualitative and competitive-quantitative nested polymerase chain reaction (PCR) assays were developed for human herpesvirus 7 (HHV-7). These assays amplify a DNA sequence encoding part of the HHV-7 homologue of the human herpesvirus 6 (HHV-6) U42 gene. The PCR assays were used to analyze peripheral blood DNA (pbDNA) and saliva from 24 healthy volunteers. The prevalence of HHV-7 in saliva was 96%, with a median virus load of $1.1 \times 10^6$ copies/mL. Longitudinal analysis revealed sustained virus load, suggesting continued active viral replication. Analysis of 1 μg of pbDNA showed the prevalence of HHV-7 to be 83%, with a median virus load of 40 copies (267 copies/10^6 cells). Analysis of sequential pbDNA samples showed individuals to have stable levels of HHV-7 virus load. These data demonstrate persistence of HHV-7 at two distinct sites and provide baseline data allowing comparisons with HHV-7 load in immunocompromised patients.

Materials and Methods

Construction of viral DNA library. HHV-7 strain RK (supplied by N. Frenkel, Tel Aviv University, Israel) was propagated in SUP-T1 cells (see Acknowledgments). HHV-7–infected cells were harvested, and viral DNA was extracted [9] and digested with HindIII. Fragments were ligated into a pUC18 vector (Pharmacia Biotech, St. Albans, UK) followed by transformation of competent Escherichia coli. An HHV-7 193-bp clone was selected for further analysis. DNA and derived amino acid sequences were compared using FASTA (Genetics Computer Group, University of Wisconsin, Milwaukee) examination of GenBank and European Molecular Biology Laboratory (EMBL) databases. Sequence alignment was optimized using ALIGN (Protein Information Resource, National Biomedical Foundation, Washington, DC).

PCR primers. Primer sequences delineating 183 bp (HHV-7MK1, 5′-TTTTTACATTGGCTTTTGTTG-3′, and HHV-7MK2, 5′-ATATTTCTGTACCTATCTTCCAA-3′) and 143 bp (HHV-7MK3, 5′-GAA TTT ATGGAGTTTGGTCTG-3′) of the 193-bp sequence were synthesized (R&D Systems, Abingdon, UK). For

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