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High-dose (5000-µg) intravitreal ganciclovir combined with highly active antiretroviral therapy for cytomegalovirus retinitis in HIV-infected patients in Venezuela

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PURPOSE. *To describe the use of high doses of intravitreal ganciclovir combined with highly active antiretroviral therapy (HAART) for the treatment of cytomegalovirus (CMV) retinitis in human immunodeficiency virus (HIV)-infected patients.*

METHODS. *Thirteen HIV-infected patients (18 eyes) with active CMV retinitis (83.3% in zone 1 and 38.4% resistant) participated in this prospective interventional case series. Patients were treated with high dose intravitreal ganciclovir (5.0 mg/0.1 mL once a week) in combination with HAART therapy. Intravitreal injections were discontinued once CMV retinitis healed if there was a significant increase in CD4+ count (any increase of ≥50 cells/µL to levels over 100 cells/µL sustained for at least 3 months). Mean follow-up was 15.6 months. Main outcome measures included assessment of visual acuity and retinal inflammation (CMV retinitis activity). A matched historical control group of 20 eyes (15 patients) with CMV retinitis treated with systemic ganciclovir (intravenous [induction] and oral [maintenance]) was included.*

RESULTS. *Complete regression of the retinitis was obtained with high doses of intravitreal ganciclovir in 88.8% of eyes (two patients died during follow-up) at a mean of 4.5 weeks (2 to 8 weeks). Visual acuity improved two or more lines in 61.1% of eyes. No ganciclovir retinal toxicity was identified. Three eyes presented CMV retinitis reactivation at a mean of 25.6 days after their last injection. Complications (33.3%) included retinal detachment (RD; 3 eyes), immune recovery uveitis (IRU; 2 eyes), and endophthalmitis (1 eye). In our control group complete regression of the retinitis was obtained in 100% of eyes at a mean of 4 weeks (3 to 7 weeks). However, 12 eyes (60%) presented with CMV retinitis relapse at a mean of 29 days (21 to 32 days) after initiating oral ganciclovir (maintenance). Complications included RD (7 eyes, 35%) and IRU (3 eyes, 15%). Severe neutropenia occurred in 2 patients (13%).*

CONCLUSIONS. *High doses of intravitreal ganciclovir (5.0 mg) once a week in combination with HAART therapy is effective to control CMV retinitis, and may be discontinued after CMV retinitis has healed if immune reconstitution with a significant increase in CD4+ count has occurred. (Eur J Ophthalmol 2005; 15: 610-8)*

KEY WORDS. *Cytomegalovirus retinitis, High-dose intravitreal ganciclovir, Highly active antiretroviral therapy, HIV-infected patients*.

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INTRODUCTION

Cytomegalovirus (CMV) retinitis is the most common sight-threatening complication of acquired immunodeficiency syndrome (AIDS), and is associated with profound immunodeficiency and a CD4+ T lymphocyte count below 100 cells/mm3 (usually <50 cells/mm3) (1-3). In the past few years, dramatic advances have occurred in the management of patients infected with human immunodeficiency virus (HIV). The introduction of highly active antiretroviral therapy (HAART), including HIV-specific protease inhibitors, in the treatment of AIDS has resulted in a significant improvement in immune status in many patients, as indicated by increased levels of CD4+T lymphocytes and decreased levels of plasma HIV messenger RNA (4, 5). All protease inhibitors currently available competitively inhibit the protease-mediated cleavage of viral polyproteins, preventing the maturation of infectious virions. The result is inhibition of HIV replication.

In 1996, for the first time since the beginning of the AIDS pandemic, a reduction in AIDS-related mortality and opportunistic infections occurred in the United States (6). HAART has resulted in a decrease in the incidence of CMV retinitis. In addition, some patients who respond to HAART with an increase in CD4 T-lymphocyte count show partial immune recovery and regain the ability to suppress CMV without specific anti-CMV therapy (7-9).

Intravitreal ganciclovir (10-16) has proven an important therapy in controlling CMV retinitis in patients who have failed or cannot take systemic therapy. Initially the dose was 200 to 400 µg, and it was well tolerated (10-12). However, as viral resistance was encountered, the amount was increased first to 2000 µg (13, 14), and then, in a more recent publication, to 4000 µg (15). Even with 4000-µg doses, no adverse effects were encountered. Local therapy with high-dose intravitreal ganciclovir (5.0 mg) is very inexpensive, and easy to prepare in the office without the aid of a hospital pharmacy. The latter is the main reason for using 5000 µg ganciclovir; the solution is made adding 10 mL of balanced salt solution (BSS) to a 500 mg vial of ganciclovir and stored at -8 °C for repeated use for up to 3 weeks.

The purpose of this report is to describe the use of a high dose (5.0 mg) of intravitreal ganciclovir combined with HAART for the treatment of CMV retinitis in HIV-infected patients in Venezuela.

PATIENTS AND METHODS

A total of 13 HIV-infected patients (18 eyes) with active CMV retinitis (83.3% in zone 1 and 38.4% resistant to intravenous [IV] ganciclovir) (Tab. I) participated in this prospective study. These patients elected treatment with high dose (5.0 mg) intravitreal injections of ganciclovir from May 1998 to May 2000 (study group). Each patient made a decision whether to undergo intravitreal treatment after discussing the advantages and disadvantages of local versus systemic therapy of CMV retinitis. All patients received HAART, including one or two reverse transcriptase inhibitors (lamivudine, stavudine, zidovudine) and one or two protease inhibitors (indinavir, ritonavir, nelfinavir, saquinavir). Only patients without evidence of extraocular CMV disease were included. None of the patients received any concomitant systemic anti-CMV therapy. The investigations were performed according to the guidelines of the Declaration of Helsinki. Approval was obtained from the Clinica Oftalmologica Centro Caracas Institutional Review Board. A matched historical control group (20 eyes [15 patients] with CMV retinitis) treated with IV ganciclovir at 5 mg/kg twice a day for 3 weeks (induction therapy) followed by oral ganciclovir at 3 g per day in three divided doses as maintenance therapy was included.

A full ophthalmic examination was performed on all patients at each visit, including bilateral indirect ophthalmoscopy. Diagnosis of CMV retinitis and assessment of activity was based on typical ophthalmoscopic appearance (1, 2, 17, 18) and evidence of progression of retinitis borders in subsequent examinations. Retinitis was classified according to location (three retinal zones) (19) and size of the lesion (percentage of the retina affected by CMV). This was recorded with retinal drawings and confirmed with 30-45° fundus photographs at each visit. In addition, the levels of CD4+ T lymphocytes and plasma viral HIV messenger RNA were checked every 3 months to monitor antiretroviral therapy.

Treatment was delivered on an outpatient basis and intravitreal injections performed in the clinic area under sterile conditions. Bilateral injections were given as required. The solution was made adding 10 mL of BSS (Alcon Laboratories, Fort Worth, TX) to a 500 mg vial of ganciclovir (Cymevene, F. Hoffmann-La Roche, Switzerland) and stored at -8 °C for repeated use for

up to 3 weeks. The eye was prepared with povidone-iodine 5%, and anesthetized with subconjunctival 2% lidocaine (Cifarcaina, Behrens Laboratories, Caracas, Venezuela) before manual ocular decompression (20, 21). Each injection was made in the superior quadrant at 3.5 mm from the limbus using a short (1/2 inch) 30-gauge needle fully inserted and aimed at the mid vitreous cavity.

Thirteen HIV-infected patients (18 eyes) were treated with high dose intravitreal ganciclovir (5.0 mg/0.1 mL once a week) in combination with HAART therapy. Intravitreal injections were discontinued once CMV retinitis healed if there was a significant increase in CD4+ count. A significant increase in CD4+ T lymphocyte count was defined as any increase of ≥50 cells/μL to levels over 100 cells/μL sustained for at least 3 months (7-9). Relapse was defined as the presence of new lesions or extension of previously inactive areas by 750 μm. Relapse was treated in the same way with intravitreal ganciclovir at a dose of 5.0 mg/0.1 mL once a week until healed CMV retinitis was observed. Resistance to previous therapy was defined by the presence of new activity or by advancement of the border of retinitis by more than 750 μm, despite continuous induction doses of IV ganciclovir over at least 8 weeks. Mean follow-up was 15.6 months (1 week to 37 months) after local therapy of CMV retinitis.

Main outcome measures included assessment of visual acuity (a change of more than two lines was considered significant) and retinal inflammation (CMV retinitis activity).

RESULTS

We treated in our study group 13 patients with AIDS (18 eyes) with active CMV retinitis, 5 of whom had bilateral and 8 of whom had unilateral disease. All of our patients were on HAART therapy and received weekly intravitreal injections of ganciclovir (5.0 mg). Our 13 patients had an average age of 39 (27 to 64) years. All patients were Hispanic and 84.6% male (Tab. I). All patients responded to HAART with an increase in CD4+ T-lymphocyte count from a mean of 92.6 cells/μL (range: 7 to 327 cells/μL) to a mean of 276.3 cells/μL (range: 100 to 510 cells/μL) and a reduction of plasma HIV messenger RNA to undetectable levels. The CD4+ T-lymphocyte levels increase had a mean of 183.6 cells/μL (range: 0 to 460 cells/μL) (Tab. II).

TABLE I - CLINICAL FINDINGS OF EYES TREATED WITH HIGH-DOSE INTRAVITREAL GANCICLOVIR (18 EYES)

Eye	Sex	Age (yr)	Lat.	Fellow eye	AIDS-CMV months	Anti-CMV meds before injection
1	M	42	OD	OK	90	IV DHPG
2	M	34	OD	OK	36	IV DHPG
3	M	34	OD	OK	24	IV DHPG
4	M	35	OD	5	40	No
5	M	35	OS	4	40	No
6	M	27	OS	OK	20	No
7	M	64	OD	8	5	No
8	M	64	OS	7	5	No
9	M	54	OD	OK	18	No
10	M	50	OD	11	23	IV DHPG
11	M	50	OS	10	23	IV DHPG
12	M	31	OD	OK	71	No
13	F	33	OD	14	12	No
14	F	33	OS	13	12	No
15	M	28	OD	16	2	No
16	M	28	OS	15	2	No
17	F	44	OI	OK	24	IV DHPG
18	M	31	OD	OK	53	No

Lat = Laterality; AIDS-CMV Ret = Period of time between diagnosis of AIDS and cytomegalovirus (CMV) retinitis; Meds = Medications; CMV ret = CMV retinitis location; VA = Visual acuity; OD = Right eye; IV DHPG = Intravenous ganciclovir;

The diagnosis of AIDS preceded the diagnosis of CMV retinitis by a median of 27.7 months (range: 2 to 90 months). Previous anti-CMV treatment involved IV ganciclovir in five patients (6 eyes) and was withdrawn because of failure to respond. Eight patients (12 eyes) chose local therapy over IV ganciclovir because of quality of life considerations. In addition, in 10 patients (15 eyes, 83.3%) local therapy was recommended due to the presence of CMV retinitis in zone 1. Nineteen eyes in our study had a retinal CMV surface area with a mean of 35.6% (range: 5 to 60%) (Tab. I). None of our patients had evidence of extraocular CMV disease. Clinical findings in eyes that received weekly intravitreal injections of ganciclovir (5.0 mg) are depicted in Table I.

Complete regression of the retinitis was obtained with high dose of intravitreal ganciclovir in 88.8% of eyes (two patients died during follow-up due to CMV-related complications of AIDS) at a mean of 4.5 weeks (2 to 8 weeks) (Fig. 1). Snellen visual acuity (VA) improved 2 or more lines in 11 (61.1%) of 18 eyes, and 7 (38.9%) remained with the same VA or improved less than two lines. No eye had worsening of VA after intravitreal injections of high dose ganciclovir. No ganciclovir retinal toxicity was identified. Three eyes (16.6%) presented with CMV retinitis relapse at a mean of 25.6 days (21 to 28 days) after their last injection. These three eyes underwent a repeated cycle of high dose (5.0 mg/0.1 mL/week) intravitreal ganciclovir, and CMV retinitis healed after three injections in each case. Two (15.3%) patients developed extraocular CMV disease and died during follow-up. None of these patients had evidence of extraocular CMV disease when entered into the study. One of the patients survived for a month after starting local therapy and CMV retinitis was healing at his last examination. The other patient died only 1 week after his first injection before evaluation of his CMV retinitis could be performed. No patient developed CMV retinitis in the contralateral unaffected eye.

Complications occurred in 33.3% of eyes in our study group and included retinal detachment (3 eyes, 16.6%), immune recovery uveitis (2 eyes, 15.3%), and endophthalmitis (1 eye, 7.6%) (Tab. II). Two of the retinal detachments (one patient) were repaired with vitrectomy and silicone oil injection, and one patient refused surgery. These patients had from 45 to 60% (mean: 51.6%) of retinal surface area involved with CMV retinitis. Two eyes with immune recovery uveitis (22-25) were treated with posterior sub-Tenon injections of

TABLE I - *continued*

Indication	CMV ret (zones)	Extent CMV ret	Initial VA	Final VA
Resistance, Zone 1 disease	1,2,3	25%	20/150	20/60
Resistance	2,3	15%	20/25	20/20
Resistance	2,3	30%	LP	LP
QL, Zone 1 disease	1,2,3	45%	20/150	20/60
QL, Zone 1 disease	1,2,3	50%	20/40	20/30
QL, Zone 1 disease	1,2,3	40%	20/400	20/200
QL, Zone 1 disease	1,2,3	45%	HM	HM
QL, Zone 1 disease	1,2,3	50%	CF	CF
QL	2,3	15%	20/200	20/60
Resistance, Zone 1 disease	1,2,3	60%	HM	20/400
Resistance, Zone 1 disease	1,2,3	50%	HM	20/400
QL, Zone 1 disease	1,2,3	40%	20/100	20/100
QL, Zone 1 disease	1,2,3	30%	20/400	20/150
QL, Zone 1 disease	1,2,3	33%	20/80	20/50
QL, Zone 1 disease	1,2,3	50%	HM	20/150
QL, Zone 1 disease	1,2,3	33%	CF	20/70
Resistance, Zone 1 disease	1	5%	20/100	20/25
QL, Zone 1 disease	1	25%	HM	HM

Resistance = Presence of new activity or advancement of the border of retinitis by more than 750 µm, despite continuous induction doses of IV DHPG over at least 8 weeks; ERG = Electroretinogram; LP = Light perception; QL = Quality of life; OS = Left eye; HM = Hand motions; CF = Counting fingers

40 mg of triamcinolone acetonide (Kenacort, Squibb & Sons, Caracas, Venezuela) at 3-week intervals (Arevalo and Azar-Arevalo, American Academy of Ophthalmology annual meeting, New Orleans, LA, November 2001). One of our patients developed a culture-negative endophthalmitis and responded to intravitreal antibiotics (vancomycin and amikacin), and VA was preserved.

In our control group (20 eyes [15 patients]), treated with systemic ganciclovir, complete regression of the retinitis was obtained in 100% of eyes at a mean of 4 weeks (3 to 7 weeks). Snellen VA improved two or more lines in 7 (35%) of 20 eyes, and 13 (65%) remained with the same VA. No eye had worsening of VA after IV and oral ganciclovir. Twelve eyes (60%) presented with CMV retinitis relapse at a mean of 29 days (21 to 32 days) after initiating oral ganciclovir. These 12 eyes underwent a repeated cycle of IV and oral ganciclovir, and CMV retinitis healed after in 3 to 5 weeks in each case. No patient developed extraocular CMV disease or died during follow-up. No patient developed CMV retinitis in the contralateral unaffected eye.

Complications occurred in 50% of eyes in the control group and included retinal detachment (7 eyes, 35%) and immune recovery uveitis (3 eyes, 15%). The retinal detachments were repaired with vitrectomy and silicone oil injection. These patients had from 35 to 60% (mean: 49.2%) of retinal surface area involved with CMV retinitis. Severe neutropenia occurred in 2 patients (13%).

DISCUSSION

The first AIDS case in Venezuela was reported in 1982. Until 1994 a total of 6,916 AIDS cases had been reported. AIDS-related morbidity (51:1,000,000 persons) and mortality (40:1,000,000 persons) have been rising. The HIV/AIDS epidemic has not been equal throughout the country; Distrito Capital (the state where the study was held) has had the highest number of cases. Most patients are male; however, the number of females has raised to 10% of the affected population by 1997. Although the initial cases were diagnosed

TABLE II - CLINICAL FINDINGS OF EYES TREATED WITH HIGH-DOSE INTRAVITREAL GANCICLOVIR (18 EYES)

Eye	F-U	Initial CD4 (cells/µL)	Final CD4 (cells/µL)	CD4 increase	Number of injections	Relapse	Complications	Outcome
1	24 months	92	267	175	4	28 days/healed with 3 more injections	Vitreitis and CME (IRU)	Healed
2	1 month	74	134	60	2	Died	No	Healing
3	1 month	104	280	176	3	No	No	Healed
4	37 months	140	299	159	6	No	No	Healed
5	37 months	140	299	159	6	No	No	Healed
6	31 months	50	510	460	5	No	No	Healed
7	6 months	25	279	254	8	No	RRD	Healed
8	6 months	25	279	254	8	No	No	Healed
9	5 months	13	281	268	6	21 days/healed with 3 more injections	Endophthalmitis	Healed
10	18 months	40	256	216	3	No	RRD	Healed
11	18 months	40	256	216	3	No	RRD	Healed
12	1 week	327	327	0	1	Died	No	Active
13	26 months	78	279	201	3	No	No	Healed
14	26 months	78	279	201	3	No	No	Healed
15	17 months	7	100	93	6	No	No	Healed
16	17 months	7	100	93	6	No	No	Healed
17	3 months	104	280	176	2	No	No	Healed
18	9 months	150	300	150	6	28 days/healed with 3 more injections	Vitreitis (IRU)	Healed

F-U = duration of follow-up after discontinuation of local therapy; CME = cystoid macular edema; IRU = immune recovery uveitis; RRD = rhegmatogenous retinal detachment.

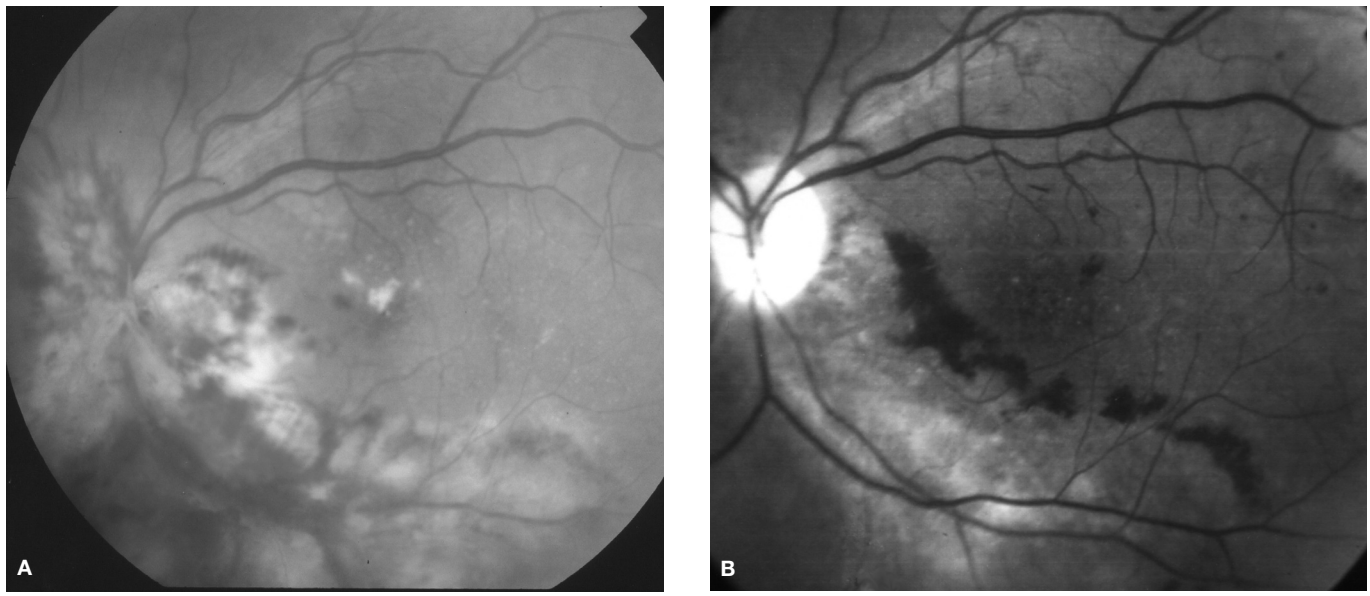

Fig. 1 - *Patient with acquired immunodeficiency syndrome (AIDS) and cytomegalovirus (CMV) retinitis.* **A)** *Active CMV retinitis before local therapy with intravitreal ganciclovir.* **B)** *Healed CMV retinitis after 4 injections of high dose (5.0 mg) intravitreal ganciclovir.*

in homosexual males, the incidence of heterosexual transmission has increased (unpublished data, Centro de Investigaciones Económicas y Sociales, CIES, Venezuela, 1998). The incidence of CMV retinitis in Venezuela before the HAART era was 16.6% (26). IV ganciclovir and/or intravitreal ganciclovir have been the most common types of therapy used to control CMV retinitis in Venezuela up until 2003.

HAART was introduced in Venezuela in 1996; however, people with HIV/AIDS had very limited access to antiretroviral therapies and treatments for opportunistic infections under Venezuela's health and social security systems. Lawsuits had to be launched on behalf of several individuals living with HIV/AIDS, and that resulted in the courts ordering the government to provide treatments for these individuals and, eventually, for all people with HIV/AIDS in Venezuela (27).

CMV retinitis, a potentially blinding disease, is the most common ocular complication of AIDS; it usually occurs in the late phase of the disease when immunosuppression is profound. Most cases respond to systemic treatment; however, it has a number of important disadvantages, including significant rates of relapse, toxicity, sepsis, cost, and deterioration of quality of life.

While 80% to 100% of patients respond to initial induction therapy, reactivation and progression of retinitis while on maintenance dosages occurs eventually in nearly all patients (28-30). Although not precisely understood, this phenomenon may be due to viral resistance or inadequate intraocular drug concentrations (31). To determine this, Arevalo and associates (32) studied intravitreous and plasma ganciclovir and foscarnet concentrations after IV administration in patients with AIDS with CMV retinitis and varying degrees of retinal detachment. The mean intravitreal ganciclovir and foscarnet concentrations in that study were below the ID 50 and ID 90 of some pretreatment and many post-treatment clinical CMV isolates. No correlation was found between intravitreal concentrations and extent of retinitis or extent of retinal detachments. The authors conclude that current drugs and dosing for CMV retinitis result in borderline or progressively subtherapeutic concentrations during the course of chronic therapy. This may explain reactivation while on maintenance therapy and resistance of CMV retinitis.

The advantage of local therapy is that it achieves an immediate therapeutic concentration of the drug in the vitreous cavity. In addition, the quality of life of our patients is significantly increased by obviating the need of an indwelling central catheter (needed for induction therapy with ganciclovir and foscarnet). However, the advantages of IV ganciclovir or foscar-

net include the ability to treat patients with bilateral disease (and to prevent activation of disease in fellow unaffected eyes) and possible prevention or control of CMV infections at other body sites. In addition, local therapy may not be as efficacious as standard IV ganciclovir or, in particular, IV foscarnet, regarding patient survival (28, 33).

In Venezuela, the cost of the ganciclovir implant is not covered by the government or insurance companies. Only a handful of patients are able to afford the placement of a ganciclovir implant for the management of CMV retinitis (33). Therefore, intravitreal ganciclovir is the most accessible means of local therapy for CMV retinitis. In addition, during our study period, valganciclovir (Valcyte, F. Hoffmann-La Roche, Switzerland) was not available in Venezuela (34, 35). Valganciclovir is an orally administered prodrug that is rapidly hydrolyzed to ganciclovir. Orally administered valganciclovir appears to be as effective as IV ganciclovir for induction treatment and is convenient and effective for the long-term management of CMV retinitis in patients with AIDS (35).

In the present study, we treated 13 patients with AIDS (18 eyes) with active CMV retinitis (study group). All of our patients were on HAART therapy and received weekly intravitreal injections of ganciclovir (5.0 mg). Complete regression of the retinitis was obtained with high dose intravitreal ganciclovir in 88.8% of eyes at a mean of 4.5 weeks. Three eyes (16.6%) presented CMV retinitis relapse at a mean of 25.6 days after their last injection. In 61.1% of eyes, VA improved more than two lines. This finding can be explained by the fact that all but one of those eyes had CMV retinitis in zone 1 with optic nerve involvement or foveal edema.

Two (15.3%) patients developed extraocular CMV disease, and started systemic therapy with intravenous ganciclovir. One of the patients survived for a month after starting local therapy and CMV retinitis was healing at his last examination. The other patient died only 1 week after his first injection before evaluation of his CMV retinitis could be performed. No patient developed CMV retinitis in the contralateral unaffected eye.

The development of extraocular CMV disease while undergoing local therapy of CMV retinitis is an important issue. Do we need concomitant specific systemic anti-CMV therapy in the setting of HAART? Martin et al (33) have previously reported a randomized clinical trial including 377 patients with AIDS and unilateral CMV retinitis assigned to one of three treatments: a ganciclovir implant plus oral ganciclovir (4.5 g daily), a ganciclovir implant plus oral placebo, or IV ganciclovir alone. They found that the incidence of new CMV disease at 6 months was 44.3% in the group assigned to the ganciclovir implant plus placebo, as compared with 24.3% in the group assigned to the ganciclovir implant plus oral ganciclovir ($p=0.002$) and 19.6% in the group assigned to IV ganciclovir alone ($p<0.001$). As compared with placebo, oral ganciclovir reduced the overall risk of new CMV disease by 37.6% over the 1-year period of the study ($p=0.02$). However, in the subgroup of 103 patients who were on HAART, the rates of new CMV disease were low and of similar magnitude, regardless of treatment assignment. These results may support in part the use of local therapy alone for the treatment of CMV retinitis if the patient is on HAART therapy (and has responded), and if extraocular CMV disease is not present. The incidence of extraocular CMV disease in our study was 15.3%, and compares favorably to Martin et al's study. Systemic specific anti-CMV therapy may not be necessary when local therapy is combined with HAART for the management of CMV retinitis, and if extraocular CMV disease is not present. Currently, with the availability of valganciclovir, systemic therapy needs to be considered in these patients.

Complications occurred in 33.3% of eyes in the study group and included retinal detachment, immune recovery uveitis, and endophthalmitis. Two of the retinal detachments (one patient) were repaired with vitrectomy and silicone oil injection, and one patient refused surgery. These patients had from 45 to 60% (mean: 51.6%) of retinal surface area involved with CMV retinitis. Two eyes with immune recovery uveitis (22-25) were treated with posterior sub-Tenon injections of triamcinolone acetonide at 3-week intervals. One of our patients developed a culture-negative endophthalmitis and responded to intravitreal antibiotics, and VA was preserved.

Our study group compared favorably to our control group. Although complete regression of the retinitis was obtained in 100% of eyes (vs 88.8% in the study group) treated with systemic ganciclovir, 12 eyes (60%) presented with CMV retinitis relapse (vs 16.6% in the study group) at a mean of 29 days after initiating oral ganciclovir (maintenance). No patient developed extraocular CMV disease or died during follow-up (vs

15.3% in the study group). No patient developed CMV retinitis in the contralateral unaffected eye. Complications occurred in 50% of eyes (vs 33% in the study group). Severe neutropenia occurred in 2 patients (13%).

We are not aware of any other study utilizing higher doses of ganciclovir (5.0 mg) at less frequent intervals and discontinuation of anti-CMV medication while on HAART therapy. The use of ganciclovir intravitreal injections once a week can be well tolerated by the patient, with healing of the retinitis in a mean of 4.5 weeks, and reactivation does not occur in over 83% while on HAART therapy.

Limitations of our study include that it was not a randomized series, our numbers are small, and studies regarding the pharmacokinetics of injecting 5.0 mg of intravitreal ganciclovir would be desirable. In addition, during our study period, valganciclovir was not available in Venezuela (34, 35).

In summary, high doses of intravitreal ganciclovir (5.0 mg) in combination with HAART therapy is very effective, and may be discontinued after CMV retinitis has healed if immune reconstitution with a significant increase in CD4+ count has occurred. Relapse may occur (16.6% at 25.6 days); however, local therapy is very effective in controlling it. Visual acuity improved or remained stable in all patients in our series. Complications may occur in a significant number of cases due to immune recovery, and to the injections. Systemic therapy with IV and oral ganciclovir may lead to a higher rate of relapses and retinal detachment. However, systemic therapy needs to be considered in these patients especially now that oral valganciclovir is available to avoid extraocular CMV disease, and contralateral involvement. Combination therapy including intravitreal ganciclovir, HAART, and systemic therapy with oral valganciclovir should be considered for future studies.

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