Intravenous versus oral ganciclovir: European/Australian comparative study of efficacy and safety in the prevention of cytomegalovirus retinitis recurrence in patients with AIDS

The Oral Ganciclovir European and Australian Cooperative Study Group*

Objectives: To evaluate the efficacy and safety of oral ganciclovir for the maintenance treatment of cytomegalovirus (CMV) retinitis in patients with AIDS.

Design: A 20-week, randomized, multicentre, open-label study. Progression of retinitis was assessed by funduscopy and masked reading of fundus photographs.

Methods: Adult patients with AIDS and stable CMV retinitis following a 2–3-week induction course of intravenous ganciclovir (5 mg/kg every 12 h) were randomized 2 : 1 to receive maintenance therapy with oral ganciclovir 500 mg six times daily, or 5 mg/kg intravenous ganciclovir once daily infused over 1 h. The primary efficacy variable was time to progression of CMV retinitis from initiation of maintenance therapy.

Results: A total of 159 patients were enrolled; 112 received oral ganciclovir and 47 intravenous ganciclovir. By masked assessment of fundus photographs, CMV retinitis progressed in 72% of patients in the oral group and 76% in the intravenous group. Mean time to progression was 51 days with oral ganciclovir and 62 days with intravenous ganciclovir ($P = 0.15$). By funduscopy, CMV retinitis progressed in 59% of oral ganciclovir patients and 43% of intravenous ganciclovir patients. Mean time to progression was 86 and 109 days, respectively ($P = 0.02$). Diarrhoea and neutropenia (absolute neutrophil count $< 500 \times 10^6$/l) were the most frequently reported adverse events in both groups. The incidence of sepsis for the oral and intravenous ganciclovir patients was 3 and 8.5%, respectively. Infection at the intravenous site occurred in 0 and 9% of patients, respectively.

Conclusions: Oral ganciclovir offers an effective and safe alternative to intravenous ganciclovir in the maintenance therapy of CMV retinitis.

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Introduction

Cytomegalovirus (CMV) retinitis is the most common opportunistic ophthalmic infection in patients with AIDS [1], with the incidence ranging from 20 to 34% in adult patients with AIDS [2–6]. If untreated, CMV retinitis results in retinal necrosis and eventually in permanent loss of vision [2,3]. As the life expectancy of HIV patients increases with improved pharmacologic intervention, morbidity from CMV retinitis may also be expected to increase.

Intravenous ganciclovir has been shown to be effective in controlling retinitis and in halting its progression [7–11]. The dosage regimen is an initial high dose (induction) for 2–3 weeks followed by lower doses (maintenance)

*See Appendix for details.

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for an extended period. The recommended induction dose is 5 mg/kg infused at a constant rate over 1 h, every 12 h for 14–21 days. The maintenance dose is 5 mg/kg infused over 1 h daily on 7 days per week, or 6 mg/kg once daily on 5 days per week.

An oral form of ganciclovir has been developed which may prove to be more acceptable for maintenance therapy of CMV retinitis than the intravenous formulation. The safety and bioavailability of oral ganciclovir in doses ranging from 1000 to 6000 mg daily have been assessed in a pilot study of 69 patients with AIDS who were shedding CMV (n = 19) or had received more than 4 weeks of prior intravenous ganciclovir therapy (n = 50) [12]. Oral ganciclovir was shown to have relatively low bioavailability (6%) but had prolonged absorption from the gastrointestinal tract. A dose of oral ganciclovir of 3000 mg daily was well tolerated and yielded plasma concentrations of ganciclovir with an average concentration of between 0.5 and 1.0 μg/ml. Within this concentration range, ganciclovir exceeds the median *in vitro* inhibitory concentration (IC_{50}) of most CMV clinical isolates [13].

The purpose of the present study was to compare the efficacy and safety of a 3000 mg total daily dose of oral ganciclovir with the recommended intravenous ganciclovir dose (5 mg/kg daily) for maintenance treatment of CMV retinitis in AIDS patients.

Subjects and methods

Patients were enrolled into the study in 12 sites in Europe and Australia. Patients were at least 18 years of age, had AIDS and CMV retinitis which had achieved remission or stabilization (i.e., lesions were not progressing or were totally inactive) following a 2–3 week induction course of intravenous ganciclovir (5 mg/kg every 12 h). Patients were excluded from entering the study if they had more than three induction courses of any anti-CMV therapy, clinical manifestations of CMV disease requiring additional treatment, Karnofsky performance score < 50%, significant gastrointestinal signs and symptoms, absolute neutrophil count (ANC) $< 750 \times 10^6$/l, platelet count $< 50 \times 10^9$/l, creatinine clearance < 70 ml/min per 1.73 m^2, or alanine aminotransferase levels > 225 IU. All patients gave written informed consent and the procedures followed were in accordance with the 1975 Helsinki Declaration, as revised in 1983.

Patients entering the study were randomized in a 2 : 1 ratio to receive 20 weeks of maintenance therapy with either oral ganciclovir 500 mg six times daily during waking hours (preferably with a snack or meal), or 5 mg/kg intravenous ganciclovir given once daily over 1 h. Maintenance therapy started immediately after the 2–3 week induction course of intravenous ganciclovir. Patients who had never received anti-CMV therapy other than the one induction course of intravenous ganciclovir that immediately preceded this maintenance study were considered 'naive' and were randomized separately from those patients who had a previous history of induction treatment for CMV retinitis. The following medications were not permitted during treatment: selected antimetabolites and alkylating agents, acyclovir for prophylaxis, foscarnet, CMV hyperimmune globulin, and imipenem-cilastatin. Bleomycin, vincristine, and vinblastine were permitted for treatment of Kaposi's sarcoma. Zidovudine (ZDV; up to 600 mg daily), didanosine (ddI) or zalcitabine (ddC), and oral or intravenous acyclovir for the treatment of herpes simplex infection, were permitted for periods up to 14 days.

Physical examinations, laboratory evaluations and ophthalmological examinations were performed at baseline, and a complete HIV disease history was taken. Patients were assessed every 2 weeks throughout the study for Karnofsky score, physical and ophthalmological examinations, diarrhoeal status, blood tests (haematology and biochemistry), and the occurrence of adverse events. CD4+ lymphocyte count (absolute and percentage) was measured at baseline and at the end of treatment. The protocol did not include any virological assessments of the patients.

Efficacy assessments

The primary efficacy variable was time to progression of CMV retinitis from initiation of maintenance therapy. Ophthalmological examinations included best corrected vision, slit-lamp examination, dilated fundus examination, and serial fundus photography. Clinical assessment of CMV progression was made by direct visualization and photographic assessment. Although this was an open-label study, treatment efficacy as determined by fundus photography was masked by central reading of the photographs by an independent assessor at the University of Wisconsin (Madison, Wisconsin, USA). Progression of CMV retinitis was defined in the protocol as evidence of a new, discrete lesion of CMV retinitis in a previously uninvolved area of the fundus of either eye, or an advancement of the edge of any existing lesion of CMV retinitis by one-half disc diameter or by ≥ 750 μm. If CMV retinitis progressed as assessed by funduscopy, the patient was discontinued from the study but seen again at 20 weeks from the start of treatment. All patient management decisions were made by unmasked practitioners on the basis of results from funduscopic evaluations. Fundus photographs were read centrally by a single, masked practised observer after the clinical phase of the study was completed.

Additional analyses for time to progression were conducted between various subgroups: naive/non-naive status, use of concomitant antiretrovirals, and the use of concomitant ddI. Comparisons were made between the study treatment groups for time to development of bilateral disease and progression into zone 1 (the most central part of the retina) from the start of maintenance. Changes in visual acuity (i.e., improvement, stabilization

or deterioration) were recorded as compared with baseline assessments.

Clinical outcomes assessment included the development of extraocular CMV disease, herpesvirus infections, and changes in Karnofsky performance scores.

Safety assessments

Safety was assessed by laboratory tests and monitoring clinical adverse events. Laboratory tests included haemoglobin, haematocrit, red blood cell count, white blood cell count, differential count, platelets, and serum biochemistry. All adverse events were reported regardless of severity and relationship to study medication. Adverse events were categorized according to body system and preferred term within body systems. All patients were included in the analyses of safety data.

Statistical analysis

Time to progression of CMV retinitis, assessed by funduscopy and fundus photography, was estimated using Kaplan–Meier methods and treatments were compared using the log-rank test. The difference between treatment groups in relation to mean time to progression was quantified by 95% confidence intervals (CI) calculated using normal approximations to the distribution of the Kaplan–Meier estimates of the mean times to progression. All statistical tests were two-tailed and carried out at the 5% significance level. Estimates of mean and median times to progression were obtained from the estimated survival functions.

Results

Patients

A total of 159 patients were enrolled in the study and randomized to receive oral (n = 112) or intravenous ganciclovir (n = 47). Demographic and baseline disease characteristics are shown in Table 1. The majority of patients were men. Only 10 women participated in the trial, and all, by chance, received oral ganciclovir. The study design did not include any stratification by sex and the women were from six different centres. For all patients, the time from first diagnosis of CMV retinitis to entering the study ranged from 0 to 41 months (mean, 2.5 and 1.3 months for oral and intravenous, respectively). The group mean for patients receiving oral ganciclovir was probably skewed by a single high value of 41 months (median, 1 month for both groups). The mean duration of the previous induction course with intravenous ganciclovir was 18.6 ± 3.6 days in the oral group and 18.1 ± 4.6 days in the intravenous group. All other demographic and baseline disease characteristics were similar for both treatment groups.

Funduscopic data were available for 154 of the 159 patients enrolled and data from 141 patients were included in evaluations of fundus photographs. Baseline fundus photographs were available for 130 patients. For the 11 patients with no baseline photographs, fundus photographs from the first available visit were used as baseline. According to funduscopic examinations, all evaluable patients had stable CMV retinitis at baseline (Table 2). In contrast, according to fundus photography, CMV retinitis was active (but not progressing and therefore considered stable) in the eyes of 82 (87%) patients in the oral group and 28 (78%) patients in the intravenous group at baseline. All patients entered in the study were evaluated for safety.

Table 1. Demographic data and baseline disease characteristics.

	Oral ganciclovir (n = 112)	Intravenous ganciclovir (n = 47)	P
Age (years)			
Mean (range)	38.6 (23–58)	39.4 (25–62)	0.57*
Race (%)			
White	95 (85)	45 (96)	0.35†
Black	2 (2)	1 (2)	
Other	15 (13)	1 (2)	
Sex (male/female)	102/10	47/0	0.03‡
Karnofsky score			
Mean ± SD	80.4 ± 13.7	77.8 ± 14.0	0.28*
CD4+ cell count (× 10^6/l)			
Mean (range)	21.1 (0–320)	18.5 (0–100)	0.60§
Months with AIDS			
Mean ± SD	14.8 ± 12.2	17.9 ± 14.6	0.17*
Months since CMV retinitis diagnosis			
Mean ± SD	2.5 ± 6.1	1.3 ± 2.1	0.06§
No. induction courses (%)			
1	87 (78)	40 (85)	0.41†
2	15 (13)	4 (9)	
3	10 (9)	3 (6)	

*Student's t test. †Cochran–Mantel–Haenszel test. ‡Fisher's exact test. §Student's t test adjusted for unequal variances. CMV, cytomegalovirus.

Table 2. Baseline ophthalmic characteristics.

	% Patients		
	Oral ganciclovir (n = 110)	Intravenous ganciclovir (n = 44)	P
Unilateral retinitis	67	77	0.25*
Retinitis in zone 1†	42 (46)	34 (47)	0.16‡ (1.0*)
Retinal detachment	4	0	0.58*
Retinal tear	3	0	0.56*
Macular oedema	11	16	0.42*
Disc swelling	13	14	1.00*
Visual acuity of 6/12 or better			
Worse eye	84	77	
Better eye	99	98	

*Fisher's exact test. †Values in parentheses indicate results based on fundus photograph. ‡Cochran–Mantel–Haenszel test.

Twenty (18%) out of 112 patients completed 20 weeks of treatment with oral ganciclovir and 19 (40%) out of 47

completed 20 weeks with intravenous ganciclovir. Sixty-four patients (57%) in the oral group and 15 (32%) in the intravenous group were discontinued using funduscopic evidence of progression. Sixteen (14%) patients in the oral group and seven (15%) in the intravenous group discontinued treatment because of adverse events.

Progression of CMV retinitis

Fundus photographs indicated that CMV retinitis progressed in 72% (75 out of 104) of patients in the oral group and in 76% (28 out of 37) of patients in the intravenous group. The mean time from the start of maintenance to the first progression of retinitis was 51 days (median, 41 days) in the oral group and 62 days (median, 60 days) in the intravenous treatment group, a difference of 11 days between the two survival curves ($P=0.15$) by log-rank test. The percentage of patients remaining free from progression at each time from the start of maintenance, determined by fundus photographs, is shown in Fig. 1. Based on photographic assessment, the 95% CI for the mean difference in time to progression was between −24 and 1 day, indicating that there is a 95% chance that the true mean time to progression for oral ganciclovir treatment was not more than 24 days earlier or 1 day later than the true mean time to progression for intravenous ganciclovir treatment.

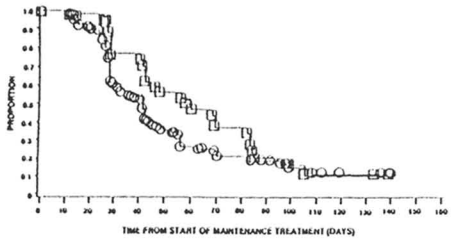

Fig. 1. Proportion of patients remaining free from progression at each time from the start of maintenance as determined by fundus photograph assessments (Kaplan–Meier estimates). (○), Oral ganciclovir group (n = 104); (●), intravenous ganciclovir group (n = 37). $P=0.15$ by log-rank comparison test.

Based on funduscopy, CMV retinitis progressed during maintenance in 59% (65 out of 110) of patients in the oral ganciclovir group and 43% (19 out of 44) of patients in the intravenous group (Table 3 and Fig. 2). The mean time from the start of maintenance treatment to the first progression of retinitis was 86 days (median, 84 days) in the oral treatment group and 109 days (median, 137 days) in the intravenous treatment group, a difference of 23 days between the two Kaplan–Meier curves ($P=0.02$, log-rank test).

Progression in naive versus non-naive patients

According to funduscopy, the mean time to progression for naive patients was 91 days for patients in the oral group and 109 days for patients in the intravenous group ($P=0.09$). By fundus photographic assessment,

Table 3. Time to initial progression of cytomegalovirus retinitis.

	Oral ganciclovir	Intravenous ganciclovir	P^a
Funduscopy assessment (n)	110	44	0.02
No. patients progressing (%)	65 (59)	19 (43)	
Mean days (SEM)	85.9 (4.5)	108.7 (6.8)	
Median days (95% CI)	84 (68–98)	137 (NC)	
Difference between oral/intravenous means (95% CI)	−23 (−39 to −7)		
Photographic assessment (n)	104	37	0.15
No. patients progressing (%)	75 (72)	28 (76)	
Mean days (SEM)	50.8 (3.3)	62 (5.1)	
Median days (95% CI)	41 (31–45)	60 (42–83)	
Difference between oral/intravenous means (95% CI)	−11 (−24 to 1)		

[a]Value for treatment comparisons. CI, confidence interval; NC, not calculable.

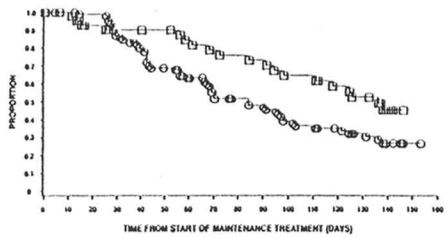

Fig. 2. Proportion of patients remaining free from progression at each time from the start of maintenance as determined by funduscopy assessments (Kaplan–Meier estimates). (○), Oral ganciclovir group (n = 110); (●), intravenous ganciclovir group (n = 44). $P=0.02$ by log-rank comparison test.

mean times to progression were 54 days in the oral group and 64 days in the intravenous group ($P=0.22$). Times to progression for non-naive patients were shorter than those for naive patients. The means were 65 and 93 days, respectively, for the oral and intravenous groups according to funduscopy ($P=0.21$) and 37 and 38 days, respectively, according to photographic evaluations ($P=0.96$).

Progression in patients taking concomitant antiretrovirals

Fifty per cent (22 out of 44) of patients in the intravenous ganciclovir group and 62% (68 out of 109) of patients in the oral ganciclovir group received one or more antiretroviral agents during ganciclovir maintenance treatment. By photographic assessment, mean time to progression for patients who received concomitant antiretrovirals were 48 and 73 days for oral and intravenous ganciclovir, respectively ($P=0.02$); for patients who did not receive concomitant antiretrovirals, mean time to progression was 54 days and 47 days, respectively ($P=0.35$). Direct funduscopic assessment estimated mean time to progression for patients who received concomitant antiretrovirals as 86 and 127 days for oral and intravenous ganciclovir, respectively ($P=0.0009$); for patients who did not receive concomitant antiretrovirals,

mean time to progression was 85 days for both treatment groups.

ddI was used by more patients than either ZDV or ddC. In patients receiving ddI together with ganciclovir, mean time to progression by photographic assessment was 45 and 71 days in the oral and intravenous ganciclovir groups, respectively ($P=0.04$). Mean time to progression by funduscopic assessment was 83 and 128 days in the oral and intravenous ganciclovir groups, respectively ($P=0.01$).

Other ophthalmologic evaluations

Visual acuity remained stable during maintenance treatment for the majority of patients. Visual acuity deteriorated in 16% (18 out of 110) of patients in the oral ganciclovir group and in 11% (five out of 44) of patients in the intravenous ganciclovir group ($P=0.29$).

Eleven per cent (eight out of 74) of patients in the oral ganciclovir group and 12% (four out of 34) of patients in the intravenous group progressed from unilateral to bilateral retinitis during maintenance treatment, as assessed by funduscopy. Mean times to progression were comparable, 125 and 122 days in the oral and intravenous groups, respectively. Photographic assessment showed that 10% (seven out of 70) of oral ganciclovir-treated patients and 19% (six out of 31) of intravenous ganciclovir-treated patients progressed to bilateral disease. Mean time to progression by photographic assessment was 42 days in the oral group and 74 days in the intravenous group. The difference between the treatment groups for time to progression to bilateral disease was not statistically significant ($P=0.55$).

Time to progression of CMV retinitis into zone 1 from other parts of the retina was also assessed by both funduscopy and fundus photographs. According to funduscopic assessment, 12% (12 out of 103) of patients in the oral group and 7% (three out of 43) of patients in the intravenous group showed progression into zone 1. Mean time to progression was 125 days in the oral group and 121 days in the intravenous group ($P=0.16$). Fundus photography indicated that retinitis progressed into zone 1 in 1% (one out of 86) of patients in the oral group and in 3% (one out of 33) of patients in the intravenous group.

Clinical outcome

New episodes of extraocular CMV disease, herpes simplex virus infections, and herpes zoster infections occurred in only three patients (2%) throughout the study. One patient taking oral ganciclovir developed new disseminated CMV disease, none of the patients developed new herpes simplex infections, and only one patient in each treatment group reported a new episode of herpes zoster infection. Three (6.4%) of the intravenous ganciclovir group and four (3.6%) of the oral group received acyclovir. Karnofsky performance scores were generally unchanged from baseline at all the study visits.

Safety

The majority of patients in both treatment groups reported an adverse event; there were no significant differences in incidence or type of adverse event between treatment groups. The most frequently reported adverse events were diarrhoea and neutropenia (Table 4); neutropenia (ANC $<500\times10^6$/l) occurred more frequently in the intravenous compared with the oral ganciclovir group (23 versus 14%, respectively; $P=0.23$) and diarrhoea occurred more frequently in the oral ganciclovir group compared with the intravenous ganciclovir group (33 versus 21%, respectively; $P=0.18$). Anaemia (haemoglobin <9.5 g/dl) occurred equally in both groups (40% intravenous, 36% oral). The incidence of thrombocytopenia (platelet count $<50\times10^9$/l) was also similar in both groups (9% intravenous, 7% oral).

Table 4. Adverse events.

	No. patients (%)		
	Oral ganciclovir (n = 112)	Intravenous ganciclovir (n = 47)	*P*
All adverse events	91 (81)	41 (87)	
Neutropenia*	15 (14)	10 (23)	0.23
Thrombocytopenia†	7 (7)	4 (9)	
Anaemia‡	38 (36)	17 (40)	
Diarrhoea	37 (33)	10 (21)	0.18
Fever	15 (13)	9 (19)	
Asthenia	11 (10)	3 (6)	
Abdominal pain	13 (12)	2 (4)	
Rash	11 (10)	0	
Sepsis	3 (3)	4 (8.5)	0.20
Infection at intravenous site§	0	4 (9)	

Neutropenia, thrombocytopenia, and anaemia based on 43 and 107 patients with laboratory data. *Absolute neutrophil count $<500\times10^6$/l. †Platelet count $<50\times10^9$/l. ‡Haemoglobin <9.5 g/dl. §Based on 44 patients.

The incidence of sepsis was almost three times greater in the intravenous group than the oral group (8.5 versus 3%; $P=0.20$). Infection at the intravenous site also occurred more often in the intravenous group (9%) compared with the oral group (0%). Unfortunately, no information was specifically collected concerning the presence or absence of a central venous catheter in patients taking oral ganciclovir. Rash was also reported more frequently in the oral group than the intravenous group (10 versus 0%). It is unclear whether this is of clinical significance.

Discussion

Untreated CMV-related diseases are associated with a high incidence of morbidity and mortality [14]. Almost a decade ago, published studies indicated that ganciclovir

was effective in treating CMV retinitis in immunocompromised patients [15,16]. Subsequent published clinical studies of intravenous ganciclovir, administered on an induction regimen and then continuously as maintenance therapy, demonstrated that progression of retinitis could be forestalled for a median of 42–128 days [17–20]. Regardless of efficacy, however, continual maintenance therapy with intravenous ganciclovir requires establishment of permanent venous access that may further compromise a deteriorating quality of life. Furthermore, a permanent, indwelling venous catheter carries the potential for sepsis and catheter-related adverse events.

Administration of ganciclovir by the oral route results in plasma concentrations that exceed the *in vitro* IC_{50} of most CMV clinical isolates [12]. The ability to deliver an oral dose of ganciclovir that is effective in maintaining the stability of CMV retinitis, and well-tolerated, would be of significant benefit. The purpose of this 20-week study was to compare the efficacy and safety of oral ganciclovir therapy (3000 mg daily) and intravenous ganciclovir therapy (5 mg/kg daily) in maintaining the stability of CMV retinitis in patients with AIDS.

The principal efficacy parameter was time to progression of retinitis. Progression was assessed by direct funduscopic visualization during the course of the study, and by evaluation by a masked experienced reader at the conclusion of the study. Patients withdrawing before 20 weeks were considered to be censored at the time of withdrawal in the analysis. Kaplan–Meier curves showing the time to progression (Fig. 1) were used to evaluate treatment differences. At each timepoint, the plot shows the estimated proportion of subjects who are free from progression, from which the mean time to progression can be estimated. In this study the mean time to progression was considered to be a more valid summary measure because of the 'step down' effect in the time-to-progression curve, which affected median but not mean values.

On the basis of masked assessment of fundus photographs, patients receiving oral ganciclovir experienced progression earlier (mean, 11 days) than patients receiving intravenous ganciclovir. Statistically, the 95% CI around the difference between the mean days to progression in the two treatment groups indicated that there is a 95% chance that the true mean time to disease progression with oral ganciclovir maintenance was no more than 24 days earlier or 1 day later than the mean time to progression with intravenous ganciclovir therapy. These results contrast with those obtained when progression of retinitis was determined by the evaluating (unmasked) ophthalmologist using funduscopy. This method of assessment resulted in longer times to progression for both treatment groups, and a statistically significant difference between time to progression with oral and intravenous ganciclovir treatment. While it is important to consider the results from both assessments, in the clinical trial setting, assessment of serial fundus photographs is more objective and may be a more sensitive method for determining retinitis progression. Assessment of serial fundus photographs by a masked third party removes observer bias that may skew study results, since the treating physician and the ophthalmologist were aware of the treatment received by each patient. In the previously published, multicentre, randomized clinical trial designed to compare ganciclovir and foscarnet, only masked fundus photographs were used to determine and compare times to progression [8].

Naive patients (i.e., those who were not previously treated for CMV retinitis) had longer times to progression than non-naive patients. This is not unexpected since studies have shown the median time to progression becomes shorter with each subsequent reactivation [21,22]. Based on masked photographic assessment there was no difference in time to progression of CMV retinitis between oral and intravenous ganciclovir in patients who did not receive concomitant antiretrovirals. For patients who received concomitant antiretrovirals, there was a statistically significant longer time to retinitis progression among patients randomized to intravenous rather than oral ganciclovir. These same results were reported when assessment was by direct observation via funduscopy. In two similar studies of oral and intravenous ganciclovir in CMV retinitis this phenomenon has not been observed [23,24]. Furthermore, if data are divided into too many subgroups, significant differences between the groups start to appear by chance.

As assessed by funduscopy, there was no difference between the treatment groups in the percentage of patients who developed bilateral disease during treatment, or the time to progression. However, by photographic assessment the percentage of patients who developed bilateral disease during intravenous treatment was almost twice that of orally treated patients, although the time to progression was not significantly different. Neither funduscopic assessment nor fundus photographs showed significant differences in the percentage of patients with progression of retinitis into zone 1.

Although the patients in this study were in an advanced stage of HIV disease, only one new diagnosis of extraocular CMV disease was made during the study. This low incidence of extraocular CMV disease may reflect a secondary benefit of systemic CMV retinitis treatment and should be considered in discussions about types of intravitreal therapy.

The majority of patients in the study experienced adverse events; however, many could be related to advanced HIV disease, opportunistic diseases, or other concomitant medication. The safety benefits of oral ganciclovir maintenance treatment included a lower incidence of sepsis and neutropenia compared with intravenous administration. Sepsis and infection at the intravenous site occurred more often in the intravenous-treated patients (8.5% sepsis, 9% intravenous-site infection) than the orally treated patients (3% sepsis, 0% intravenous-site infection). The rate of neutropenia in the intravenous ganciclovir group was nearly double that of the oral group, 23 versus 14%, respectively.

Based on the results of funduscopic and photographic assessment of progression, stability of visual acuity, progression from unilateral to bilateral disease and progression of retinitis into zone 1 from the remainder of the retina, this study demonstrated that the efficacy of oral ganciclovir for maintenance treatment of CMV retinitis is comparable with intravenous ganciclovir. Oral ganciclovir was well tolerated and, as shown by this study, has a distinct advantage over intravenous ganciclovir by alleviating a potential site of infection caused by the intravenous catheter. Oral ganciclovir offers the patient and physician an alternative to intravenous administration in the maintenance therapy of CMV retinitis.

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Appendix

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