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High dose intravitreal foscarnet in the treatment of cytomegalovirus retinitis in AIDS

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Abstract

The efficacy and tolerance of high dose intravitreal foscarnet for cytomegalovirus retinitis in patients with AIDS was studied. Foscarnet in a dose of 2400 μg was injected directly into the vitreous of 11 patients (15 eyes). Five patients had active retinitis (eight eyes, 53·3%), and received a 3 week induction therapy of six injections as the first step. Six patients had initial inactive retinitis (seven eyes, 46·7%), and received only maintenance therapy which consisted of a weekly injection. The main indications for intravitreal therapy were: myelosuppression, kidney toxicity, catheter related sepsis, or refusal of intravenous therapy. The patients were followed for a mean period of 16 weeks (range 8–28 weeks) and received a total of 304 injections. Vitreous foscarnet levels were measured by high performance liquid chromatography. After a 3 week course of induction therapy, complete resolution of the active retinitis was seen in 62·5% (5/8 cases), while 37·5% (3/8 cases) had partial resolution. No cases failed to respond or progress. The rate of relapse on maintenance therapy was 33% (five of 15 eyes) by 20 weeks, and two of these eyes did not respond to reinduction and progressed in involvement of the macula or optic nerve. Neither important local complications nor intraocular drug toxicity were observed. Vitreous foscarnet levels in two different patients were 896 μmol/l and 749 μmol/l at 22¾ hours and 42½ hours after the injection. Intravitreal foscarnet appears to be a safe, effective, and useful alternative in patients with intolerance to intravenous antiviral therapy.

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Cytomegalovirus (CMV) retinitis is the most common opportunistic ocular infection in patients with AIDS. It has been reported in up to 45% of patients during the average 20 month course of survival of AIDS patients,[1-7] and it often leads to blindness.

Only two virostatic drugs have been shown to be effective in CMV retinitis when administered systemically: foscarnet[8-10] and ganciclovir,[11-15] but severe side effects often limit their use and lead to their discontinuation. In such cases both drugs, when vitreally injected, proved to be effective alternatives in stopping the progression of retinitis.[16-20].

Diaz-Llopis *et al*[20] have shown the efficacy of foscarnet in halting the progression of CMV retinitis in a patient after intravitreal doses of 1200 μg. She *et al*[21] have reported the absence of retinal toxicity in rabbits after intravitreal doses of up to 1000 μg.

We present a prospective study of courses of intravitreal foscarnet at a dose of 2400 μg per injection. Provided there is no retinal toxicity, the higher dose is more desirable for both clinical and pharmacokinetic reasons, as it is believed that there is a correlation between intraocular concentration of foscarnet and the resulting virostatic effect.

Patients and method

GENERAL CHARACTERISTICS OF THE STUDY

This prospective open study was performed between September 1991 and January 1993. All patients met Centers for Disease Control criteria for the diagnosis of AIDS[22] and were treated after obtaining permission from the ethics and clinical trials committee of La Fe University Hospital. Informed consent was obtained from all patients. Table 1 summarises the clinical characteristics of these patients at the beginning of the study. Ophthalmic evaluations were performed at baseline and were repeated every week, including determination of best corrected visual acuity, slit-lamp biomicroscopy, indirect ophthalmoscopy, retinal drawings, and wide angle fundus photography. The location of CMV retinitis was identified by zones as described by Holland *et al*.[23] Zone 1 extended up to 3000 μm from the fovea and 1500 μm from the optic disc (sight threatening area). Zone 2 was anterior to zone 1 up to the equator, and zone 3 was anterior to the equator.

DIAGNOSTIC CMV RETINIS CRITERIA

The diagnosis of CMV retinitis was made by indirect ophthalmoscopy. A characteristic lesion consisted of a zone of necrotising retinitis with more or fewer haemorrhages and vascular sheathing. Older healed areas showed an atrophic zone with fine pigment stippling and sometimes there were associated focal deposits of lipid or glial tissue.

INCLUSION AND EXCLUSION CRITERIA

Intravitreal foscarnet was used in two different conditions: (1) patients with active retinitis who refused systemic therapy; (2) patients with completely halted retinitis who were intolerant to the intravenous anti-CMV treatment (foscarnet or ganciclovir) because of kidney toxicity and/or myelosuppression. Renal toxicity was defined as an increase in baseline serum creatinine level

higher than 50%. Patients were considered neutropenic if they had an absolute neutrophil count of less than 1×10^9/l at any time during the 30 days before the enrolment. All types of CMV retinitis were treated. Those patients who showed evidence of active systemic CMV infection were ruled out. The patients who were on zidovudine continued on the same treatment after being included in the study.

INTRAVITREAL TECHNIQUE

Induction therapy followed by a maintenance treatment was only performed in patients with active retinitis. Induction therapy included an initial series of six injections, 2400 μg/0·1 ml per injection, given at intervals of 72 hours during the first 18 day period. Initial maintenance therapy was given to patients with inactive retinitis. Maintenance therapy consisted of a single weekly injection which was continued indefinitely. Recurrences were treated with repeated courses of induction therapy with a series of six injections given in 3 weeks. Patients were instructed to use topical tobramycin drops 2 days before and after each injection.

Foscarnet with pH of 7·4 prepared for intravenous infusion was provided by Schering Plough-Astra Spain Laboratories, Astra Group, Sweden. Each millilitre of the commercial solution contains 24 mg (80 μmol) of foscarnet trisodium hexahydrate as well as both hydrochloric acid and water for injection. The isotonic solution was taken directly from the infusion bottle and was passed through a 0·22 μm filter before injection.

Injections were performed on an outpatient basis with modifications of a previously described technique.[24] Conjunctiva was cleaned with topical 5% povidone iodine solution. Topical 4% cocaine hydrochloride was used as an anaesthetic. We usually injected in the lower temporal quadrant but other areas were selected in those cases in which there was retinal necrosis in order to avoid iatrogenic retinal tears. The injections were performed with a 30 gauge needle attached to a tuberculin syringe containing 0·1 ml of foscarnet (2400 μg) solution. A point 4 mm posterior to the corneoscleral limbus was chosen, and the needle was passed with the needle tip directed towards the mid vitreous. When the needle tip was in the mid vitreous, foscarnet was slowly injected, then the needle was withdrawn from the eye and a cotton tip applicator was put on the injection point to avoid reflux. Pulsation of the central retinal artery was monitored after injection using indirect ophthalmoscopy.

RESPONSE CRITERIA

Determination of the efficacy of the treatment was based on the ophthalmoscopic appearance of retinal lesions. Visual acuity was not used as a response criterion. 'Progression or no response' was considered if the extent of the retinitis from

Table 1 Clinical characteristics of patients at the time of enrolment in the study

No	Sex and age	Risk factor	Previous systemic antiviral therapy	Indication for intravitreal foscarnet	Zidovudine therapy	AIDS before intravitreal therapy (months)	Eye	Area	Activity of retinitis	Time between systemic and intravitreal therapy (days)
1	M 44	Homosexual	Foscarnet	Kidney toxicity	–	4	R	2/3	Inactive	7
2	F 37	Heterosexual	Ganciclovir	Myelotoxicity	–	16	R	1	Active	27
							L	1	Active	
3	M 34	Drug misuser	–	Refuse	+	5	R	3	Active	0
							L	3	Active	
4	M 36	Homosexual	Foscarnet	Kidney toxicity	+	15	R	1	Inactive	9
5	M 34	Heterosexual	Ganciclovir	Myelotoxicity	–	12	R	1	Inactive	10
6	M 41	Drug misuser	–	Refuse	+	24	L	2	Active	0
7	M 42	Homosexual	Foscarnet	Kidney+ myelotoxicity	–	8	R	1	Inactive	6
							L	1	Inactive	
8	M 29	Homosexual	–	Refuse	–	18	R	1	Active	0
							L	1/2	Active	
9	F 39	Heterosexual	Ganciclovir	Catheter sepsis	+	6	L	2/3	Inactive	8
10	M 37	Homosexual	Foscarnet	Kidney toxicity	–	3	R	2	Active	29
11	M 30	Homosexual	Ganciclovir	Myelotoxicity	+	13	L	1/2	Inactive	8

Table 2 Characteristics of intravitreal treatment with foscarnet

No	Eye	Visual acuity		Number of injections	Type of intravitreal therapy	Grade of response	Recurrence (months)	Foscarnet follow up (weeks)	Current status
		Initial	Final						
1	R	20/25	20/25	11	Maintenance	Partial	–	8	Deceased
2	R	20/50	LP	27	Induction+	Partial	3	20	Deceased
	L	20/80	NLP	27	maintenance	Partial	3		
3	R	20/20	20/20	31	Induction+	Complete	–	28	Alive
	L	20/30	20/25	31	maintenance	Complete	–		
4	R	20/60	20/60	21	Maintenance	Complete	–	18	Deceased
5	R	20/60	20/100	13	Maintenance	Complete	–	10	Alive
6	L	20/30	20/30	19	Induction+ maintenance	Complete	–	16	Deceased
7	R	20/200	CF	22	Maintenance	Partial	4	19	Deceased
	L	20/80	20/200	22		Partial	4		
8	R	20/40	20/30	11	Induction+	Complete	–	8	Alive
	L	20/60	20/30	11	maintenance	Complete	–		
9	L	20/30	20/30	11	Maintenance	Complete	–	8	Deceased
10	R	20/50	20/100	30	Induction+ maintenance	Partial	5	25	Deceased
11	L	20/200	20/400	17	Maintenance	Complete	–	14	Alive

LP=light perception; NLP=no light perception; CF=counting fingers.

the onset of the treatment was an advance of 750 μm or more of any pre-existing CMV lesion or development of new retinal foci. An initial progression during induction therapy in the first 10 days could be seen in the cases with a good response and was not considered a real sign of progression. 'Complete response or resolution' was defined as arresting the progression of necrosing retinitis together with resolution of retinal opacification, haemorrhage, and vasculitis. We also considered cases of initial inactive retinitis without signs of reactivation during the treatment to be a complete response. 'Partial response or stabilisation' was defined as a lack of progression over healthy retina or a development of new foci. We also considered to be partial response the cases of resolution of the retinitis with persistence of oedema and opacification along the border. 'Recurrence or reactivation' was defined as the presence of new lesions, or opacification along the border of a previously complete inactive lesion.

VITREOUS SAMPLES AND FOSCARNET LEVELS

Two samples of vitreous were obtained during maintenance therapy from two different patients (Nos 2 and 10) at 22¾ and 42½ hours after the injection. Special informed consent was obtained from these two patients. Vitreous aspiration was performed under retrobulbar anaesthesia using a 21 gauge needle with prior sclerotomy. All vitreous samples were frozen immediately at −20°C until analysis via a high performance liquid chromatography assay with electrochemical detection and a lower limit of detection of 33 μmol/l.[25]

Results

Table 2 summarises the efficacy of the treatment. Eleven patients (15 eyes) were studied and followed between 8 to 28 weeks (mean 16 weeks). Six were homosexual men, two were male injecting drug users, and three were heterosexual partners of seropositive subjects. Mean age was 36·6 years (range 29 to 44 years). Diagnosis of AIDS preceded the diagnosis of CMV retinitis by a mean of 11·2 months (range 4 to 24 months). In the last follow up we found that seven of the 11 patients had died from opportunistic infections.

Cytomegalovirus retinitis was unilateral in seven patients (63·6%) and bilateral in four patients (36·4%). At recruitment, retinitis affected only zone 1 in seven out of the 15 eyes, zone 2 in two eyes, zone 3 in two eyes, both zones 2 and 3 in two eyes, and both zones 1 and 2 in two eyes. A total of 304 injections were given. Bilateral injections were given when needed. The main indications for intravitreal therapy were: myelosuppression (27·2%) (3/11), myelosuppression plus kidney toxicity (9%) (1/11), kidney toxicity alone (27·2%) (3/11), refusal of intravenous therapy (27·2%) (3/11), and catheter related sepsis (9%) (1/11). None of the patients with unilateral retinitis had developed CMV retinitis in the other eye at the last follow up. Active retinitis showed no progression in all eyes 3 weeks after the beginning of intravitreal treatment. Complete halt and replacement by atrophic retina occurred within 5 to 9 weeks. Among 15 eyes, eight received induction plus maintenance therapy and seven received only maintenance therapy. Reinduction was made in five of 15 eyes (33·3%) because of retinitis reactivation during maintenance therapy. In two of these five eyes (13·3%) CMV retinitis progressed leading to blindness by involvement of macula or optic nerve. No intraocular complications such as retinal detachment, intravitreal haemorrhage, endophthalmitis, or cataract were observed during intravitreal therapy.

The concentration of foscarnet in the vitreous was 896 μmol/l and 749 μmol/l at 22¾ and 42½ hours respectively after the injection of 8 μmol (2400 μg) in 0·1 ml.

Discussion

Several studies using intravenous treatment with either foscarnet or ganciclovir have achieved a similar degree of success in terms of the initial response rate of CMV retinitis in AIDS patients. Nevertheless, a high incidence of side effects, especially myelotoxicity with ganciclovir and kidney toxicity with foscarnet, results in discontinuation of therapy in almost one third of patients. Intravitreal administration has been shown to be an effective alternative in these patients.[16-20]

Local intravitreal therapy has two main disadvantages compared with systemic treatment: a poorer survival rate and a greater incidence of progression to bilateral CMV retinitis.[13 17 24 26 27] The main advantages of intravitreal therapy are: (i) it avoids the necessity of hospitalisation during induction intravenous therapy, (ii) it eliminates the high incidence of sepsis associated with chronic home administration during maintenance intravenous treatment, and (iii) it improves patient quality of life. An alternative to multiple repeated intravitreal injections is the surgical implantation of an intravitreal device, which delivers ganciclovir intraocularly over approximately 4 to 5 months. This implant has demonstrated resolution of the CMV retinitis in all cases in a long term clinical study,[28] but with a high rate of complications, such as intraoperative vitreous haemorrhage and suprachoroidal implantation of the device.

Since foscarnet (trisodium phosphonoformate hexahydrate) and ganciclovir are virostatic agents, they must be administered continuously for life so as to avoid the progression of CMV infection. Compared with ganciclovir, foscarnet has the advantage of in vitro activity against both HIV and CMV. The drug has been shown to be effective in ganciclovir resistant CMV retinitis.[29] When compared with intravenous administration, intravitreal foscarnet has the advantage of lacking renal toxicity which occurs in as many as 46% of patients during systemic treatment.[30]

Encouraged by our initial results with low dose intravitreal foscarnet,[20] we have treated a series of 11 patients with multiple high dose intravitreal injections. Because of the virostatic nature of foscarnet, all patients remained on maintenance therapy. CMV retinitis showed no progression in all eyes 3 weeks after induction

therapy began. Resolution of exudative borders occurred within 5 to 6 weeks, and a complete area of atrophic retina could be seen as late as 8 to 10 weeks after the onset of the treatment. Despite successful induction and maintenance therapy, we have found evidence of relapse in five out of 15 eyes while on maintenance therapy (33·3% at 20 weeks). All relapses presented as an insidious active front at the margin of the scarred lesion ('smouldering'), without the appearance of new 'brushfire' lesions. Three responded to a second course of induction therapy.

Considered as a whole, these results showed clinical efficacy of intravitreal foscarnet similar to anti-CMV therapies previously reported, but with a lower relapse rate than those previously reported with intravitreal ganciclovir (33% to 45% at 8 to 12 weeks of maintenance therapy).[17 19 24] This difference may be attributed to the proved development of resistance in patients treated with ganciclovir,[31] which has not been reported with foscarnet. With intravenous foscarnet, a better response to the treatment seemed to be observed when zidovudine was added.[10] In this study the percentage of patients who responded to intravitreal foscarnet therapy with a complete resolution was higher in the group treated with zidovudine than in the group treated with foscarnet alone (without zidovudine).

Our experience has demonstrated that multiple intravitreal injections are well tolerated. Good intraocular tolerance is shown by the visual acuity remaining at 20/30 or more in seven eyes throughout the follow up period. The absence of retinal detachments in the present study shows a substantially lower incidence of this complication than in other clinical studies using intravitreal ganciclovir injections[24] or an intravitreal device.[28] Although retinal detachments have been attributed to microbreaks located in the porous junction of normal and atrophic retina, vitreous anomalies induced by ganciclovir (pH 10·14) may be a contributing factor.[24] The pH of foscarnet (7·4) which is closer to the physiological value could be an added advantage. Previous series using intravitreal therapy have reported an incidence of endophthalmitis of 0·4% to 0·6%.[17 18] The lack of intraocular infections in our series, consistent with that previously reported,[24] could be attributed to the use of povidone iodine eyedrops before the injection.

Henry *et al*[16] have reported that the vitreal levels of ganciclovir remain above the 50% inhibitory concentration of most human CMV strains for a period of about 62 hours after a single 200 μg injection. Cochereau-Massin *et al*[24] have reported no differences in clinical efficacy using 400 μg per injection instead of 200 μg. The mean 50% inhibitory value of foscarnet for most strains of human CMV and for the HIV are 271 μmol/l[32] and 10–25 μmol/l[30] respectively. Diaz-Llopis *et al*[20] have reported a vitreous level of 292 μmol/l at 49½ hours after the intravitreal injection of 1200 μg of foscarnet. Although the dose used in this series is twice the amount used in a previous study, the intravitreal levels of foscarnet found (749 μmol/l at 42½ hours after injection of 2400 μg) are proportional to those previously described. Since these data were from different patients, no pharmacokinetic curve could be produced.

In conclusion, intravitreal foscarnet is a safe and effective local therapy for CMV retinitis in AIDS patients when intravenous administration of antiviral agents is not recommended. The 2400 μg dosage does not cause clinical toxicity and has a better intravitreal absorption than intravitreal ganciclovir. Since intravitreal therapy does not control systemic infection, a close follow up is required to detect extraocular CMV involvement.

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