

CYTOMEGALOVIRUS RETINITIS IN A RENAL TRANSPLANT PATIENT WITH RECURRENT OPPORTUNIST INFECTION: TREATMENT WITH FOSCARNET AND CMV HYPERIMMUNE GLOBULIN

D R J Singer, T J Fallon, W E Schulenburg, A S Boyd, J Cohen, G Williams

Hammersmith Hospital, London, United Kingdom

Summary

A white heterosexual man with renal failure from focal segmental glomerulosclerosis developed recurrent opportunist infection following renal transplantation. Antibody to HTLV III was also detected. After primary cytomegalovirus infection, unilateral, necrotizing retinitis occurred, which, untreated, progressed to blindness. There was no response of recurrent CMV retinitis to CMV hyperimmune globulin; however, 12 days after the introduction of foscarnet, the retinal lesions began to resolve, acuity improved and viral excretion abated. Relapse of the retinitis 12 weeks later resolved on foscarnet alone. Further trials are indicated of foscarnet in CMV retinitis, which untreated runs an aggressive course in severely immunocompromised patients.

Introduction

Cytomegalovirus (CMV) retinitis typically runs an aggressive course, with disappointing response to treatment in patients severely immunosuppressed, in particular those with the acquired immune deficiency syndrome [1,2]. We report a renal transplant patient who had antibody to human T-cell lymphotropic virus III [3], in whom CMV retinitis developed, and describe his response to treatment with CMV hyperimmune globulin and with the virostatic agent, foscarnet.

Case report

At 54, a white Caucasian musician working in California was found to have accelerated hypertension and renal impairment, with focal segmental glomerulosclerosis on renal biopsy. From October, 1981, he required chronic hospital haemodialysis, and received three separate blood transfusions. The patient's treatment was continued in England from June, 1982; following cadaver renal

transplantation, in January, 1983, he rapidly recovered normal renal function on our standard immunosuppressive regime of corticosteroid and azathioprine. There ensued recurrent opportunist infection associated with profound lymphopenia, $0.13 \times 10^9/L$ (helper subset, $0.07 \times 10^9/L$, NR 1.0–1.6): oral and oesophageal candidiasis, recurrent *Pneumocystis carinii* pneumonia, primary and reactivation CMV infection, oral and genital Herpes simplex virus infection. In September, 1983, eight weeks after primary CMV IgG seroconversion, the patient complained of blurred vision, initially thought to be due to steroid-induced cataract; examination of the retina was reported to be normal.

In November, 1983, visual acuity was 6/7.5 (right) and 6/18 (left); bilateral posterior subcapsular cataracts were noted. Examination of the right fundus was normal, but the left showed active retinitis with scattered haemorrhages, cotton-wool spots and necrosis. In view of the recent CMV IgG seroconversion and the retinal appearance, a presumptive diagnosis of CMV retinitis was made. Over the following five months, the lesions progressed to complete retinal atrophy, visual acuity falling to counting fingers (CF) and an afferent pupillary defect developing. The right fundus remained unaffected.

In July, 1984, the patient noted a sudden deterioration in vision in his right eye and developed diffuse mild epigastric pain. His drug treatment was prednisolone 10mg/day, azathioprine 50mg/day, co-trimoxazole (1 tablet/day). He was normotensive, had mild epigastric tenderness and multiple sacral herpeticiform

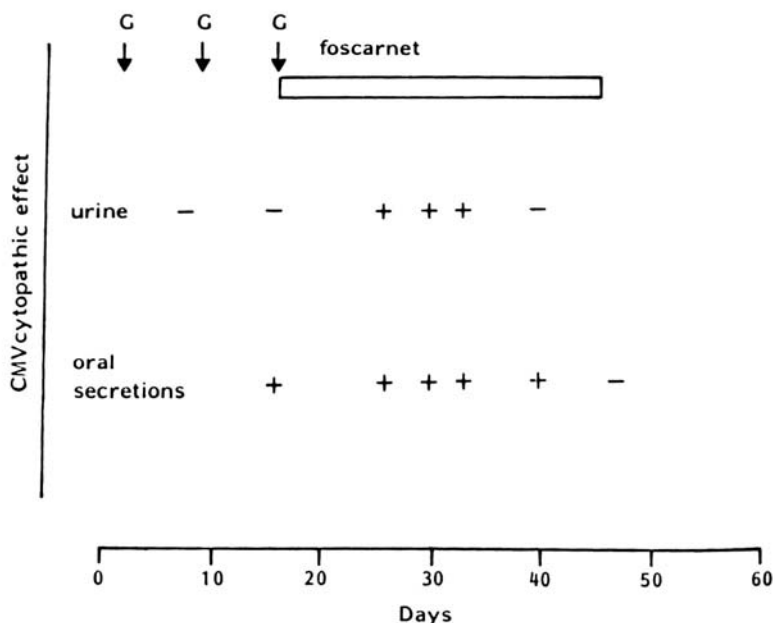


Figure 1. Results of culture for cytomegalovirus from urine and oral secretions

lesions. Relevant investigations were: normal renal function, alkaline phosphatase 173IU/L (NR <130IU/L), aspartate aminotransferase 44IU/L (NR <35IU/L), amylase 410IU/L (NR <300IU/L), haemoglobin 12.7g/dl, WBC 8.2×10^9 /L, lymphocyte count 0.32×10^9 /L, platelets 320×10^9 /L. Chest X-ray was normal; ultrasonography demonstrated mild common bile duct (CBD) dilatation without calculi. Sacral vesicle culture yielded Herpes simplex virus. Culture of oral secretions grew CMV; urine initially negative, then also grew CMV (Figure 1). Ophthalmic examination (8.8.84) showed visual acuity 6/18 (right), CF (left), left afferent pupillary defect, bilateral cataracts and an atrophic left retina. The right eye showed moderate vitreous activity, widespread retinal haemorrhages, a few cotton-wool spots and large areas of retinal necrosis temporal and infero-temporal to the macula.

Azathioprine was stopped, immunosuppression continuing as low dose prednisolone alone. CMV hyperimmune globulin 6g intravenously was given on three occasions (10.8.84, 17.8.84, 24.8.84). Ophthalmic examination (13.8.84, 17.8.84, 20.8.84, 23.8.84) revealed progressive deterioration with extension of the area of retinal necrosis, continued vitreous activity and development of anterior chamber activity. Visual acuity was static at 6/18.

On 24.8.84, an intravenous bolus of foscarnet (Astra) was administered (600mg over 10 minutes), followed by continuous intravenous infusion (0.078mg/kg/min for 4 weeks). Progression of the retinitis continued until 6.9.84 when gradual improvement began: visual acuity increased to 6/12, anterior chamber and vitreous activity reduced, the number and size of retinal haemorrhages decreased and retinal oedema and cotton-wool spots resolved (Figures 2a and 2b). In addition, the epigastric pain settled and liver enzymes and the diameter of the CBD returned to normal. By 24 days, CMV viraemia had ceased; oral secretions revealed no further growth by 32 days. The mean plasma foscarnet concentration achieved during the continuous infusion was $65.6 \pm 10.2 \mu\text{g/ml}$ (95% confidence limits). There were two abnormalities attributable to the foscarnet: thrombophlebitis, necessitating conversion from a peripheral to a central venous line and transient hypercalcaemia at the outset and end of treatment (Figure 3).

At this stage the patient was found to have had antibody to HTLV III, present since arrival in England, seven months before transplantation [3]. He denied any homosexual encounters or intravenous drug abuse; however, he had received the blood transfusions noted above.

Three months after finishing treatment, examination showed that the retinitis had reactivated, with fresh haemorrhages, progressive necrosis and decline in visual acuity to 6/24. A further course of foscarnet (protocol as above, infusion for two weeks) was given, without CMV hyperimmune globulin. Follow-up examinations revealed the onset of resolution 10 days after the start of therapy. Sustained remission was noted at follow-up one month after stopping foscarnet. The patient died in February, 1985; post-mortem examination was not performed.

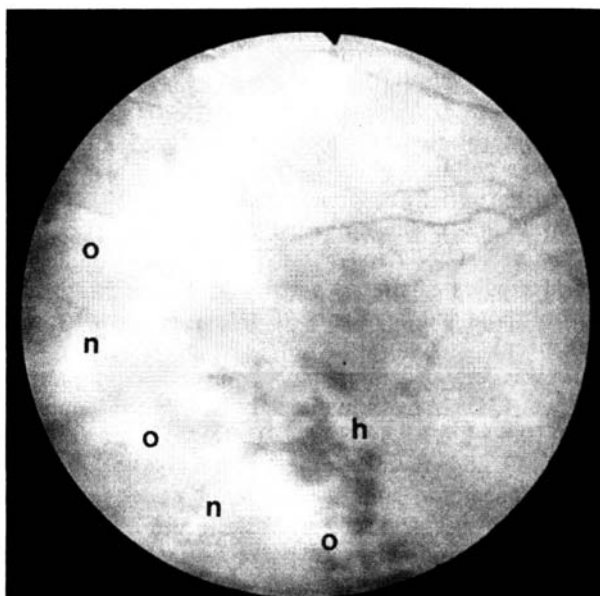


Figure 2a. Day 13: maximal retinal necrosis (n) with oedema (o) and multiple haemorrhages (h)

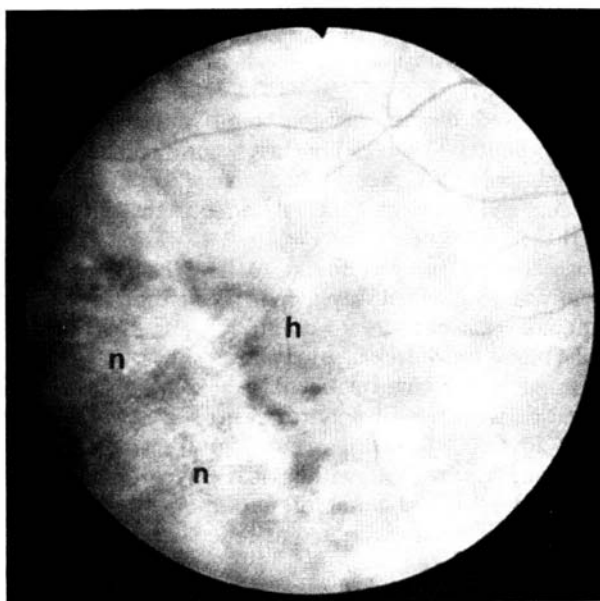


Figure 2b. Day 28: resolution of oedema; arrest of progression of necrotic area (n) and healing of haemorrhages (h)

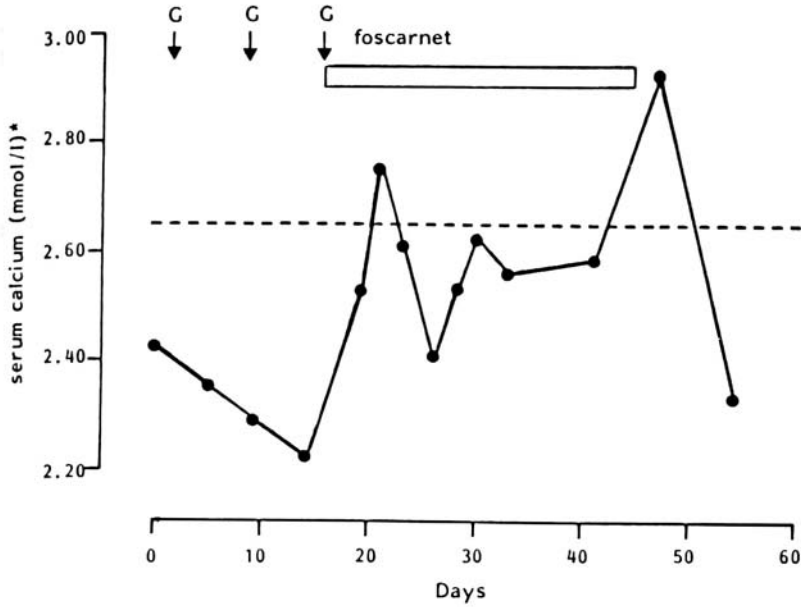


Figure 3. Serum calcium (corrected for albumin) during treatment with CMV hyperimmune globulin (G) and foscarnet

Discussion

In a study of patients immunosuppressed for transplantation or because of lymphoma, CMV retinitis was noted to resolve spontaneously, on withdrawal of immunosuppression or following treatment with adenosine arabinoside [1]. This has not, to our knowledge, been reported in AIDS patients. Indeed, Palestine et al [4] suggest that CMV retinitis always progresses in these cases, unaffected by acyclovir, interferon, interleukin-2 or vidaribine.

Our patients recovered in association with three treatment manoeuvres: reducing immunosuppression, adding CMV IgG and then foscarnet. This recovery was despite a strong pathogenetic risk factor for AIDS in the form of antibody to HTLV III and a background of recurrent, opportunist infection. Of particular note was the rapid response to treatment, in contrast to the minimum time to recovery of four weeks in the drug/lymphoma immunosuppressed group [1]. Also in support of a response to treatment rather than spontaneous recovery, was the rapid resolution of viral excretion. Immunosuppressed patients typically excrete virus for prolonged periods.

Foscarnet is a virostatic pyrophosphate analogue which specifically inhibits herpes DNA virus polymerase [5]; the early maturation of CMV is therefore inhibited. Clinical use of foscarnet has been confined to topical treatment for herpes simplex and to open trials in renal and bone marrow transplant patients with evidence of severe CMV infection [6].

The reasons for the initial remission are potentially multifactorial: three treatment actions were performed (see above). Nevertheless, recovery from the relapse, again rapid, and associated with a second course of foscarnet and no other change in therapy, strongly favours this virostatic agent as an effective treatment for CMV retinitis.

There have recently been anecdotal reports of recovery of CMV retinitis on treatment with another virostatic agent, DHPG. As with our patient, relapse following successful treatment has been a feature, a predictable outcome of virostatic treatment for an intracellular chronic infection such as CMV.

This is the first report of response to treatment of CMV retinitis attributable to foscarnet, in an AIDS patient. Our experience provides support for a further study of foscarnet in the treatment of CMV infection in immuno-compromised patients.

Acknowledgments

We thank Dr Cheinsong-Popov for performing HTLV III serology. Plasma foscarnet levels were measured by the Astra Clinical Research Unit. JC is supported by the Wellcome Trust.

References

- 1 Pollard RB, Egbert PR, Gallagher JG, Merigan TC. *Ann Int Med* 1980; 93: 655
- 2 Holland GN, Pepose JS, Pettit TH et al. *Ophthalmol* 1983; 90: 859
- 3 Oliveira D, Winearls CG, Cohen J et al. *Transplantation*: in press
- 4 Palestine AG, Rodrigues MM, Macher AM et al. *Ophthalmol* 1984; 91: 1092
- 5 Helgstrand E, Eriksson B, Johansson NG et al. *Science* 1978; 201: 819
- 6 Apperley JF, Marcus RE, Goldman JM et al. *Lancet* 1985; i: 1151