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Case Report

Simultaneous Treatment of Cytomegalovirus and Varicella Zoster Infections in a Renal Transplant Recipient With Ganciclovir: Use of Viral Load to Monitor Response to Treatment

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Disseminated zoster occurring simultaneously with cytomegalovirus (CMV) disease in a renal transplant recipient is potentially life threatening. We describe the use of intravenous ganciclovir to treat both infections. The efficacy of treatment was assessed clinically and by the measurement of CMV viral load using the hybrid capture (Murex version 2) and varicella zoster (VZV) viral load using an in-house assay. Results from this case suggest that clinical resolution in severe viral infections such as described below may be related to early control of viraemia. ***J. Med. Virol. 59:412–414, 1999.***

INTRODUCTION

Reactivation of varicella zoster virus to cause shingles occurs in 20–40% of patients undergoing solid and bone marrow transplantation [Miller et al., 1993]. Untreated, the rash can spread to involve many dermatomes resulting in widespread haemorrhagic lesions of the skin, lungs, and other organs and in some cases death. The routine use of prophylactic aciclovir (ACV) or ganciclovir (GCV) to prevent CMV disease in the most immunocompromised transplant patient groups, e.g., allogeneic bone marrow transplant recipients, may have reduced the mortality from zoster [Masaoka et al., 1993] but does not appear to have affected the incidence [Han et al., 1994]. Prophylactic regimens are used less widely in renal transplant recipients who are less severely immunocompromised. In these patients prompt treatment with aciclovir or its analogues is required to contain the spread of the virus and prevent the development of disseminated zoster. The case is described of a 44-year-old Ghanaian man who, 8 weeks following renal transplantation, developed simultaneously CMV disease and disseminated zoster. In this case monotherapy with GCV was used to treat both infections and the patient's response to treatment monitored by measurement of CMV and VZV viral loads.

CASE REPORT

A 42-year-old CMV seropositive Ghanaian man in end stage renal failure received a cadaveric renal transplant from a CMV seronegative donor. Immunosuppression consisted of mycophenolate 2 g/day, cyclosporin A 300 mg/day and prednisolone 12.5 mg/day. Forty-five days following transplantation cytomegalovirus was detected in the blood by shell vial analysis (Fig. 1). Samples were then taken weekly and tested for CMV viral load (Murex DNA capture assay version 2). Two weeks later, the patient developed symptoms of fatigue, fever, abdominal pain, and a vesicular rash over the face, trunk, and arms. In addition he became leukopoenic and his CMV viral load increased to over 10^5 copies/ml. A serum sample taken at the time of transplantation was positive for VZV IgG, whilst immunofluorescence of vesicle scrapings taken at onset of the rash was positive for varicella zoster virus. A diagnosis of dual CMV disease and disseminated zoster was made and a 10 day course of intravenous ganciclovir (GCV) 170 mg twice daily was started. On this regimen the patient improved clinically, his rash healed and he was discharged home 2 weeks later.

CMV viral load in whole blood (Murex hybrid capture version 2) and VZV lymphoctye viral load were measured. The latter was determined using an "in-house"

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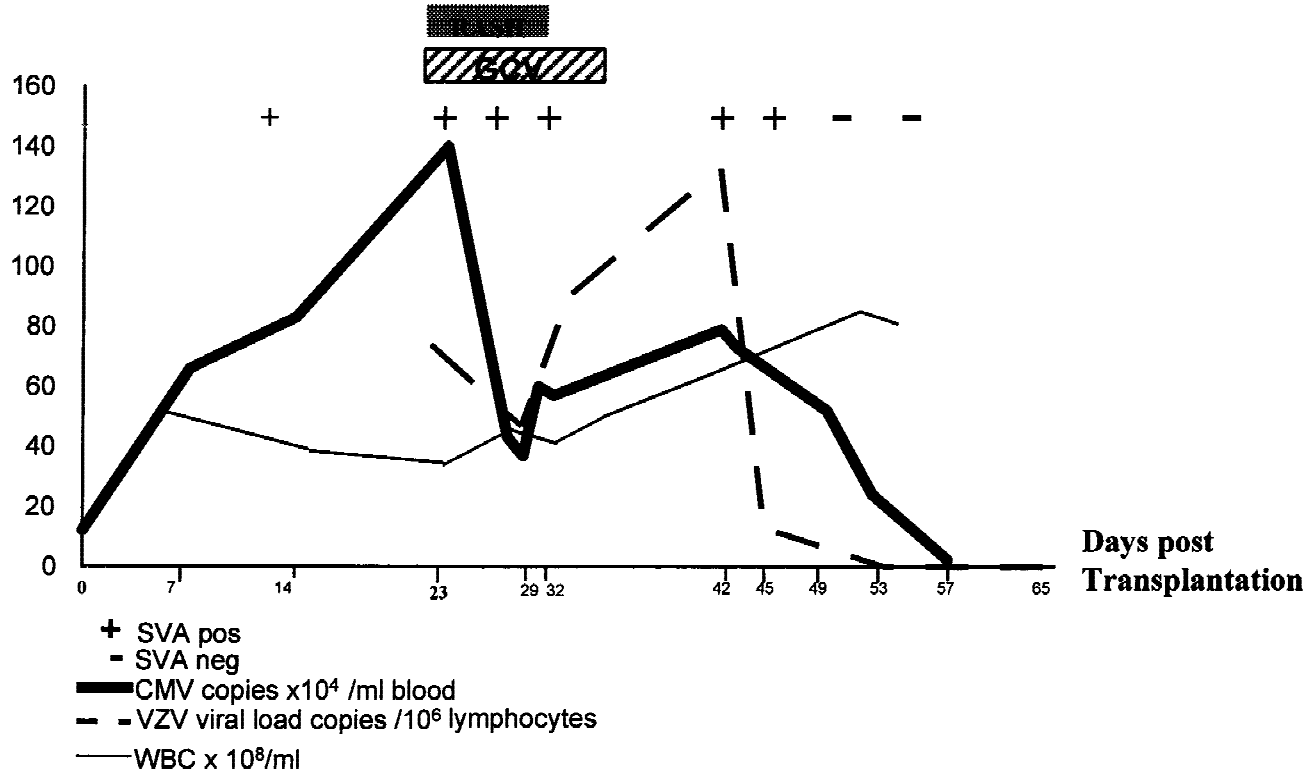

Fig. 1. Response of VZV and CMV viral loads to treatment with ganciclovir.

method involving TaqMan technology [Hawrami et al., 1998]. Briefly, lymphocytes were separated by Ficoll gradient, and the DNA extracted and amplified through 30 cycles using established conditions [Hawrami et al., 1998]. A probe labelled with a fluorescent dye and a quencher was incorporated into each reaction and fluorescence was measured using the LS-50B PCR Detection system. Each sample was repeated in triplicate. A high (>10,000), medium (1,000), and low (< 50) copy number control was included. Thirty cycles of amplification were used to ensure that the signal fell on the linear part of the curve and results were read off against a calibration curve [Hawrami et al., 1998]. The VZV copy number was adjusted for lymphocyte count and the results of VZV and CMV viral load plotted.

RESULTS

The CMV and VZV viral loads in relation to GCV treatment are shown in Figure 1. Both the CMV and VZV viral loads fell initially increasing towards the end of the course of GCV. The nadir of the fall on day 6 was coincident with the patient becoming apyrexial and the crusting over of the shingles rash. The subsequent rise in VZV and CMV viral loads mirrored a rise in the patient's white cell and lymphocyte counts. In view of the rapid clinical improvement, a decision was made to stop antiviral therapy after 12 days and to monitor the patient virologically and clinically. Despite a rise in both the CMV and VZV viral loads following the cessation of therapy, the patient remained clinically well and antivirals were not restarted.

DISCUSSION

Dual infection with disseminated varicella-zoster and CMV in a transplant recipient is rare and potentially life threatening. Ganciclovir is the preferred treatment for CMV in renal transplant patients. The only alternative, foscarnet is nephrotoxic. Although ganciclovir is not the first line of treatment for VZV-related disease, the virus is sensitive to the drug in in vitro experiments. Ganciclovir has also been used successfully to treat VZV meningoencephalitis [Poscher et al., 1994] and in combination with foscarnet, progressive outer retinal necrosis, a condition that occurs in patients with AIDS and which can be caused by VZV [Moorthy et al., 1997]. Successful treatment with ganciclovir and foscarnet, of VZV-related progressive outer retinal necrosis and CMV retinitis occurring simultaneously in patients with AIDS has also been described. Since combination ganciclovir and foscarnet therapy was not an option in this patient he was commenced on GCV alone and both the CMV and VZV viral loads were monitored to ensure an adequate response to therapy.

CMV viraemia is known to result in increases in peripheral blood mononuclear (PBMC) viral load with spill over into the plasma allowing detection of viraemia. By contrast, VZV is overwhelmingly lymphocyte associated and viral levels in acute zoster occurring in

immunocompetent patients are, by and large, undetectable [Mainka et al., 1998]. In patients with chickenpox and immunosuppressed patients with shingles, lymphocyte associated viraemia is detectable [Hawrami et al., 1998], [Mainka et al., 1998] but to our knowledge this is the first time such measurements have been used for the monitoring of response to therapy. The TaqMan assay used to measure the VZV load was developed in our laboratory and has the advantage of being a single tube PCR assay which avoids the risk of contamination and reduces the time for manipulation [Hawrami et al., 1998]. The assay in this case was calibrated to detect between 4 and over 4×10^9 copies of virus/reaction [Hawrami et al., 1998].

After the start of treatment the patient responded clinically to ganciclovir (Fig. 1) with return of his temperature to normal within 3 days and complete healing of the rash within 6 days. The clinical improvement coincided with an immediate decline in CMV and VZV viral loads, although both rebounded upwards towards the end of therapy and continued to rise after treatment had been stopped. The explanation for these observations is not clear especially as the increases in viral loads began before the cessation of ganciclovir treatment. The initial drop in viral loads may represent drug-related clearance of the virus from plasma (CMV) and PBMCs (VZV and CMV). Since CMV is marrow suppressive, partial treatment of the infection may well have allowed some bone marrow recovery, as evidenced by the rise in PBMC counts following the start of therapy. Infection of these PBMCs may then have resulted in an apparent rise in CMV viral load. Similarly, ongoing replication of VZV in the ganglia infecting the increased numbers of lymphocytes trafficking through might explain the increase in VZV viral load after the start of treatment. In both VZV and CMV, the control of viraemia by the patient' s own recovering cellular immunity is likely to account for the eventual reduction in viral loads. In neither case did viral replication beyond the period of ganciclovir treatment appear to be detrimental clinically, perhaps because of the protective effect of prior immunity. Finally, the shapes of the curves may reflect the turnover of infected lymphocytes with an apparent delay, particularly in VZV viral clearance, reflecting its persistence for the lifespan of the lymphocytes infected.

At therapeutic blood levels, VZV is ten times more sensitive to aciclovir than to ganciclovir [Faulds et al., 1990]. Had the patient received aciclovir, it is possible that the VZV viral load would have fallen more rapidly. Notwithstanding, many studies have shown that early treatment of both chickenpox and shingles correlates with a better outcome, suggesting that viral events occurring in the first few days of infection are crucial. The initial fall in VZV and CMV viral loads immediately after the commencement of ganciclovir may therefore have been a more important predictor of the good clinical outcome than events occurring later in the course of treatment. This hypothesis remains to be tested.

REFERENCES

Faulds D, Heel RC. 1990. Ganciclovir. A review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. Drugs 39:597–638.

Han CS, Miller W, Haake R, Weisdorf D. 1994. Varicella zoster infection after bone marrow transplantation: incidence, risk factors and complications. Bone Marrow Transplant 13:277–283.

Hawrami K and Breuer J. 1999 Development of a flurogenic polymerase chain reaction assay (TaqMan) for the detection and quantitation of varicella zoster virus. J Virol Methods 79:33–40.

Mainka C, Fub B, Geiger H, Hofelmayr H, Wolff MH. 1998. Characterization of viraemia at different stages of varicella zoster virus infection. J Med Virol 56:91–98.

Masaoka T, Hiraoka A, Teshima H, Tominaga N. 1993. Varicella-zoster virus infection in immunocompromised patients. J Med Virol Suppl 1:82–84.

Miller E, Marshall R, Vurdien J. 1993. Epidemiology, outcome and control of varicella-zoster infection. Rev Med Microbiol 4:222–230.

Moorthy RS, Weinberg DV, Teich SA, Berger BB, Minturn JT, Kumar S, Rao NA, Fowell SM, Loose IA, Jampol LM. 1997. Management of varicella zoster virus retinitis in AIDS. Br J Ophthalmol 81: 189–194.

Poscher ME. 1994. Successful treatment of varicella zoster virus meningoencephalitis in patients with AIDS: report of four cases and review. AIDS 8:1115–1117.