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Effect of ganciclovir prophylaxis on cytomegalovirus-enhanced allograft arteriosclerosis

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Abstract Clinical and experimental studies have established the accelerating role of cytomegalovirus (CMV) infection on cardiac allograft arteriosclerosis, i.e. chronic rejection. In this study, we investigated the effect of ganciclovir prophylaxis on the development of CMV-enhanced allograft arteriosclerosis. Rat aortic allografts were done from DA donors to WF recipients and either infected with 10^5 plaque-forming units of rat CMV (RCMV) 1 day after transplantation or left uninfected. RCMV-infected allografts received ganciclovir at an initial dose of 20 mg/kg and a maintenance dose of 10 mg/kg twice a day for 14 days. Grafts were removed at 7, 14 days, and 1 and 3 months after transplantation and processed for morphometry and autoradiography. The results of this study demonstrated that ganciclovir prophylaxis significantly delays and reduces RCMV-enhanced allograft arteriosclerosis in the rat.

Key words CMV · Chronic rejection · Heart transplantation

Introduction

Allograft arteriosclerosis, i.e. chronic rejection, is the main cause of death among heart allograft recipients in the long run. There is strong clinical evidence indicating the role of cytomegalovirus (CMV) infection in the pathogenesis of cardiac allograft arteriosclerosis [1]. We demonstrated earlier that rat CMV (RCMV) infection enhances smooth muscle cell proliferation and intimal thickening of rat aortic allografts [2]. In this study, the effect of ganciclovir (DHPG) prophylaxis on RCMV-enhanced aortic allograft arteriosclerosis was investigated.

Materials and methods

Aortic allografts from DA (AG-B4, $RT1^a$) to WF (AG-B2, $RT1^v$) rat strains were applied, using a 3-cm-long segment of descending thoracic aorta as the transplant [3]. Total ischaemic time varied from 45 to 60 min, during which the graft was kept in an ice bath at +4 °C for 15 min. Allograft recipients were inoculated with 10^5 plaque-forming units of RCMV Maastricht strain 1 day after transplantation or left uninfected and used as controls.

DHPG infusion substance was dissolved in 100 ml 0.9% natrium chloride at a final concentration of 5 mg/ml and administrated i.p. from the day of transplantation at an initial dose of 20 mg/kg and a maintenance dose of 10 mg/kg twice a day for a period of 14 days.

Biopsies from the liver, spleen and salivary glands were taken for plaque assays to demonstrate the presence of infectious virus. The grafts were removed at 7 and 14 days, and 1, 3 and 6 months after transplantation and processed for histology and autoradiography. The histological changes in the aortic cross-section were quantitated according to standard morphometric principles and expressed in

point score units (PSU). To demonstrate cell proliferation, all rats received 300 μCi of [methyl-^{3}H]thymidine (Amersham International, UK) by i.v. injection 3 h before graft removal. Data are expressed as mean ± SEM or, in the case of non-grafted aortas, as mean ± SD. The Mann-whitney U-test was used to evaluate the significance. *P* values less than 0.05 were regarded as statistically significant.

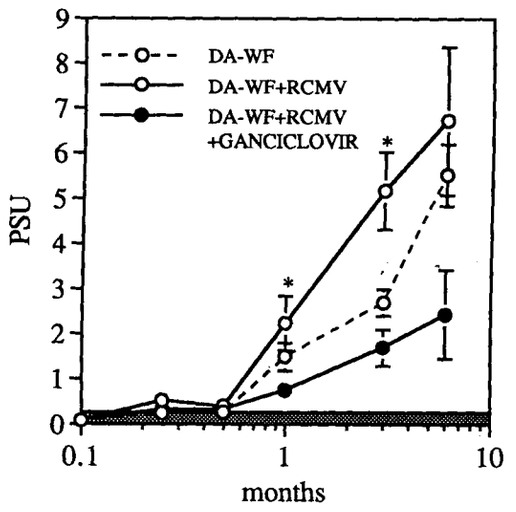

Fig. 1 The effect of ganciclovir prophylaxis on RCMV-enhanced intimal thickening. *Shaded area* indicates intimal thickness in non-transplanted aortas (± SD) ($P < 0.05$ when RCMV-infected treated allografts were compared with RCMV-infected non-treated allografts)

Results

In RCMV-infected non-treated rats, the liver/spleen were usually positive on day 7, but not thereafter, whereas the salivary glands did not appear positive until 1 month, remaining positive up to 3 months after transplantation. Under DHPG prophylaxis, no infectious RCMV could be demonstrated by plaque assays from the organ biopsies of RCMV-infected allograft recipients.

In the adventitia of uninfected control allografts, the inflammatory response peaked at 11.5 ± 1.2 PSU 1 month after transplantation, but declined thereafter. In RCMV-infected allografts, the inflammatory response took place earlier, with 11.6 ± 1.5 PSU on day 7 and 15.7 ± 1.5 PSU at 1 month, also declining thereafter. DHPG prophylaxis significantly reduced the number of inflammatory cells in the adventitia to 6.1 ± 0.2 PSU on day 7 ($P < 0.01$) and to 11.4 ± 1.3 PSU at 1 month ($P < 0.05$). The arteriosclerotic alterations in the intima (Fig. 1) and proliferation of smooth muscle cells were both reduced by 50%–70% under DHPG prophylaxis.

Discussion

The observations from the present study in the rat are very promising and suggest that DHPG might be useful in the clinical prophylaxis of CMV infection in heart transplant recipients, not only because it decreases morbidity in acute infection, but also as it inhibits accelerated allograft arteriosclerosis even below the level of uninfected control allografts.

References

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