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Intravenous ganciclovir prophylaxis for cytomegalovirus in heart, heart-lung, and lung transplant recipients

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Abstract Cytomegalovirus (CMV) disease has had a significant clinical impact on the heart, heart-lung and lung transplant recipients in our centre. CMV disease has been so severe with CMV antibody-negative heart-lung transplant patients receiving organs from CMV antibody-positive donors (CMV-mismatched patients) that in 1986 we adopted the policy of not transplanting CMV-positive organs into CMV-negative heart-lung or lung recipients. In December 1992, we instituted a policy of providing intravenous ganciclovir (5 mg/kg twice a day for 28 days) during the immediate post-operative period for CMV-mismatched heart recipients and CMV antibody-positive heart-lung and lung patients, who have been the patients at greatest risk of severe CMV disease in our centre. A placebo group was not employed because of ethical considerations, ganciclovir having been shown to be effective for the treatment of CMV infections among transplant patients. Compared with a historical control group of patients receiving no prophylaxis, prophylactic ganciclovir reduced the incidence of CMV infection (39% vs 91%, $P = 0.0006$) and CMV disease (17% vs 74%, $P = 0.0004$) among CMV antibody-positive heart-lung recipients. Prophylactic ganciclovir did not significantly reduce the incidence of CMV infection or disease among heart or isolated lung recipients. Ganciclovir was well tolerated, with few adverse reactions. In the case of heart-lung transplant patients, one month of intravenous prophylactic ganciclovir significantly reduced the incidence of both CMV infection and disease when compared with patients who received no prophylaxis. With the lung transplant and heart transplant patients, there were no significant differences between the prophylaxis and nonprophylaxis groups, although there was a consistent trend towards less infection and disease in the prophylaxis groups.

Key words Ganciclovir · Cytomegalovirus · Heart transplantation · Heart-lung transplantation · Lung transplantation · Prophylaxis

Introduction

Cytomegalovirus (CMV) infection is a significant cause of morbidity and mortality among heart, heart-lung and lung transplant recipients [10]. Eighty percent of heart transplant recipients who are mismatched for CMV (CMV antibody-positive donor, CMV antibody-negative recipient) acquire primary CMV infection, which may be severe or fatal [12]. CMV antibody-positive heart transplant recipients may experience CMV reactivation or reinfection, and although some may develop CMV disease, deaths attributable to CMV are rare [10].

CMV disease occurs more frequently with heart-lung and lung transplant recipients than with heart recipients. Fatal CMV disease may occur among CMV antibody-positive and CMV-mismatched patients [10]. CMV pneumonitis is particularly serious among lung transplant recipients, especially CMV-mismatched patients, because it affects the allograft directly.

At Papworth Hospital, because severe CMV disease and deaths occurred among CMV-mismatched heart-lung recipients, we instituted a policy of CMV-matching (i.e. not transplanting CMV antibody-positive donor organs into CMV antibody-negative recipients (January 1986). This was extended to lung transplant patients when this programme began.

In 1992 we instituted a policy of giving 28 days intravenous ganciclovir prophylaxis (10 mg/kg per day) to CMV-mismatched heart recipients and CMV antibody-positive heart-lung and lung recipients. At that time, Merigan et al. [7] had shown that intravenous ganciclovir given for one month after transplantation reduced the incidence of CMV infection and symptoms with CMV antibody-positive heart transplant recipients, but had no significant effect on CMV-mismatched patients.

In this report we compare the incidence of CMV infection and disease among patients receiving 28 days intravenous ganciclovir prophylaxis with a historical control group of patients who underwent transplantation during the period before prophylaxis was given. A placebo-controlled trial of intravenous ganciclovir was not regarded as ethical because there was already evidence from controlled trials that it was effective in reducing CMV infection and disease among transplant recipients. Therefore, the aim of this study was to compare CMV infection and disease rates in our two study groups.

Patients and methods

Inclusion criteria

All the heart transplant patients included in the study were CMV-negative patients who received organs from CMV-positive donors. All the heart-lung and lung patients were CMV-positive patients who received organs from either CMV-positive or -negative donors. Patients were excluded from the study if they died less than 40 days after transplantation. This study was approved by the Papworth Hospital ethics commitee.

Patients who were given prophylaxis received intravenous ganciclovir (5 mg/kg b.d.) for 28 days after transplantation.

Heart transplant patients

Prophylaxis goup

Fourteen CMV-mismatched heart transplant recipients (11 male, 3 female) aged 15 to 59 years (average age 40.7 years) were given intravenous ganciclovir.

Historical control group

Seventeen heart transplant recipients (12 male, 2 female) aged 21 to 56 years (average age 45.9 years).

Heart-lung transplant patients

Prophylaxis group

Twenty-three heart-lung transplant recipients (10 male, 13 female) aged 19 to 50 years (average age 36.3 years) were given intravenous ganciclovir.

Historical control group

Twenty-two heart-lung transplant recipients (15 male, 8 female) aged 21 to 59 years (average age 41.6 years).

Lung transplant patients

Prophylaxis group

Twenty-seven lung transplant recipients (13 male, 11 female) aged 45 to 68 years (average age 54.5 years) were given intravenous ganciclovir.

Historical control group

Seventeen lung transplant recipients (10 male, 8 female) aged 32 to 59 years (average age 48.8 years). Details of these patients are shown in Table 1.

Immunosuppression

In the heart-lung and lung transplant groups, immunosuppression consisted of induction with rabbit antithymocyte globulin (RATG 1 mg/kg for three days), azathioprine and methylprednisolone. Thereafter, cyclosporine-based triple therapy was introduced, maintaining cyclosporine levels between 300 and 500 μg/ml for the first two months and thereafter between 200 and 400 μg/ml. Azathioprine dosage was adjusted to maintain the white cell count in the range 4–6 $\times 10^9$/l, and prednisolone was given at 0.2 mg/kg per day.

Until the end of 1993, the immunosuppressive protocol for the heart transplant group was identical to that used for the heart-lung and lung transplant groups, except that the cyclosporine levels were maintained between 200 and 400 μg/ml for the first two months and thereafter between 150 and 300 μg/ml. In August 1993, in the heart transplant group, the induction protocol was changed to cyclosporine-based triple therapy and the routine use of RATG was stopped, except for patients with marked renal impairment. Following the induction period, the protocol remained unchanged.

CMV antibody status and diagnosis

The CMV antibody status of all heart, heart-lung and lung transplant recipients and donors was assessed by means of the CMV scan latex agglutination test (Becton Dickinson, Oxford, UK) [5],

Table 1 Patient details

Heart			Heart-lung			Lung		
	No prophylaxis	Prophylaxis		No prophylaxis	Prophylaxis		No prophylaxis	Prophylaxis
Number	17	14	Number	22	23	Number	17	27
Transplantation dates	14.07. 90 to 22.11. 92	11.12. 92 to 24.02. 95	Transplantation dates	10.04. 90 to 15.10. 92	04.11. 92 to 30.07. 95	Transplantation dates	27.08. 89 to 19.02. 93	16.01. 93 to 29.07. 95
Etiology: Ischaemic heart disease	9 (53%)	5 (36%)	Etiology: Bronchiectasis	6 (27%)	3 (13%)	Etiology: Bronchiectasis	1 (6%)	1 (4%)
Dilated cardiomyopathy	7 (41%)	7 (40%)	Eisenmenger's syndrome	4 (18%)	7 (30%)	Emphysema (inc. AAT)	10 (59%)	16 (59%)
Valvular heart disease	1 (6%)	1 (7%)	Emphysema (inc. AAT)	5 (23%)	1 (4%)	Cryptogenic fibrosing alveolitis	3 (18%)	4 (15%)
Congenital heart disease	0 (0%)	1 (7%)	Cystic fibrosis	4 (18%)	7 (30%)	Pulmonary fibrosis	2 (12%)	4 (15%)
			Primary coronary disease	2 (9%)	1 (4%)	Sarcoidosis	1 (6%)	–
			Primary pulmonary hypertension	1 (5%)	2 (9%)	Chronic lung disease	–	1 (4%)
			Cryptogenic fibrosing alveolitis	–	1 (4%)	Obliterative bronchiolitis	–	1 (4%)
			Sarcoidosis	–	1 (4%)			
Rejections/ patient	1.5	1.3	Rejections/ patient	2.0	1.3	Rejections/ patient	1.9	1.2
Azathioprine dose (mg) mean (SD)			Azathioprine dose (mg) mean (SD)			Azathioprine dose (mg) mean (SD)		
1 month	1.78 (0.42)	1.19 (0.62)	1 month	1.79 (0.55)	1.37 (0.57)	1 month	1.63 (0.81)	1.52 (0.52)
3 months	1.29 (0.67)	1.14 (0.47)	3 months	1.22 (0.78)	1.44 (0.38)	3 months	1.00 (0.63)	1.39 (0.61)
Cyclosporine dose (mg) mean (SD)			Cyclosporine dose (mg) mean (SD)			Cyclosporine dose (mg) mean (SD)		
1 month	6.02 (1.32)	6.06 (4.37)	1 month	16.87 (17.23)	10.63 (6.35)	1 month	11.48 (5.65)	8.52 (3.07)
3 months	5.40 (1.37)	5.56 (4.29)	3 months	14.31 (12.24)	10.61 (6.34)	3 months	10.03 (5.69)	5.98 (2.43)
Prednisolone dose (mg) mean (SD)			Prednisolone dose (mg) mean (SD)			Prednisolone dose (mg) mean (SD)		
1 month	0.192 (0.024)	0.195 (0.026)	1 month	0.246 (0.056)	0.259 (0.064)	1 month	0.255 (0.074)	0.241 (0.056)
3 months	0.197 (0.028)	0.189 (0.024)	3 months	0.234 (0.063)	0.243 (0.058)	3 months	0.221 (0.059)	0.221 (0.051)
Follow-up period	34 months (3–56 months)	32 months (3–47 months)		33 months (2–62 months)	30 months (2–46 months)		29 months (2–66 months)	28 months (3–44 months)

Table 2 Results of Papworth Hospital trial of 1 month i. v. ganciclovir for the prevention of CMV infection and disease in heart-lung and lung transplant recipients

	Prophylaxis group	Total	Number (%) with CMV infection	Number (%) with CMV disease	Average days on prophylaxis	Average days ganciclovir treatment
Heart-lung transplants	i. v. ganciclovir	23	9 (39)	4 (17)	28	4.1
	no ganciclovir	22	20 (91)	17 (74)	0	10.6
Lung transplants	i. v. ganciclovir	27	16 (59)	9 (33)	28	5.8
	no ganciclovir	17	14 (82)	9 (53)	0	14.1
Heart transplants	i. v. ganciclovir	14	9 (64)	4 (29)	25	5.9
	no ganciclovir	17	12 (71)	9 (53)	0	6.4

CMV complement fixation test (CFT) [2] or CMV IgG ELISA (Diamedix, Miami, Fla.).

Serum samples were taken from all transplant recipients immediately before transplantation, at weekly intervals during the postoperative period and then at each outpatient visit. These were tested for evidence of CMV infection by CFT, CMV IgG ELISA and/or CMV IgM ELISA [11].

Samples of urine and/or blood were taken at regular intervals for the diagnosis of CMV infection, tested in the detection of early antigen flourescent focus (DEAFF) test [6] and cultured in MRC-5 cells. When patients had respiratory symptoms, transbronchial lung biopsies or bronchoalveolar lavage specimens were tested in the DEAFF test and cultured for CMV in MRC-5 cells.

CMV infection

Patients were diagnosed as having CMV infection when there was a significant rise in CMV IgG and/or CMV IgM and/or when CMV was grown or the DEAFF test was positive.

CMV disease

CMV disease was classified into three groups: systemic disease, CMV pneumonitis and gastrointestinal disease. In systemic CMV disease, patients showed serological or culture-based evidence of CMV infection in association with symptoms of systemic disease characterised by fever and malaise or other nonlocalising features. Other typical features such as low white cell count were taken into consideration in these cases.

CMV pneumonitis and gastrointestinal disease were diagnosed when there was serological or culture-based evidence of CMV infection in association with appropriate clinical signs and/or histopathological evidence of disease in biopsy specimens.

Statistical analysis

The three transplant groups, heart, heart-lung and lung, are analysed separately. The incidence of CMV infection and disease is reported as the frequency and proportion in each group. Incidence in the prophylaxis and no prophylaxis groups are compared using Pearson's chi-squared test for contingency tables. For heart-lung and lung transplant patients, logistic regression on CMV infection and disease was completed to assess the effects of prophylaxis, donor CMV antibody status and the interaction between the two.

Results

Heart-lung recipients

Nine (39%) of the 23 CMV antibody-positive heart-lung transplant recipients who received ganciclovir prophylaxis acquired CMV infection, compared with 20 (91%) patients in the control group ($P = 0.0006$). Four (17%) of the 23 heart-lung transplant patients who received prophylaxis developed CMV disease, compared with 17 (74%) patients in the control group ($P = 0.0004$) (Table 2).

Lung recipients

Sixteen (59%) of 27 CMV antibody-positive lung transplant recipients who received ganciclovir prophylaxis acquired CMV infection, compared with 14 (82%) of 17 patients in the control group ($P = 0.06$). Nine (33%) of the 27 lung transplant patients who received prophylaxis developed CMV disease, compared with 9 (53%) of 17 patients in the control group ($P = 0.20$) (Table 2).

Heart Recipients

Nine (64%) of 14 CMV-mismatched heart transplant recipients who received ganciclovir prophylaxis acquired CMV infection, compared with 12 (71%) of 17 patients in the control group ($P = 0.96$). Four (29%) of the 14 heart transplant patients who received prophylaxis developed CMV disease, compared with 9 (53%) patients in the control group ($P = 0.58$) (Table 2).

Sixty-four percent of the heart transplant patients who had been given ganciclovir prophylaxis received i. v. ganciclovir treatment for suspected symptomatic CMV infection, compared with 67% of the patients in the control group. Patients who had been given prophylactic ganciclovir received 5.9 days ganciclovir treatment, compared with 6.4 days in the case of those who had not (Table 2). In all three groups, patients treated

Table 3 CMV donor and recipient status of lung and heart-lung transplant patients

Transplant group	Patient group	CMV status		Total	Number (%) with CMV infection	Number (%) with CMV disease
		Donor	Recipient			
Lung	Prophylaxis	–	+	17	10 (59)	5 (29)
		+	+	10	6 (60)	4 (40)
	No prophylaxis	–	+	3	1 (33)	0 (0)
		+	+	14	13 (93)	9 (64)
Heart-lung	Prophylaxis	–	+	8	2 (25)	0 (0)
		+	+	15	7 (47)	4 (27)
	No prophylaxis	–	+	4	3 (75)	3 (75)
		+	+	18	17 (94)	14 (78)

Table 4 Spectrum of disease

	Systemic disease	GIT disease	Pneumonitis
Heart-lung transplants			
Prophylaxis (23)	2	0	2
No prophylaxis (22)	4	1	12
Single and double lung transplants			
Prophylaxis (27)	1	2	7
No prophylaxis (17)	2	0	9
Heart transplants			
Prophylaxis (14)	4	0	1
No prophylaxis (17)	5	3	0

received 10–14 days intravenous ganciclovir (5 mg/kg b.d.). Twenty-six percent of the heart-lung transplant patients with symptomatic CMV infection were given i.v. ganciclovir treatment in the prophylaxis group, compared with 78% in the control group. Patients who had received prophylactic ganciclovir were given 4.1 days ganciclovir treatment, compared with 10.6 days in the case of those who had not (Table 2). Thirty-seven percent of lung transplant patients were given i.v. ganciclovir treatment in the prophylaxis group, compared with 78% in the control group. Patients who had received prophylactic ganciclovir were given 5.9 days ganciclovir treatment, compared with 14.1 days in the case of those who had not (Table 2).

The effect of donor CMV antibody status was analysed. Ten (37%) of the 27 lung transplant recipients in the prophylaxis group (for whom donor serum samples were available) had organs from CMV antibody-negative donors, compared with only 3 (18%) of 17 patients in the control group (Table 3). Eight (35%) of the 23 heart-lung transplant recipients in the prophylaxis group had organs from CMV antibody-negative donors, compared with 4 (18%) in the control group (Table 3).

In multivariate logistic regression, for lung transplant patients neither prophylaxis nor donor status had a significant effect on CMV infection when considered in isolation, but there was a significant interaction: that is, there was a significant excess of infection episodes among recipients of donor-positive organs who did not receive prophylaxis ($P = 0.04$). For heart-lung transplant patients, adjusting for donor status in a logistic regression, there was a significant decrease in CMV infection episodes after prophylaxis was introduced ($P = 0.004$). There were no significant associations between CMV disease and prophylaxis, donor CMV antibody status, or the interaction between the two, but the number of episodes may have been too few to detect small differences. There was no significant association found between CMV infection or disease and chronic rejection or death. The disease syndromes experienced by the patients with CMV infection in this study are shown in Table 4.

More patients were treated with ganciclovir than had proven CMV disease because some patients with symptoms compatible with CMV disease were treated and subsequently found not to have CMV disease. We found that ganciclovir was well tolerated by these patients. Only 1 of the 64 patients who received prophylactic ganciclovir had this treatment discontinued because of side effects.

Discussion

This study compared the efficacy of 28 days i.v. ganciclovir in preventing CMV infection and disease among heart, heart-lung and lung transplant recipients. A placebo group was not employed because it was regarded as unethical to do so, ganciclovir having been shown to be effective in reducing the severity of CMV disease among transplant recipients at the time ganciclovir prophylaxis was introduced [4, 7, 8].

Ganciclovir was chosen as the prophylactic antiviral agent because, although aciclovir had been shown to have an effect on reducing CMV disease among renal transplant patients [1], ganciclovir was thought likely to be more effective, being the treatment of choice for CMV infection among transplant recipients [3]. Merigan et al. [7] had shown that a two week course of i.v.

ganciclovir at treatment doses (5 mg/kg twice daily) with additional lower dose regimen for a further two weeks (6 mg/kg for 5 days a week) did not significantly reduce the impact of CMV disease among CMV-mismatched heart transplant recipients.

In our centre, CMV disease has been a significant problem in this group [10]. We therefore decided to give 28 days i.v. ganciclovir prophylaxis at treatment doses (5 mg/kg b.d.) to CMV-mismatched heart transplant recipients. The same regime was also given to CMV antibody-positive lung and heart-lung transplant recipients, who have also had a significant incidence of CMV disease [10].

With respect to the heart-lung transplant patients in this study, prophylactic ganciclovir significantly reduced the incidence of CMV infection and CMV disease. Significantly less i.v. ganciclovir was used to treat the groups of heart-lung and lung patients who received prophylactic ganciclovir than in those who did not. The CMV antibody status of the organ donor may have influenced the incidence and severity of CMV infection among these CMV antibody-positive heart-lung transplant recipients and was analysed in Table 3. There was no significant difference between the number of patients receiving organs from CMV antibody-positive donors in the two groups, but the numbers were too small to make valid comparisons. The percentages of patients with a CMV antibody-positive donor who experienced CMV infection and disease in the prophylaxis group were lower (47% and 27%) than in the comparable group who did not receive prophylaxis (94% and 78%) and in the group with CMV antibody-negative donors who did not receive prophylaxis (75% and 50%). Whilst in our series the CMV antibody status of heart-lung transplant recipient organ donors has not overall affected the incidence and severity of CMV disease [10], this factor needed to be evaluated since the two groups were not exactly matched for donor CMV antibody status.

Seventeen (63%) of the 27 lung transplant recipients who were given prophylactic ganciclovir received organs from a CMV-negative donor, compared with only 3 (18%) of the 17 lung transplant patients who received no prophylaxis. If the donor CMV status was contributory to CMV infection and disease in this group of patients, this would tend to invalidate these findings. However, 10 (59%) of 17 lung transplant patients who received organs from a CMV-negative donor and were given ganciclovir prophylaxis had CMV infection and 6 (35%) developed CMV disease, compared with 33% of similar patients who received no prophylaxis with CMV infection and 0% with CMV disease.

Although the numbers of patients in these groups are too small to draw definite conclusions, these data would suggest that ganciclovir prophylaxis appears to have a beneficial effect among recipients of CMV-positive lungs.

Ganciclovir prophylaxis did not significantly affect the incidence of CMV infection or disease among CMV-mismatched heart and CMV antibody-positive lung transplant recipients. However, there was a trend toward less CMV infection and disease in both prophylaxis groups.

It is unclear why lung transplant patients should respond less well to ganciclovir prophylaxis and have more severe CMV disease than heart-lung recipients, although the diseases which preceded transplantation are different and may be a factor (Table 1). It is probable that if a larger number of lung recipients had been given prophylaxis, a statistically significant benefit would have been found, since there was a beneficial trend in favour of ganciclovir prophylaxis in this group.

The results of this study are similar to those reported by Merigan et al. [7], but in this study we used a higher dose of ganciclovir during the second two weeks (5 mg/kg twice a day). Merigan et al. found that their prophylactic regimen did significantly reduce the incidence of CMV illness in CMV antibody-positive heart recipients (9% vs 46%, $P = < 0.001$). We have not employed prophylactic ganciclovir in this patient group because of a much lower incidence of CMV disease among our CMV antibody-positive patients.

There have been few other studies of ganciclovir prophylaxis with respect to solid organ transplant recipients and no published studies for heart-lung and lung recipients. Winston et al. [9] presented results of a randomised comparison of i.v. ganciclovir (6 mg/kg per day from postoperative day 1 to 30, then 6 mg/kg per day, five days a week, until postoperative day 100) and intravenous aciclovir (10 mg/kg three times a day from postoperative day 1 to date of discharge and then 800 mg oral aciclovir four times a day until postoperative day 100) in connection with liver transplant recipients. During the first 120 days after transplantation, CMV infection occurred in 38% of the aciclovir and 5% of the ganciclovir patients ($P = < 0.0001$). CMV disease developed in 10% of the aciclovir patients but in only 0.8% of the ganciclovir patients. Ganciclovir reduced the incidence of CMV infection among both CMV antibody-positive (37% vs 4%, $P = 0.001$) and -negative (42% vs 11% $P = 0.06$) patients.

In order to further reduce the impact of CMV infection and disease among solid organ transplant recipients, either higher doses of intravenous ganciclovir need to be given for longer, which is expensive and impractical, new antivirals used, or oral ganciclovir (and valaciclovir [pro-drug of aciclovir]) employed.

The benefit of ganciclovir over aciclovir shown in the study performed by Winston et al. [9] has persuaded us to embark on oral ganciclovir prophylaxis (3 g/day for 3 months) for mismatched heart, heart-lung and lung transplant recipients and CMV antibody-positive heart-lung and lung patients.

References

1. Balfour HH, Chace BA, Stapleton JT, Simmons RL, Fryd DS (1989) Randomized, placebo-controlled trial of oral aciclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. N Engl J Med 320: 1381–1387
2. Bradstreet CMP, Taylor CED (1962) Technique of complement fixation test applicable to the diagnosis of virus diseases. Mon Bull Minist Health Public Health Lab Serv 21: 96–104
3. Collaborative DHPG Treatment Study Group (1986) Treatment of serious cytomegalovirus infections with 9-(1,3-dihydroxy-2-propoxymethyl) guanine in patients with AIDS and other immunodeficiencies. N Engl J Med 314: 801–805
4. Goodrich JM, Mori M, Gleaves CA, DuMond C, Cays M, Ebeling DF, Buhles WC, DeAmond B, Meyers JD (1991) Early treatment with ganciclovir to prevent cytomegalovirus disease after allogeneic bone marrow transplantation. N Engl J Med 325: 1601–1607
5. Gray JJ, Alvey B, Smith DJ, Wreghitt TG (1987) Evaluation of a commercial latex agglutination test for detecting antibodies to cytomegalovirus in organ donors and transplant recipients. J Virol Methods 16: 13–19
6. Griffiths PD, Panjwani DD, Stirk PR, Ball MG, Ganczakowski H, Blacklock HA, Prentice HG (1984) Rapid diagnosis of cytomegalovirus infection in immunocompromised patients by detection of early antigen fluorescent foci. Lancet 2: 1242–1245
7. Merigan TC, Renlund DG, Keay S, Bristow MR, Starnes V, O'Connell JB, Resta S, Dunn D, Gamberg P, Ratkovek RM, Richenbacker RE, Millar RC, DuMond C, DeAmond B, Sullivan V, Chenery T, Buhles W, Stinson EB (1992) A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. N Engl J Med 326: 1182–1186
8. Schmidt GM, Horak DA, Niland JC, Duncan SR, Forman SJ, Zaia JA, and the City of Hope-Stanford-Syntex CMV study group (1991) A randomized, controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplants. N Engl J Med 324: 1005–1011
9. Winston DJ, Wirin D, Shaked A, Busuttil RW (1995) Randomised comparison of ganciclovir and high dose aciclovir for long-term cytomegalovirus prophylaxis in liver transplant recipients. Lancet 346: 69–74
10. Wreghitt TG (1993) Cytomegalovirus infections in heart and heart-lung transplant recipients. In: Rose ML, Yacoub MH (eds) Immunology of heart and lung transplantation. Edward Arnold, London, pp 232–242
11. Wreghitt TG, Gray JJ, Chandler C (1986) Prognostic value of cytomegalovirus IgM antibody in transplant recipients. Lancet 1: 1157–1158
12. Wreghitt TG, Hakim M, Gray JJ, Kucia S, Wallwork J, English TAH (1988) Cytomegalovirus infections in heart and heart and lung transplant recipients. J Clin Pathol 41: 660–667