Management of cytomegalovirus infection by weekly surveillance after renal transplant: analysis of cost, rejection and renal function

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Abstract

Background. Recently published guidelines recommend anti-viral prophylaxis as the best method of preventing cytomegalovirus (CMV) disease in the post-transplant period, but some authors have suggested that surveillance strategies may be as effective and less costly. The aim of the present study was to analyse the effectiveness and cost of a deferred treatment strategy using weekly CMV polymerase chain reaction (PCR) surveillance in high risk renal transplant recipients.

Methods. We used weekly surveillance for plasma CMV PCR positivity for the first 3 months in consecutive renal transplants between CMV seropositive donors and seronegative recipients, and analysed incidence of CMV infection, timing of infection, acute rejection and renal function at 1 year.

Results. There was evidence of CMV infection in 27/41 (65.9%) patients and of CMV disease in 20/41 (48.8%). Only 8/20 (40%) patients were PCR positive before disease onset. Patients were treated on the basis of clinical evidence of CMV disease (deferred strategy), but we used the data to compare the potential costs of a pre-emptive strategy (all patients PCR positive before the onset of clinical features of disease treated with intravenous ganciclovir) and prophylaxis (oral ganciclovir for 3 months in all patients). The deferred strategy cost £1159 per patient (excluding the cost of hospitalization) while a pre-emptive strategy would cost £1381 per patient. Prophylaxis costs £1500–£2213 per patient depending on published estimates of relative risk reduction. Mean estimated creatinine clearance at 1 year was 70.0 ml/min in patients who experienced no infection, 47.7 ml/min in patients who experienced infection but no disease, and 39.6 ml/min in patients who experienced CMV disease ($P < 0.001$). The incidence of acute rejection in these groups was 7.1, 14.3 and 35%, respectively ($P = 0.13$).

Conclusions. CMV surveillance strategies may cost slightly less but may have a deleterious effect on long-term outcome compared with prophylaxis.

Keywords: cost; cytomegalovirus; kidney transplant; polymerase chain reaction; prophylaxis; renal function

Introduction

Cytomegalovirus (CMV) disease continues to be a major clinical problem after solid organ transplantation, with significant morbidity and mortality. Transplants between donors who are seropositive for CMV and recipients who are seronegative (D+R−) have the highest incidence (60–80%) of subsequent CMV infection [1]. In D+/R− transplants, the median time to detection of CMV by serological tests (primary infection) is 5 weeks post-transplantation, and ~60% of patients who develop primary CMV infection also have evidence of CMV disease. CMV disease most commonly presents as a febrile illness, but can present with only blood abnormalities (leukopenia, thrombocytopenia, elevated liver enzymes) or with symptoms of solid organ involvement (pneumonia, retinitis, colitis). CMV infection can be identified by several methods, including antigen detection on leukocytes, polymerase chain reaction (PCR) to detect CMV DNA in plasma indicating active viral replication, viral culture, identification of IgM antibody and a rising IgG antibody titre. PCR methods are emerging as the most clinically useful diagnostic method, as high sensitivity and specificity are combined with rapid availability of results.

Several strategies have been proposed to reduce the incidence of CMV disease following renal
transplantation. Evidence from well-designed studies supports prophylaxis with ganciclovir or valacyclovir in the first 3 months after transplant in high risk (D+/R–) patients receiving anti-lymphocyte globulin, with a relative risk reduction of 0.21–0.84 [2,3]. The evidence that CMV prophylaxis is beneficial in kidney transplantation recipients not receiving anti-lymphocyte products is less convincing. Recently published best practice guidelines, however, recommend 3 months of anti-viral prophylaxis for all D+/R– renal transplants [1]. D+/R– transplants account for ~25% of renal transplants, and there are concerns that a prophylactic policy may expose patients to unnecessary side effects, may encourage CMV resistance and may be expensive [4,5]. Post-transplant surveillance to detect and treat CMV infection or disease may therefore be a more attractive strategy [5,6]. Two forms of post-transplant surveillance have been suggested: a deferred strategy and a pre-emptive strategy. A deferred strategy involves regular assessment and treatment of early disease, while in a pre-emptive strategy treatment is started as soon as tests of CMV infection become positive before the onset of clinical features of disease. Criticisms of deferred and pre-emptive strategies include the fact that patients are still allowed to develop infection and disease [7]. This may have long-term implications, since CMV infection is associated with increased risk of acute rejection (AR) [8], and AR is a strong risk factor for subsequent chronic allograft nephropathy [9].

In the present study, we have used weekly monitoring using real-time PCR to detect plasma CMV DNA in consecutive D+/R– renal transplants. We have examined the effectiveness of this strategy by measuring CMV IgG antibodies to determine the sensitivity of PCR monitoring and by measuring the time between the PCR test becoming positive and the onset of clinical features of disease. During the course of the study, patients were treated on the basis of evidence of CMV disease (deferred strategy), but we have used the data to compare the estimated potential costs of a deferred strategy, a pre-emptive strategy (where all patients who become PCR positive before the onset of clinical features of disease are treated with intravenous ganciclovir) and a prophylactic strategy (using oral ganciclovir for 3 months in all patients) in the same cohort of D+/R– patients. We have followed the patients for 1 year and compared incidence of AR and renal function at 1 year in patients who had no evidence of CMV infection, patients who developed infection only and patients who developed CMV disease.

**Patients and methods**

Serological CMV IgG status of the donor and recipient were determined at the time of transplantation for all renal transplants performed in our centre between January 1998 and December 2000. All CMV D+/R– transplants were identified and had plasma and serum samples taken weekly for 3 months following transplant. Real-time PCR was performed to identify active CMV replication. Once a positive result was obtained, a second plasma sample was requested for immediate confirmation and the serum sample was tested for CMV IgM and CMV IgG. Clinicians were alerted if PCR was positive. Medical review with recording of clinical progress and measurement of haematological parameters and liver biochemistry was performed at least weekly in the transplant clinic. At the end of the monitoring period, enzyme-linked immunosorbent assay (ELISA) for CMV IgG antibody was performed to determine if seroconversion had occurred. CMV infection was defined if PCR was positive or if CMV IgG seroconversion was demonstrated at the end of the monitoring period with or without the presence of clinical features of CMV disease. CMV disease was defined as laboratory evidence of CMV infection and at least one of the following: febrile illness with no other source of infection; features consistent with organ invasion such as pneumonitis, retinitis or colitis; transient thrombocytopenia, transient leukopenia or transient increase in aspartate aminotransferase (AST) and γ-glutamyl transferase (γ-GT) without another explanation. A transient abnormality of these blood tests was defined as a decrease or increase out of the laboratory reference range on two consecutive measures. Patients were treated for CMV disease at the discretion of the attending clinician with a 7–14 day course of intravenous ganciclovir and a temporary reduction in immunosuppression. Temporary reduction of immunosuppression usually involved stopping mycophenolate mofetil or azathioprine for 1–2 weeks and restarting at a lower dose. No post-treatment prophylaxis was given, and weekly surveillance stopped at this point. Clinicians maintained a high index of suspicion for recurrence of CMV disease, but no patients developed a second episode within 3 months of transplant. CMV IgG and clinical features were used to determine the sensitivity of PCR for the detection of CMV infection and CMV disease. The number of days between identification of PCR positivity and onset of disease was recorded to determine the utility of weekly screening to allow pre-emptive treatment.

Initial daily immunosuppression in the majority of patients was with prednisolone 20 mg, azathioprine 1 mg/kg and cyclosporin microemulsion (Neoral) 10 mg/kg body weight adjusted according to trough blood concentration to avoid toxic levels. High risk patients (previous failed transplant, panel-reactive antibody >50%, live unrelated donor transplant) were given mycophenolate mofetil 2 g daily instead of azathioprine. During the period August 1999–April 2000, initial daily immunosuppression was prednisolone 20 mg daily, tacrolimus 0.2 mg/kg body weight and mycophenolate mofetil 2 g as part of a multicentre randomized study [10]. One patient received prednisolone, mycophenolate mofetil (because of concomitant allopurinol therapy) and basiliximab (because of delayed graft function) with later introduction of tacrolimus when function was established. No patients received induction therapy with polyclonal antibody. AR was defined on clinical grounds and usually confirmed by biopsy. AR was treated with high dose corticosteroid, and steroid-resistant AR was treated with conversion from cyclosporin to tacrolimus. No patients received antibody therapy for AR.

Renal function at 1 year was assessed by estimated creatinine clearance (CrCl) using the formula of Cockcroft and Gault.

DNA initially was extracted manually, then more recently from 200 μl of citrated plasma using the QIAROBOT 9604...
Detection of CMV infection by weekly surveillance

There was evidence of primary CMV infection in 27/41 (65.9%) patients and of CMV disease in 20/41 (48.8%) in the first 3 months after transplant. CMV disease consisted of leukopenia or thrombocytopenia and biochemical hepatitis in six patients; febrile illness and leukopenia or thrombocytopenia in five patients; leukopenia or thrombocytopenia only in four patients; febrile illness, leukopenia or thrombocytopenia and biochemical hepatitis in three patients; febrile illness only in one patient; and biochemical hepatitis only in one patient. The last patient had concurrent acute cholecystitis and transplant urine leak, but his general condition and biochemical hepatitis improved after intravenous ganciclovir.

Twenty-seven of the 41 (65.9%) patients became PCR positive and IgM positive but developed no disease compared by one-way ANOVA. Differences in the proportion of patients experiencing AR in the same three groups were compared using a 3 × 2 χ² test.

Results

Forty-four patients were identified as CMV D+/R- transplants over the period January 1998–December 2000. This represents 20% of all the renal transplants carried out over that period. Two patients experienced graft loss for technical reasons within 1 week of transplant and are excluded. One patient did not attend for weekly PCR surveillance and is also excluded from the analysis. The data from the remaining 41 patients are summarized in Table 1. Three patients received a transplant from a living donor, and the remaining 38 were cadaveric transplants. Twenty-eight recipients were male, and the mean recipient age was 35.7 years.

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Twenty-seven of the 41 (65.9%) patients became PCR positive, and 24 of these 27 patients also became CMV IgM positive. All patients who developed features of CMV disease were also PCR positive at some point in the first 3 months. Seven patients became PCR positive and IgM positive but developed no

Cost analysis

The estimated cost of using weekly PCR surveillance in a deferred strategy or a pre-emptive strategy was compared with the cost of 3 months of oral ganciclovir prophylaxis in the same group of patients. In the deferred strategy, the assumption was made that all patients who developed evidence of CMV disease would receive 14 days of intravenous ganciclovir 250 mg twice daily. For the pre-emptive strategy, drug costs were based on the assumption that all patients who became CMV PCR positive or developed features of the disease (whichever occurred earlier) would receive 14 days of intravenous ganciclovir 250 mg twice daily. In the prophylactic strategy, the calculation was based on all patients receiving oral ganciclovir 1500 mg daily for 12 weeks. The drug doses were selected as the dose required in a patient with typical body mass and typical level of renal function. The costs for the deferred strategy and the pre-emptive strategy also included the cost of weekly PCR testing for 12 weeks in all D+/R- patients and the cost of intravenous ganciclovir administered as an out-patient. Since this study was performed, an out-patient home intravenous therapy programme has been established in our centre. None of the patients required hospital admission for severe CMV disease alone and so the cost of drug administration for the deferred and pre-emptive strategies in this analysis has been based on the estimated cost of 2 weeks of ganciclovir administered in the out-patient home intravenous therapy programme. Costs are correct for 2001.

Statistics

Differences in CrCl at 1 year between patients who experienced CMV disease, patients who experienced infection but no disease and patients who experienced no infection were compared by one-way ANOVA. Differences in the proportion of patients experiencing AR in the same three groups were compared using a 3 × 2 χ² test.

Patients

There were 2000 patients who received a transplant from a living donor and the remaining 202 patients were cadaveraic transplants. Twenty-eight recipients were male, and the mean recipient age was 35.7 years.

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clinical features of CMV disease. Three patients who developed CMV disease and were PCR positive remained IgM negative during the study period. Sensitivity for detection of CMV infection by PCR was 100%, i.e. all patients who were later shown to have seroconverted for IgG antibody became PCR positive during the study period. The specificity of PCR for detection of infection in this study is 100% as all patients who were PCR positive were later shown to have seroconverted for IgG antibody. The specificity of PCR for CMV disease was 100%, with specificity of 66.7%, reflecting the fact that not all patients who have evidence of infection will develop disease. The positive predictive value of PCR for CMV disease was 74.1%. The negative predictive value of PCR was 100% for both CMV infection and CMV disease.

The positive predictive value is only of clinical use if the PCR becomes positive before the onset of disease, and so the difference between time to PCR positivity and onset of clinical disease was examined in the 20 patients who developed CMV disease (Figure 1). From Figure 1, it can be seen that only 8/20 (40%) patients who developed disease were PCR positive before the onset of disease. Four patients (20%) became PCR positive on the same day that clinical features of disease developed. The median time between DNA detection and disease onset was 0 days. The longest delay between PCR becoming positive and subsequent development of disease was 16 days. The longest delay between onset of features of disease and subsequent development of PCR positivity was 15 days. The first presentation of CMV disease in two of the three patients who had a delay of >7 days between disease onset and subsequent PCR positivity was a febrile illness with thrombocytopenia, and the third patient presented with elevated AST and γ-GT. Patients who developed CMV disease were less likely to have received prednisolone, azathioprine and cyclosporin as primary immunosuppression than patients who developed disease (35% vs 74.1%). The remaining patients received more immunopotent drug combinations (Table 1).

We analysed the compliance with requirement for weekly blood test. Of the patients who developed disease, 87.0% of scheduled samples before the onset of disease were taken and no patient missed more than two scheduled samples. All but two of the patients who became PCR positive after the onset of disease had a PCR-negative sample within 7 days before the onset of disease. The remaining two patients were PCR negative 8 and 14 days before the onset of disease, respectively. Of the patients who did not develop disease, 84.7% of scheduled samples were taken and no patient missed more than four samples.

Cost analysis

The potential estimated cost comparison for a deferred strategy and a pre-emptive strategy in the same group of patients is shown in Table 2. The majority of patients who received intravenous ganciclovir required hospitalization for initiation of treatment and completed the course as an outpatient if transportation could be arranged to attend daily for drug administration. Since this study was performed, an out-patient home intravenous therapy programme has been established. As none of the patients required hospital admission for severe CMV disease alone, the cost of drug administration in this analysis was based on the estimated cost of 2 weeks of ganciclovir administered in the outpatient home intravenous therapy programme. The deferred strategy was calculated to cost £1159 per patient, while the pre-emptive strategy would cost £1381 per patient. Three months of oral ganciclovir prophylaxis costs £1500 per patient. It is unlikely that
gancyclovir prophylaxis is 100% effective. It is difficult to obtain robust data from the literature on the effectiveness of gancyclovir prophylaxis in patients not receiving anti-lymphocyte induction. The relative risk reduction for gancyclovir prophylaxis in patients receiving anti-lymphocyte induction is 0.21–0.84 [2,3]. When these figures are applied to our cohort, the cost rises to between £1678 (four patients develop CMV disease) and £2213 per patient (16 patients develop disease).

Renal function at 1 year

The mean estimated CrCl 1 year after transplant was 51.4 ml/min. The mean CrCl was highest in those patients who experienced no infection (70.0 ml/min) and was higher in those patients who experienced infection but no disease (47.7 ml/min) compared with those who experienced CMV disease (39.6 ml/min) (Table 1). The difference in the mean CrCl between these three patient groups was statistically significant by one-way ANOVA ($P < 0.001$).

Acute rejection

Nine patients (22.0%) experienced AR in the first year after transplant (Table 1). No patients experienced more than one episode of AR. Biopsy confirmation of AR was obtained in 7/9 cases. The remaining two cases were diagnosed on the basis of a rise in serum creatinine not explained by other causes that improved after treatment with high dose corticosteroid. The incidence of AR was 7/20 (35%) in the patients who experienced...
CMV disease, 1/7 (14.3%) in the patients who experienced CMV infection but no disease, and 1/14 (7.1%) in the patients who had no evidence of infection or disease. The differences between the three groups were not significant by $3 \times 2 \chi^2$ test ($P = 0.13$). In the seven patients who experienced CMV disease and AR, four patients experienced AR after evidence of CMV infection, two episodes occurred before evidence of CMV infection, and one episode occurred on the same day that CMV PCR became positive.

Discussion

The best strategy for managing CMV infection after solid organ transplantation is not established. PCR appears to be the most sensitive, specific and robust method to detect CMV infection, but not all patients who are CMV infected will develop disease [6,13]. In this study, we confirmed that detection of PCR in weekly plasma samples in the first 3 months after D+/R– renal transplantation was highly sensitive for patients with CMV infection and disease.

Several authors have suggested that intensive surveillance has advantages over prophylaxis in patients at high risk of CMV disease. We used weekly surveillance to apply a deferred treatment strategy. We anticipated that PCR positivity would develop before the onset of disease and would allow future application of a pre-emptive strategy to prevent CMV disease whereby all patients with CMV infection would be treated to prevent the onset of disease. Of the 20 patients that experienced disease, all became PCR positive, but in only eight of these cases was the PCR positive before there was clinical evidence of disease. This contrasts with the data of Steddon et al. who also performed weekly monitoring and found that disease was universally preceded by positive tests for active viral replication in 62 renal transplant recipients who developed CMV disease [14]. Despite this, only one patient in our study developed a severe illness in association with CMV disease. In that patient, there were also technical issues including a urine leak and acute cholecystitis at the same time as the illness that make it difficult to determine how much the CMV infection was contributing to the clinical state. In the remaining 19 cases of CMV disease, the illness was mild. It seems likely that this was because the weekly surveillance allowed prompt diagnosis and treatment of CMV disease even if the diagnosis did not occur significantly before the onset of clinical features in the majority of patients. Seventeen patients were PCR positive before or within 7 days after the onset of clinical features. Nineteen out of 20 patients with evidence of CMV disease received treatment with intravenous ganciclovir, while in the remaining patient the evidence of disease disappeared without the need for treatment.

Prophylactic, deferred treatment and pre-emptive treatment strategies have been described in renal transplantation but not compared adequately to determine the best strategy. Prophylaxis of all high risk patients with ganciclovir or valacyclovir has been described in large studies and shown to be effective in reducing the incidence and cost of CMV disease [2,3,15]. This led to evidence-based practice guidelines recommending 3 months of ganciclovir prophylaxis for all D+/R– transplants [1,2]. The benefit of prophylaxis is greatest for high risk D+/R– transplants receiving anti-lymphocyte antibody induction, but the evidence for patients at lower risk including D+/R– transplants not receiving anti-lymphocyte antibody is not strong [2]. In the largest study of prophylaxis, almost half of the patients received anti-lymphocyte antibody. Prophylaxis exposes a significant proportion of patients who would never have developed disease to a prolonged course of anti-viral therapy that may encourage viral drug resistance [4,5]. Furthermore, there is evidence that prophylaxis may only delay the incidence of CMV disease in some patients [3,16]. These observations have prompted some authors to suggest that deferred or pre-emptive strategies supported by weekly surveillance to detect CMV infection may be more effective.

Pre-emptive treatment has been reported in small studies. Brennan et al. randomized 36 patients with CMV infection detected by weekly surveillance to pre-emptive therapy with intravenous ganciclovir or deferred therapy based on clinical features [16]. The patients were different from the patients in the present study as D+/R–, D+/R+ or D–/R+ transplants were all included and all patients received anti-lymphocyte globulin. Only five patients were D+/R–. When the patients receiving pre-emptive therapy and deferred therapy were compared, there were no significant differences in the number of episodes of disease, hospitalizations, AR episodes or renal function, although the study had limited power. Rayes et al. recently have reported a randomized study assessing pre-emptive therapy in liver transplantation based on monitoring CMV antigenaemia, and concluded that this was of limited value because the positive predictive value of pp65 antigenaemia for the development of CMV disease was only 32% [17]. Koetz et al. recently have reported a small controlled trial of pre-emptive ganciclovir in recipients of renal and liver transplants guided by pp65 antigenaemia [18]. The study was too small to make firm conclusions. Five of the seven patients assigned to pre-emptive placebo developed CMV-associated symptoms compared with none of the five patients assigned to receive ganciclovir ($P = 0.01$). However, there were only three D+/R– transplants, all of which were assigned to placebo and developed CMV disease.

Some authors have suggested that prophylaxis of all D+/R– transplants for 3 months is too expensive to justify the benefits of a reduced incidence of CMV disease and that surveillance strategies are likely to be less costly. A post hoc analysis of a multicentre trial, however, suggests that prophylaxis with valacyclovir is cost-effective compared with placebo [15]. In the present study, we used a deferred treatment strategy where the attending clinician was alerted to PCR
long-term graft survival, and so this would have is both statistically and clinically significant. Renal CrCl at 1 year between patients with no infection 1 year and a higher incidence of AR. The difference in renal function at 1 year in our cohort. Our data suggest that patients who received anti-lymphocyte globulin. Our data show that in these D+/R– renal transplants, a deferred treatment strategy results in ~50% of patients requiring treatment. The data suggest that a pre-emptive strategy in the same patients with treatment if the PCR became positive or if early clinical features are identified would have treated infection in 7/41 (17.1%) patients who would not subsequently have developed disease, prevented disease in 8/41 (19.5%) patients and treated clinical disease in 12/41 (29.3%) patients. The remaining 14 (34.1%) patients would have received no treatment. In contrast, a strategy of prophylaxis would have treated all of the patients with a 50% probability of developing disease with oral ganciclovir for 3 months. The deferred strategy and pre-emptive strategy are slightly less costly than the prophylactic strategy if all of the patients can be managed as out-patients. Although the majority of patients in the present study who experienced disease had a mild illness, it seems likely that at least some patients in a deferred or pre-emptive strategy would develop disease requiring hospital admission that would then make these strategies more expensive. There are limitations of the cost comparison we performed that should be acknowledged. There is an assumption with the deferred and pre-emptive strategies that if PCR is positive before the onset of disease and treatment instituted, then disease will be prevented. The published evidence does not allow an accurate estimate of how effective prophylaxis is in patients who do not receive anti-lymphocyte induction, and so we applied the evidence from patients who receive anti-lymphocyte induction and quote a corresponding range of cost. CMV disease occurring after 3 months was not considered, but we felt the incidence was likely to be similar in patients who had prophylaxis or surveillance.

One major concern with a deferred or a pre-emptive strategy is that patients are allowed to experience CMV infection and disease that may have a deleterious effect on graft function and survival. There is evidence that CMV infection is associated with an increased risk of AR because of upregulation of human leukocyte antigen (HLA) expression and deliberate reduction in immunosuppression [8]. This increase in AR is likely to have an adverse impact on long-term graft survival, as CMV disease is associated with the development of chronic allograft nephropathy [9]. For this reason, we analysed the incidence of AR and renal function at 1 year in our cohort. Our data suggest that patients who experience CMV disease have poorer renal function at 1 year and a higher incidence of AR. The difference in CrCl at 1 year between patients with no infection (70 ml/min) and patients with disease (36.9 ml/min) is both statistically and clinically significant. Renal function at 1 year is independently associated with long-term graft survival, and so this would have long-term cost implications that are not included in the cost analysis we performed. The difference in AR incidence between patients experiencing no infection (7.1%) and patients experiencing disease (35%) would be clinically significant but is not statistically significant when analysed along with the group of patients experiencing infection only, and this relates to the small number of patients in each group. One can speculate that the increased incidence of AR in patients experiencing CMV disease is the cause of worse renal function at 1 year, but it must be acknowledged that in a small retrospective analysis, other factors with an influence on AR and renal function could also explain these differences. The data in Table 1 suggest that the recipient factors, donor factors, cold ischaemia time and HLA matching were similar, but there was a trend to a higher frequency of delayed graft function in those who subsequently experienced CMV disease that might also explain a higher incidence of AR and poorer function at 1 year. In our study, three episodes of AR occurred before or at the same time as the onset of CMV disease, and one can speculate that these episodes were associated with upregulation of HLA antigen expression. Four episodes occurred after the onset of CMV disease and might have been caused by a reduction in immunosuppression.

Our data show that using our method, a pre-emptive strategy would only be truly pre-emptive in ~40% of cases because, of the patients who experienced disease, 60% developed clinical features at the same time or before the PCR became positive and seven patients who would have received treatment would not have developed disease if untreated. It is not clear why the PCR was not positive before the onset of disease in more than half of the patients. The PCR method used follows previously published methods and has been used and validated for several years in our laboratory. The criteria for diagnosing the onset of CMV disease may have been stricter than some previous studies; the first day that symptoms were reported, blood platelet or lymphocyte level fell below the reference range or the AST or GGT rose above the normal range was regarded as the onset of disease. It is possible that more frequent PCR testing may have detected CMV infection a few days before the onset of disease in the three patients who became PCR positive >7 days after the onset of disease, but this would have increased the cost of surveillance and would require more frequent visits by the patient. Our data illustrate another problem with a surveillance strategy because, despite efforts by a dedicated research nurse, almost 15% of scheduled samples were not taken. This reflects clinical reality. It does not explain the failure of PCR to be positive before the onset of disease in the majority of patients since 10 of the 12 patients who became PCR positive after the onset of disease were PCR negative within 7 days before the onset of disease. In the future, it may be possible to develop a more sensitive assay to detect viral replication. The role of quantitative DNA has not been established but may also allow targeted treatment as an alternative to prophylaxis [19].
The study was limited because of the small number of patients, but previous studies examining surveillance strategies have analysed similar sized cohorts. One potential advantage of single centre studies over multicentre studies is uniformity of clinical management. In the present study, it must be acknowledged that the immunosuppressive protocols were not uniform as the study took place in the routine clinical setting. The data suggest that patients receiving more immunopotent regimes are more likely to develop CMV disease (Table 1).

In conclusion, this study adds to the debate on whether a surveillance strategy is more effective than a prophylactic strategy in D+/R- renal transplant recipients. We have confirmed that detection of CMV by PCR in the blood of D+/R- renal transplant recipients in the first 3 months after renal transplantation is a reliable method of diagnosing CMV infection. The PCR test used became positive before the onset of disease in only 40% of patients, but became positive before or within 7 days after the onset of disease in the vast majority of patients. A strategy of weekly PCR testing with pre-emptive therapy or deferred therapy appears to be only marginally less costly than prophylaxis and likely to be more expensive if patients with disease require hospitalization. Our data suggest that surveillance strategies may be associated with a deleterious effect on long-term outcome, as patients who develop CMV infection and disease have an increased risk of AR and poorer renal function at 1 year.

Efforts to develop more sensitive methods to detect early CMV infection may be of value for surveillance strategies. Prophylaxis and treatment of CMV infection may be enhanced with the introduction of newer agents such as valganciclovir [20]. A randomized comparison of strategies to detect and manage CMV infection after renal transplantation is justified and should include comparison of AR incidence and effects on graft function and long-term outcome.

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