A simplified strategy for clinical management of late cytomegalovirus infection after oral ganciclovir prophylaxis in renal recipients

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Objectives: Late cytomegalovirus disease after completion of prophylactic therapy occurs in 5–21% of renal allograft recipients within the first year post-transplantation. Identifying patients at risk for late infection is clinically difficult; prolonged cytomegalovirus (CMV) monitoring is costly and cumbersome as follow-up intervals lengthen.

Patients and methods: We performed a prospective 1 year study in 54 de novo renal recipients to assess the minimum CMV monitoring frequency for identifying patients at risk.

Results and conclusions: CMV DNA PCR monitoring on the last day, and again 2 weeks after conclusion of oral ganciclovir prophylaxis, seemed sufficient for identifying recipients at risk for developing clinically relevant late CMV disease and for whom closer clinical follow-up is warranted.

Keywords: CMV infection, CMV disease, CMV prophylaxis, CMV monitoring, kidney transplantation

Introduction

Cytomegalovirus (CMV) disease remains an important viral opportunistic infection after (renal) transplantation. It is responsible not only for serious morbidity, but is also implicated in the development of chronic allograft rejection, concurrent infections and graft survival.1–3 Effective oral prophylactic strategies have been deployed, enabling clinicians to reduce early CMV infection and disease significantly by using ganciclovir, valaciclovir and recently valganciclovir.4–8 In addition, some of the latter drugs have shown beneficial effects on the incidence of acute rejection and chronic graft vasculopathy.6,9

Other studies have examined the best possible strategy for predicting clinically significant CMV disease in recipients at risk, and the majority of these trials concur that pre-emptive CMV therapy—based on monitoring of viral load by either CMV PCR techniques or pp65-antigenaemia—is superior to a deferred therapeutic strategy.10

Oral CMV prophylaxis for the first 3 months after renal transplantation is effective, but 5–21% of renal recipients will develop delayed CMV disease during the first post-operative year after discontinuation of prophylactic therapy, especially high-risk patients (D+/R–).4,8,11,12 It is therefore important for clinicians to identify specifically patients at risk for delayed CMV disease, without using excessive financial resources in terms of CMV monitoring methods.

We conducted a 1 year study examining the feasibility of minimal prospective quantitative CMV PCR monitoring in 54 de novo renal recipients at risk for CMV infection and previously treated with oral ganciclovir prophylaxis for 3 months. The aim of this study was to determine if minimal CMV PCR monitoring in patients after receiving prophylaxis was useful in predicting delayed CMV infection or disease in the first year post-transplantation without substantially increasing monitoring costs.

Methods

Inclusion and exclusion criteria

Fifty-four consecutive de novo recipients of a renal allograft participated in this prospective 1 year clinical study. Inclusion criteria required that patients were at least 18 years of age and had received a primary or secondary single cadaveric donor kidney. Patients had to be at risk for CMV infection (either donor CMV-positive and/or recipient-positive). Patients were not eligible for the study if cold ischaemia time exceeded 36h or if the kidney was received from...
a non heart-beating donor. Other exclusion criteria were: chronic infectious or inflammatory diseases; white blood cell count < 2.5 x 10^3 cells/mm³, platelets < 100 x 10^3 cells/mm³, haemoglobin < 6 g/dL and maintenance therapy with antiviral medication.

**CMV prophylaxis**

All recipients were started on oral ganciclovir (Cymevene; Roche Basel, Switzerland) prophylaxis on day 2 post-transplantation, at a dosage of 1000mg three times a day, adjusted to renal allograft function. Ganciclovir prophylaxis was discontinued on the last day of week 12 in all patients as per protocol. This study was performed strictly according to the ethical standards for clinical research in humans defined by the Ethics Committee of the University Hospitals Leuven, Belgium.

**CMV monitoring**

Routine quantitative blood CMV DNA PCR (Amplicor CMV-test; Roche Diagnostics) was performed at pre-set time points after transplantation; at 2, 12 and 14 weeks and again at week 20 if PCR had previously become positive by week 14. CMV PCR samples at week 12 were drawn on the last day of prophylactic ganciclovir therapy. The quantitative CMV DNA PCR had a lower limit of detection of 500 copies/mL of blood.

**Clinical monitoring**

All patients were routinely assessed for clinical signs of CMV infection. This could be either CMV syndrome or tissue-invasive CMV disease: weekly until week 14; bi-weekly until month 6 and monthly until 12 months, marking the end of the active study period. CMV syndrome was defined as documented CMV viraemia in association with fever ≥38°C (on two measurements), malaise, leucopenia, thrombocytopenia or liver function disturbances. The diagnosis of tissue-invasive CMV disease required the presence of signs or symptoms of organ dysfunction and evidence of localized CMV infection by tissue biopsy or appropriate specimen. All other types of infections were recorded as was the occurrence of biopsy-proven acute rejection and the type of immunosuppressive drug therapy.

**Treatment of CMV disease**

Patients who developed CMV disease were treated with intravenous ganciclovir at a dose of 5 mg/kg twice daily, adjusted to renal graft function for a minimum of 2 weeks or until CMV PCR became negative.

**Statistical analysis**

Distribution for continuous data was evaluated and parametric and non-parametric tests (Fisher’s exact test, χ² tests) were applied when appropriate. Data are expressed as means ± s.d.

**Results**

Patient demographics, transplantation-related characteristics, CMV risk status and immunosuppressive therapy are summarized in Table 1.

**CMV monitoring**

Six patients (11%) developed a positive CMV PCR (>500 copies/mL) by week 12, at the end of ganciclovir prophylaxis (mean viral load: 4.27±0.68 log copies/mL). None of these patients had a prior (at 2 weeks) positive CMV PCR while under prophylactic therapy. Four of the latter recipients were at high risk for CMV infection (D+/R–) whereas two were CMV-positive and received a graft from a CMV-negative donor.

**Figure 1.** Evolution of quantitative CMV PCR during and after ganciclovir prophylaxis in recipients who became PCR-positive (n = 8)
CMV monitoring in renal recipients

Two weeks after discontinuation of ganciclovir (week 14), two additional patients became CMV PCR-positive (both D+/R–), totalling to eight recipients (14.8%) exhibiting detectable viral replication (Figure 1).

CMV disease

One patient who was CMV PCR-positive at the end of prophylactic therapy developed gastrointestinal CMV disease 1 week later; a second patient who became CMV PCR-positive 2 weeks after stopping ganciclovir also contracted gastrointestinal CMV disease; a third patient developed CMV syndrome during prophylactic therapy in week 8 post-transplantation and had a recurrence of gastrointestinal tissue-invasive disease 11 weeks after stopping ganciclovir treatment. The diagnosis of CMV disease was confirmed in all patients by (gastrointestinal) tissue biopsy. Thus, in total 3/8 (38%) patients who became CMV PCR-positive at the end of prophylaxis, or 2 weeks after discontinuation of ganciclovir, developed CMV disease. All three patients were CMV-negative recipients of a CMV-positive graft and responded to intravenous ganciclovir treatment, with complete resolution of clinical symptoms and post-treatment negative follow-up PCR. This prompt response to antiviral therapy suggested that infections by resistant CMV strains were very unlikely. Interestingly, the latter three patients became CMV PCR-positive again by week 20, after successful treatment; the patient who suffered from a breakthrough CMV disease in week 8 had a CMV disease relapse by week 22. Only one recipient (1/45: 2.2%; D+/R–), who did not become CMV PCR-positive at the end of prophylaxis or 2 weeks after stopping this treatment, developed CMV syndrome followed by both respiratory and gastrointestinal disease at 25 weeks post-transplantation. During clinical follow-up, additional diagnostic CMV PCR tests were ordered in four more recipients because of clinical suspicion of infection. However, none of the latter PCR tests was positive.

Two out of eight patients (25%) who became CMV PCR-positive during this study had received at least one prior treatment for acute rejection; one of those developed CMV disease 5 weeks later. Thirty-four percent of PCR-negative recipients (16/46), suffered at least one acute rejection episode.

The incidence of other types of infections (bacterial, fungal, viral) in the first year post-transplantation was not different between recipients who became CMV PCR-positive and patients who remained PCR-negative after stopping CMV prophylaxis (data not shown). There was no difference either in the baseline immunosuppressive drug regimen or use of induction agents between the two former groups (data not shown).

Three patients in the CMV PCR-negative group lost their renal graft: two grafts were lost due to chronic rejection, and the third patient succumbed to a fungal infection of the lung with a functioning graft. One recipient, who became CMV PCR-positive but did not develop CMV disease, lost her graft due to recurrent therapy-resistant acute rejection.

Discussion

In this prospective study, it was demonstrated that a simplified CMV follow-up monitoring strategy at the end of prophylactic therapy and again 2 weeks after discontinuation—using quantitative CMV DNA PCR determinations—can identify renal recipients at risk for CMV disease, especially CMV-negative patients receiving CMV-positive grafts. Four out of 13 D+/R– recipients (30.8%) developed CMV disease; three of the latter patients were CMV PCR-positive by week 14. Three additional high-risk recipients (23%) became PCR-positive by week 14 but did not develop disease. The limitations of this study, implied by the use of an exclusively clinical follow-up as from 14 weeks post-transplantation, have to be taken into account when interpreting these results. This pragmatic approach can substantially reduce monitoring costs by focusing clinical vigilance on recipients at risk for CMV disease, in whom viral replication escapes antiviral prophylaxis or increases rapidly after discontinuation of CMV preventive treatment. A limited number of timed CMV monitoring episodes might prove advantageous, in comparison with generalized and prolonged CMV monitoring in all patients who received prophylaxis, versus no monitoring at all. The current method of minimal CMV monitoring had a high specificity (88%) and negative predictive value (97.8%) for CMV disease but a weaker sensitivity (75%) and low positive predictive value (25%). However, we were not aiming at using pre-emptive antiviral treatment in patients at risk for developing post-prophylaxis CMV disease, but rather were interested in identifying recipients who warranted closer clinical follow-up in order to detect CMV disease promptly but without the high costs of persistent monitoring in all patients. This simplified approach appealed, taking into account its high specificity and negative predictive value.

The fact that systematic CMV monitoring was not continued beyond week 14, except in recipients who had already become PCR-positive by then, suggests that viral replication occurring later after discontinuation of prophylactic therapy could not have been detected in this study. It is clear that ~50% of high-risk recipients of solid organ grafts will develop detectable CMV replication later during the first year post-transplantation after discontinuation of prophylactic therapy. However, the fact that only one patient (1/45)—who was not PCR-positive by week 14—subsequently developed clinical CMV disease, indicates that predominantly recipients exhibiting viral replication at the end or immediately after conclusion of prophylactic therapy, benefit from close clinical follow-up. Having a negative CMV DNA PCR at both these latter time points (12 and 14 weeks) has a very high negative predictive value for CMV disease in the first year after transplantation. Thereby, costs related to CMV monitoring (assay and logistics) can be substantially reduced. Because of the limited number of PCR determinations, no information could be obtained regarding the rate of viral load kinetics and subsequent risk for CMV disease. In conclusion, limited CMV PCR monitoring at the end and 2 weeks after the conclusion of oral ganciclovir prophylaxis, enables clinicians to identify renal recipients at risk for whom close clinical follow-up is warranted, and allows substantial cost savings related to the generalized and prolonged use of CMV monitoring during the first year post-transplantation.

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References


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