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REVIEW

Cytomegalovirus post kidney transplantation: prophylaxis versus pre-emptive therapy?

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Summary

Cytomegalovirus is the most important pathogen causing opportunistic infections in kidney allograft recipients. The occurrence of CMV disease is associated with higher morbidity, higher incidence of other opportunistic infections, allograft loss and death. Therefore, an efficient strategy to prevent CMV disease after kidney transplantation is required. Two options are currently available: pre-emptive therapy based on regular CMV PCR monitoring and generalized antiviral prophylaxis during a defined period. In this review, we describe those two approaches, highlight the distinct advantages and risks of each strategy and summarize the four randomized controlled trials performed in this field so far. Taken this evidence together, pre-emptive therapy and anti-CMV prophylaxis are both equally potent in preventing CMV-associated complications; however, the pre-emptive approach may have distinct advantages in allowing for development of long-term anti-CMV immunity. We propose a risk-adapted use of these approaches based on serostatus, immunosuppressive therapy and availability of resources at a particular transplant centre.

Cytomegalovirus in kidney transplantation

General introduction

Cytomegalovirus (CMV) is the most important viral pathogen and the most prevalent opportunistic infection after kidney transplantation [1]. Infection occurs by three ways (in order of incidence): (i) endogenous reactivation of CMV in the recipient, (ii) donor-derived infection transmitted by the allograft and (iii) *de novo* infection acquired from the general population. From a clinical point of view, three distinctive presentations can occur: asymptomatic viraemia, CMV viral syndrome (with fever, malaise and leukopenia) and CMV tissue invasive disease (with documented end-organ damage in histology or imaging such as colitis, hepatitis, pneumonitis or retinitis).

Apart from CMV viral syndrome and tissue invasive disease, a number of indirect immunomodulatory effects of CMV have been postulated [2], thereby increasing the incidence of acute and chronic rejection after solid organ transplantation on one side (probably via a bystander activation of alloreactive T cells during an antiviral response of the host), but also the incidence of other opportunistic infections on the other side.

Immunity against CMV

The incidence of CMV infection and serious clinical complications is highly dependent on the serostatus (presence of CMV-specific antibodies) of recipient (R) and donor (D) with the constellation D+R− bearing the highest risk, followed by D+R+, D−R+ and D−R−. Studies on anti-CMV strategies usually distinguish between these risk categories, thereby often summarizing the D+R+ and D−R+ groups in an intermediate-risk category [3]. The D−R− recipients as

a low-risk group very seldom develop CMV viraemia and generally do not need any primary anti-CMV strategy.

Apart from CMV-specific antibodies, T cells play a major role in the host defence against this virus [4]. CMV efficiently activates CD8+ T-cell responses during replication. Even during latency periods, CMV antigenic peptides are transiently 'desilenced' and stimulate virus-specific CD8 T cells leading to an increased frequency of CMV-specific CD8+ T cells in an ageing population, a phenomenon sometimes called 'memory inflation' [5].

The CMV-specific T-cell response can be assessed in peripheral blood by cell-mediated immunity (CMI) assays based on either ELISPOT (direct enumeration of CMV-specific T cells [6]) or Quantiferon® technology (indirect quantification of CMV-specific T cells after antigen-specific stimulation and subsequent measurement of interferon-γ in supernatant [7]). CMI assays have been shown to correlate with CMV serostatus (also in dialysis patients) and with the occurrence of CMV reactivation post kidney transplantation. However, no prospective randomized trials have used this method to guide antiviral strategies post kidney transplantation so far.

Risk factors for CMV disease

Apart from CMV-specific immunological memory, other factors are associated with the occurrence of CMV disease: type of transplanted organ [8], demographic factors (such as age) and genetic factors (such as natural killer cell receptor repertoire [9]) as well as the inflammatory state of the recipient.

Of particular relevance is the intensity of immunosuppression. A recent randomized trial demonstrated an increased risk for CMV disease in patients treated with modern maintenance immunosuppression based on tacrolimus/mycophenolate mofetil compared to a conventional treatment with cyclosporine/azathioprine [10]. Furthermore, induction therapies with either depletion of T cells [11] or B cells [12] have been shown to increase the incidence of CMV infection. The same is true after the treatment of acute rejection [13].

Prophylaxis against CMV infection or reactivation

Seroprophylaxis

The recognition that seronegative patients receiving a seropositive organ have a particularly high risk of CMV complications strongly pointed to the potential benefit of seroprophylaxis at a time, where no CMV-specific antiviral drugs were available. Indeed, in a randomized study including only 59 D+R− kidney, the application of CMV-specific hyperimmune globulin within 3 days after transplantation and in a 2-week interval thereafter until week 16 significantly reduced the incidence of virologically proven CMV syndrome from 60 to 5% [14]. Also the rate of other opportunistic infections, graft loss and death was reduced in the treatment group, although not significantly due to the small patient number. Interestingly, however, the rate of seroconversion was similar in both arms of the study and higher than the CMV disease incidence. Thus, most probably asymptomatic viral replication may have occurred in these patients leading to an 'endogenous vaccination'. This is an important observation for the further discussion.

Antiviral prophylaxis

A few years after this study, ganciclovir as the first CMV-specific antiviral drug became available, and its effectiveness in preventing CMV disease in heart transplant recipients was demonstrated [15]. Soon thereafter, it was shown that efficacy of antiviral prophylaxis was equal to seroprophylaxis in CMV high-risk patients after kidney transplantation and that this therapy was much cheaper than the use of CMV-specific hyperimmune globulin [16].

However, it was only after an oral antiviral drug with good bioavailability – valacyclovir – became available, that antiviral prophylaxis against CMV became standard of care at least in CMV high-risk constellations (D+R−). Its efficacy was demonstrated in a large randomized trial including more than 600 kidney transplant recipient, one-third with high-risk (D+R−) profile and two-thirds with intermediate-risk (seropositive recipients) profile [17]. In this study, valacyclovir compared to placebo reduced the incidence of CMV disease in both risk groups and the incidence of acute rejections only in the high-risk group (Fig. 1). Furthermore, also other infectious complications (other herpesviruses, candida, staphylococcal infections) were diminished by the prophylactic treatment, indicating that the postulated indirect immunomodulatory effects of CMV were prevented. No difference was seen, however, with respect to patient survival.

Equal or improved efficacy of oral valganciclovir in comparison with intravenous ganciclovir was later demonstrated in two randomized trials [18,19].

A critical view on generalized prophylaxis

These trials on seroprophylaxis and antiviral prophylaxis clearly demonstrated that a strategy to prevent CMV complications after kidney transplantation is necessary in the high-risk D+R−, but also in the intermediate-risk R+ recipients. However, there are substantial problems associated with the generalized use of antiviral prophylaxis (Table 1):

1 The currently available antiviral drugs are associated with high cost and substantial, mainly haematological toxicity,

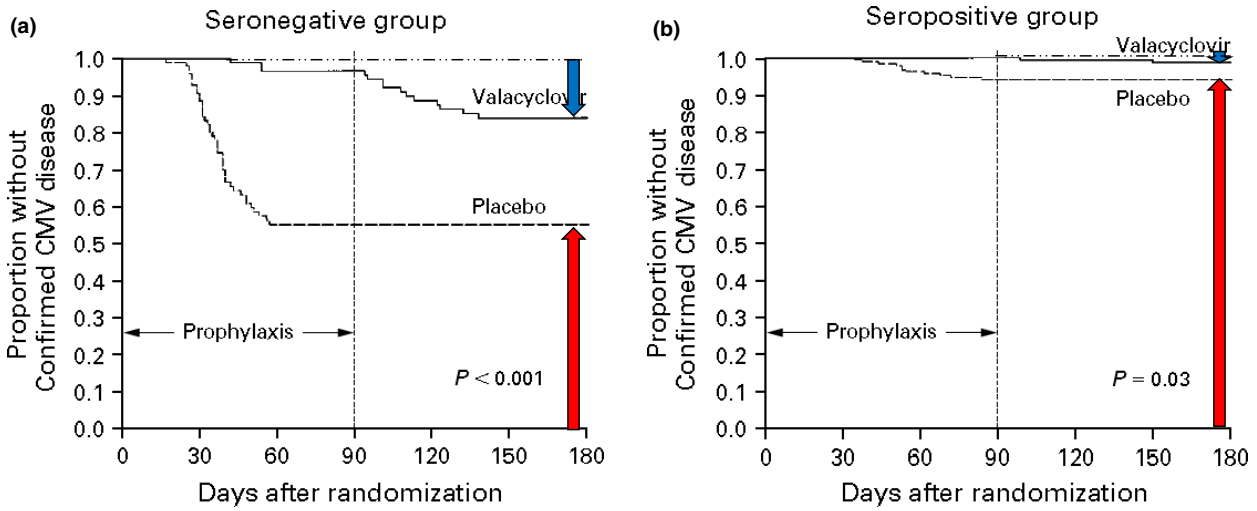

Figure 1 Incidence of CMV disease with and without prophylaxis. Kaplan–Meier curves for CMV disease-free survival in a randomized controlled trial comparing valacyclovir prophylaxis with placebo [17]. (a) D+R− recipients, (b) R+ recipients. Red arrows: patients who never developed any CMV disease, irrespective of treatment; blue arrows: patients who developed late CMV disease, despite prophylaxis during the first 3 months.

Table 1. Comparison between pre-emptive and prophylactic strategy.

	Pre-emptive strategy	Prophylactic strategy
Principle approach	CMV PCR monitoring, therapeutic intervention upon the detection of viral replication (→ cut-off definition)	Antiviral prophylaxis starting early after transplantation for a defined period (3–6 months)
Advantages	• Less drug toxicity (only patients, who need treatment, actually receive it) • Lower incidence of late CMV disease • Immunologic low-level exposure to virus allows 'endogenous vaccination'	• Reliable suppression of CMV replication during time of therapy • Avoidance of potential 'indirect CMV effects' (triggering of acute and chronic rejection; other opportunistic infections)
Risks	• Nonadherence to strict monitoring schedule bears risk of CMV disease • Potential higher risk for 'indirect CMV effects' (including late cardiovascular events)	• Drug toxicity (mainly haematological) • Late CMV disease • Development of ganciclovir-resistant mutants
Cost	• Higher for PCR monitoring • Lower for antiviral drugs	• Higher for antiviral drugs • Lower for PCR monitoring

which often requires reduction of immunosuppressive drug dosing (antimetabolites!) and therefore increases the risk of acute rejection.

2 Antiviral prophylaxis is associated with the occurrence of late CMV infection [20,21] at a time, when patients are not so often seen any more in the transplant clinic, and therefore, diagnosis may be considerably delayed.

3 From an immunological point of view, in order to allow a patient to develop robust cell-mediated immunity as well as neutralizing antibodies against CMV, antigenic exposure to the virus is important. As long as no vaccine against CMV is available, asymptomatic low-level viral replication may be the best way to actually prime CMV-specific T- and B-cell responses. This endogenous stimulation is reduced or delayed by a general antiviral prophylaxis. However, effectors of the innate immune system (such as natural killer cells) are not affected by the different antiviral strategies.

When looking again at the results of the largest randomized study on CMV prophylaxis with valacyclovir (Fig. 1) [17], we recognize that with the high-risk group 71% received unnecessary treatment, because they either never developed replication in the control group (55%) or they developed late CMV disease after stop of prophylaxis (16%) and then needed treatment anyway. This number was even higher (95%!) for the intermediate-risk group (never developed replication: 94%; late CMV: 1%). Given these arguments, a smarter way of preventing CMV complications should be evaluated apart from generalized prophylaxis.

Pre-emptive versus prophylactic strategy: randomized controlled trials

As opposed to a generalized prophylaxis, antiviral treatment in the pre-emptive strategy is guided by a regular monitoring of viral replication by PCR, formerly also by pp65+ cells. This strategy has two major advances (Table 1): (i) only patients who need it (i.e. have documented viral replication) are treated; (ii) asymptomatic viraemia allows priming of a robust anti-CMV immune response which will partly protect the patient from later endogenous or exogenous CMV exposure. The major risk associated with this strategy is nonadherence to the regular PCR monitoring, which may lead to severe CMV tissue invasive disease because of intense immunosuppression in the first months after transplantation. Although the risk of nonadherence is not very high during the first 6 months post-transplantation due to the close follow-up, it may be detrimental mainly in patients with high-risk D+R− constellation.

A total of 4 randomized trials have tested the comparative efficacy of a pre-emptive versus prophylactic anti-CMV strategy (see Table 2 [20,22–24]). They included between 70 and 396 patients randomized 1:1 in a prophylaxis group (3 months oral valganciclovir in 3 and oral valacyclovir in one study) and a pre-emptive therapy group using CMV DNAemia as a trigger for starting therapy. The cut-off for CMV viraemia measured by quantitative real-time PCR in plasma was 400 copies/ml in two and 2000 copies/ml in the other two studies. Pre-emptive therapy was performed with oral valganciclovir in three and intravenous ganciclovir in one study. The largest study only included intermediate risk (R+ recipients), whereas the other three studies had 10–30% D+R− and the remaining R+ recipients.

The main findings of these trials are the following:

1 The incidence of early (<3 months) CMV viraemia is considerably higher in the pre-emptive therapy compared to the prophylaxis group. This is expected, because viraemia is the trigger of intervention in the pre-emptive therapy group.

2 The incidence of late (>3 months) CMV viraemia is significantly higher in the prophylaxis group. This finding supports the concept of low-level antigenemia being necessary for an endogenous immunization.

3 The incidence of CMV disease is not different between the two approaches with the exception of one trial. This finding is confirmed by a recent large analysis in nonselected patients from the Swiss Transplant Cohort Study [8].

4 Patient death and graft loss were not different between the two approaches, except for late graft loss after 4 years in one trial (92.2% vs. 78.3%; $P = 0.043$, [20]).

5 The incidence of severe neutropenia, which is per se a dangerous complication [25], was significantly increased in the prophylaxis group in three of the four trials.

Table 2. Randomized controlled trials comparing pre-emptive and prophylactic strategy against CMV post kidney transplantation.

	Khoury [22]	Kliem [20]	Reischig [23]	Witzke [24]
Pre-emptive strategy arm (PRE)	Valganciclovir 900 mg b.i.d. for 21 days, if CMV DNA >2000 copies/ml	Ganciclovir 5 mg/kg i.v. b.i.d. for min 10 days, if CMV DNA >400 copies/ml	Valganciclovir 900 mg b.i.d. for min 14 days, if CMV DNA >2000 copies/ml	Valganciclovir 900 mg b.i.d. for 14 days, if CMV DNA >400 copies/ml
Prophylactic strategy arm (PRO)	Valganciclovir 900 mg/ days for 100 days	Ganciclovir 1000 mg t.i.d. for 90 days	Valacyclovir 2 g q.i.d for 90 days	Valganciclovir 450 mg b.i.d. for 100 days
Patient no	98; 29 D+R−, 69 R+	148 (ITT 130); 44 D+R−, 104 R+	70; 10 D+R−, 60 R+	396; only R+
Early CMV viraemia (3 mts)	PRE: 59% PRO: 6%	PRE: 49% PRO: 4%	PRE: 89% PRO: 9%	PRE: 35% PRO: 1%
Late CMV replication (4–12 mts)	PRE: 0% PRO: 23%	PRE: 1% PRO: 13%	PRE: 3% PRO: 47%	PRE: 4% PRO: 10%
CMV disease (12 mts)	PRE: 1 pt PRO: 4 pts	PRE: 19 pts PRO: 4 pts	PRE: 2 pts PRO: 3 pts	PRE: 5 pts PRO: 4 pts
Leukopenia	PRE: 1 pt PRO: 2 pts	PRE: 1 pt PRO: 11 pts	PRE: 3% PRO: 15%	PRE: 5% PRO: 10%
Other opportunistic infections	No difference for bacterial and fungal infections	Not reported	No difference for other viral, bacterial or fungal infections	No difference for other viral, bacterial or fungal infections
Acute rejection (1y)	PRE: 4 pts PRO: 1 pt	Not reported PRE: 4 pts	PRE: 36% PRO: 15%	PRE: 12% PRO: 18.5%
Graft loss (1y, death-cens.)	PRE: 1 pt PRO: 0 pts	PRO: 2 pts	PRE: 1 pts PRO: 2 pts	PRE: 5 pts PRO: 2 pts
Death (1y)	No death during study period	PRE: 4 pts PRO: 5 pts	PRE: 0 pt PRO: 1 pts	PRE: 2 pts PRO: 2 pts

Additional aspects have to be considered when comparing these two approaches:

1 Protocol adherence: the pre-emptive therapy approach can only be successful, when (i) a strict adherence to the regular PCR testing in guaranteed and (ii) the reaction time between a positive PCR test and start of pre-emptive therapy is rapid, particularly in the D+R− group. This can only be achieved by clear local guidelines and their strict implementation, as recently shown in our centre [26].

2 Cost: clear statements concerning cost are difficult. Only one of the three randomized trials assessed this issue, with the conclusion of no relevant cost differences [22]. However, total costs highly depend on the price of PCR testing (the main cost factor in the pre-emptive therapy approach) on one side and drugs (the main cost factor in the prophylaxis approach) on the other side. The availability of valganciclovir generics may therefore soon be to benefit the prophylaxis approach.

3 Lymphocyte depleting therapies: it is well known by now that lymphocyte depleting therapies for induction therapy or treatment of acute rejection may increase the risks for CMV replication and disease [11]. Therefore, in these situations, which have not been systematically investigated in these randomized trials, generalized anti-CMV prophylaxis may be required to prevent severe complications.

4 A considerable amount of literature refers to so-called indirect effects of CMV viraemia. This means virus-triggered acute and chronic rejection episodes, triggering of other herpesvirus infections (such as Epstein-Barr and Varicella-Zoster), but also cardiovascular complications. Whereas the two-first risks were not confirmed in the four randomized trials described here, the latter effect was not investigated, because the follow-up in those trials was too short. It is postulated that CMV triggers a generalized immune activation, which then adds to progression of atherosclerosis. However, this theory has remained quite controversial up to now [27].

Conclusions

Based on the currently available evidence, pre-emptive therapy and antiviral prophylaxis are equally successful in preventing major complications of CMV infection in kidney allograft recipients, including CMV disease, allograft loss and patient death. This is also confirmed by a recent meta-analysis looking at 40 trials including more than 5000 patients, demonstrating a lower incidence of early viraemia, but higher incidence of late onset CMV infection and neutropenia with prophylaxis, but no differences in mortality, graft loss and acute rejection rates between the two approaches [21]. Each of these two concepts has particular risks and advantages, which are described in detail in Table 1. It depends on the individual transplant centre to decide which approach suits better the local circumstances. This is also supported by the most recent International Consensus Guidelines [3].

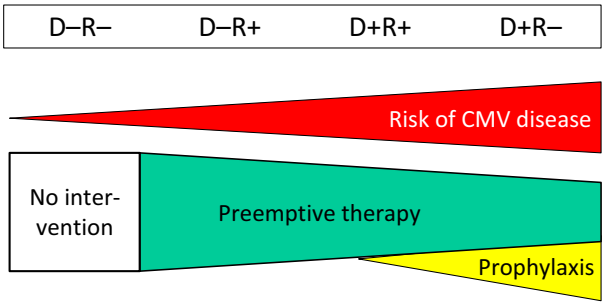

Figure 2 Proposal for use of pre-emptive therapy and anti-CMV prophylaxis. The risk of CMV disease is highly influenced by the serostatus of donor and recipient prior to transplantation. Here, we propose a risk-adapted use of pre-emptive therapy and antiviral prophylaxis with respect to the serostatus.

From an immunological view, the pre-emptive therapy approach may have interesting advantages, as it allows those patients who develop asymptomatic viraemia, to develop CMV-specific cellular and humoral immunity, and this type of endogenous vaccination may protect them from severe CMV-specific complications later on. However, the logistics to maintain strict adherence to the monitoring schedule are important and may limit its applicability in some centres. As protocol violations are particularly dangerous in D+R− recipients, we propose a mixed approach for the management of CMV in kidney allograft recipients, as depicted in Fig. 2: D−R− recipients do not need any intervention; R+ recipients can easily be followed with the pre-emptive therapy approach; however, D+R− recipients may benefit from anti-CMV prophylaxis in some circumstances, in particular when lymphocyte depleting agents are used.

A third approach would be to combine the two strategies to a 'hybrid approach' using prophylaxis early (e.g. in the first month) and a pre-emptive strategy later after transplantation, thereby profiting from some of the advantages of both strategies. Such an approach may be combined with immune monitoring using CMI assays to guide continuation or stop of prophylaxis. However, such an innovative strategy would have to been tested in future randomized trials against one of the established approaches described here.

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