

# Cytomegalovirus infection in renal transplant recipients: experience of a Paediatric centre

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## ABSTRACT

**Introduction:** Cytomegalovirus infection after renal transplantation is a significant cause of morbidity. The most effective preventative approach is yet to be determined.

**Aim:** To study the management of cytomegalovirus infection in terms of monitoring and prophylaxis.

**Patients and Methods:** Clinical records of patients who had renal transplantation between January 2000 – September 2008 (n=33) were reviewed for demographic and clinical data. Patients' cytomegalovirus serostatus was 19/33 seropositive donor (D+) and seropositive recipient (R+), 10/33 D+/R-, 3/33 D-/R+ and 1/33 D-/R-. D+/R- children received prophylaxis with immunoglobulin and antiviral drugs; other patients were managed with preemptive therapy and cytomegalovirus polymerase-chain reaction monitoring.

**Results:** After one year follow-up, cytomegalovirus infection was detected in 54.5% (18/33) patients: 63.2% (12/19) of D+/R+ group and 60% (6/10) of D+/R- group. Overall, 15.2% (5/33) patients had disease

manifestations and 39.4% (13/33) had asymptomatic infections. Prophylaxis in D+/R- children was responsible for late-onset cytomegalovirus infection: 24±13 weeks mean time for first infection compared with 11±10 weeks in D+/R+ group (Mann-Whitney test,  $p=0.018$ ). There was a moderate/weak correlation between the number of human leukocyte antigen mismatches and occurrence of cytomegalovirus infection ( $R_{bp}=0.368$ ,  $p=0.038$ ). Graft function was similar in infected and non-infected groups. There was a good response to antiviral therapy with only one patient resistant to ganciclovir.

**Conclusions:** Use of prophylactic therapy in D+/R- group and monitoring of D+/R+ and D-/R+ intermediate risk patients seems a safe and effective approach to cytomegalovirus infection prevention. We also observed that HLA mismatch may influence the risk of cytomegalovirus infection. Indirect long term consequences of cytomegalovirus infection, HLA type/ donor-recipient match and antiviral therapy side effects, need to be addressed in future prospective studies.

### Key-Words:

Cytomegalovirus (CMV); immunoglobulin; renal transplant; valganciclovir.

## ■ INTRODUCTION

Cytomegalovirus (CMV) is the most common opportunistic agent causing infection in solid organ transplant recipients<sup>1-3</sup>. It is estimated that 50 to 75% of renal transplant recipients have viral replication following transplant<sup>1,4,5</sup>. Even in the era of effective therapy, CMV infection remains a significant cause of morbidity and renal graft dysfunction<sup>6,7</sup>.

CMV may cause an asymptomatic infection, a febrile illness or mononucleosis-like syndrome or progress to invasive organ disease. Viral immunosuppressive and inflammatory mechanisms affect immunocompetent hosts as well<sup>3</sup>. Indirect CMV effects result from immune deregulation caused by low persistent viral replication and include increased allograft rejection and dysfunction, cellular immunodeficiency with other opportunistic infections and lymphoproliferative disease (B cell lymphoma)<sup>3,6</sup>.

Infection risk varies with the donor/recipient CMV serostatus<sup>1-5</sup>. It is maximal in donor positive (D+)/receptor negative (R-) patients, which have a primary infection that may be more severe and progress to invasive disease<sup>8</sup>. The immunosuppressive regimen used also increases risk, including monoclonal antibodies for induction therapy and triple immunosuppression during maintenance periods<sup>7,9</sup>.

CMV infection prophylaxis using anti-CMV immunoglobulin and antiviral drugs is still the subject of debate<sup>10,11</sup>. While prophylactic treatment suppresses viraemia and reduces direct and indirect CMV effects, it increases the risk of antiviral resistance, adverse drug reactions and late-onset disease<sup>5,7</sup>. Preemptive therapy demands rigorous CMV monitoring by polymerase-chain reaction assays (PCR) and early infection treatment, not interfering with low viral load replication and indirect CMV effects. A recently published meta-analysis involving 476 adult renal transplant patients comparing preemptive therapy with selective prophylaxis found no significant differences in disease incidence or mortality risk<sup>10</sup>.

We aimed to study the incidence and allograft/systemic complications of CMV infection in renal transplant recipients, comparing results in line with CMV serostatus and number of Human Leukocyte Antigen (HLA) matches.

## ■ PATIENTS AND METHODS

All paediatric patients who underwent renal transplantation from the year 2000 and were followed-up longitudinally for a minimum period of twelve months in our nephrology unit were included.

Records of all patients were examined and the following data collected: age and gender; cause of renal failure and time on dialysis; type of organ donor, number of HLA matches, induction and maintenance immunosuppressive regimen; CMV serostatus (D/R) by detection of specific IgG (enzyme-linked immunosorbent assay), viral monitoring and prophylaxis management; occurrence of CMV infection or disease, viral load, clinical symptoms and laboratory data (blood counts and hepatic transaminases), therapy, hospital admission, complications during CMV infection/disease; occurrence of other infections (bacterial, viral or fungal) or lymphoproliferative disease during follow-up; glomerular filtration rate (GFR) calculated by Schwartz formula at six months, one and three years after renal transplant; occurrence of acute and chronic allograft rejection episodes.

### ■ Laboratory CMV monitoring

The authors used the number of copies of CMV DNA detected by PCR assay. The limit for detection was 235 copies/mL. Patients were evaluated at least every two weeks (usually every week in the first three months) during the first semester and later at least once a month over the first year and every time there was a suspected infection. The technology used was LightCycler 2.0, Roche®.

### ■ CMV infection/disease and other definitions

CMV infection was defined by the detection of CMV DNA in any sample, with a cut-off limit of  $\geq 1000$  copies/mL. Recurring infection was considered when there was a positive viral load ( $\geq 1000$  copies/mL) after an initial CMV infection followed by  $\geq 2$  negative viral loads. CMV disease was considered when there was evidence of CMV infection associated with clinical symptoms or suggestive abnormal laboratory results with no other explanation, such as febrile illness (auricular temperature  $\geq 38^\circ\text{C}$ ) at least two days in a four day interval; leucopaenia ( $< 3000/\text{mL}$ ); thrombocytopenia ( $< 100,000/\text{mL}$ ) and organ specific disease.

Antiviral drug resistance was considered when negative viral loads were not achieved after two courses of two weeks' antiviral treatment.

### ■ Anti-CMV prophylaxis

CMV D+/R- group patients received anti-CMV prophylaxis with anti-CMV immunoglobulin day one and three after renal transplant (150mg/kg), on the 2<sup>nd</sup>, 4<sup>th</sup>, 6<sup>th</sup> and 8<sup>th</sup> weeks (100mg/kg) and 12<sup>th</sup>, 16<sup>th</sup> weeks (50mg/kg) and antiviral drugs intravenous ganciclovir/ oral valganciclovir (15-18 mg/kg/day) for at least 90 days. D-/R+ and D+/R+ group patients received no prophylaxis but underwent CMV PCR monitoring and preemptive therapy.

### ■ CMV infection/ disease treatment

Every patient with CMV infection or disease was treated with ganciclovir (5mg/kg/dose, bid) or oral valganciclovir (30-36mg/kg/day) for at least 14 days or until negative viral loads were achieved, followed by prophylaxis with valganciclovir (15-18mg/kg/day) for 3 months.

### ■ Statistical analysis

The data were analysed using SPSS® statistical software for Windows® version 16.0 (SPSS Inc, Chicago), including univariate (e.g., mean±SD, me=median) and bivariate descriptive analysis (phi coefficient, Φ; point biserial correlation coefficient, r<sub>pb</sub>) and significance parametric and non-parametric tests (Student t test; chi-square test, Fisher exact test and Mann-Whitney test). Association and correlation coefficients and significance tests were calculated for the common follow-up period of twelve months. Descriptive analysis only is presented for the rest of follow-up.

## ■ RESULTS

Fifty-five patients were selected but only 33 had a minimum posttransplant follow-up of twelve months and were enrolled.

The patients' mean age at renal transplantation was 9.91±3.4 (mean±SD) years old and mean

**Table 1**

Patient characteristics

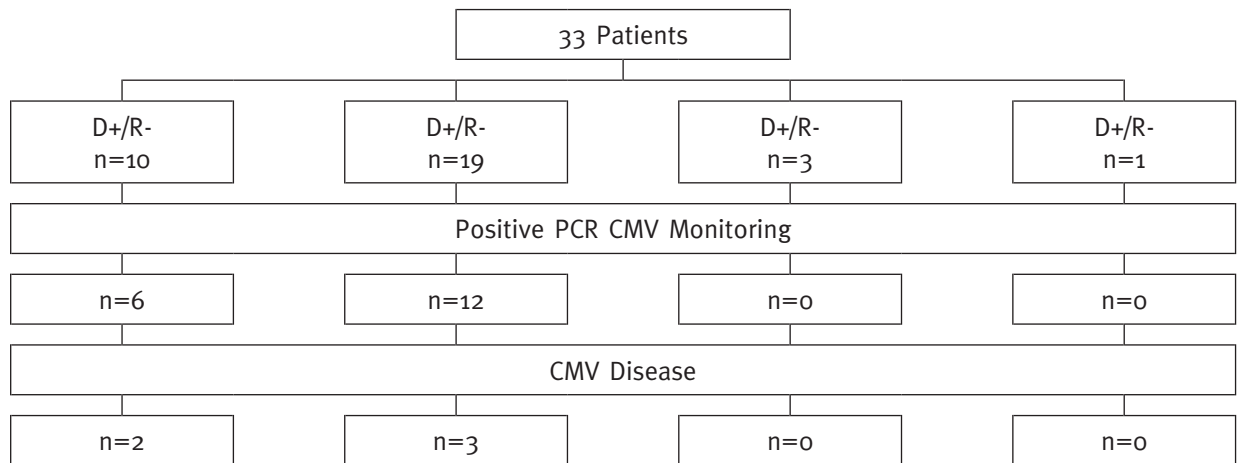
Patients	N=33
<b>Age at renal transplant (years)</b>	9.91±3.4 Mode=13, Median=10
<b>Gender</b>	17 boys / 16 girls
<b>Cause of chronic renal failure</b>	
Obstructive uropathy/ renal dysplasia	13
Glomerulopathies	8
Hereditary syndromes	5
Vascular disease	3
Unknown	3
Others	1
<b>First transplant</b>	N=33
<b>Time on dialysis (years)</b>	4.42±2.11
<b>Live donor/ cadaveric donor</b>	6/ 27
<b>HLA incompatibilities</b>	3.72±1.05 Mode=4, Median=4
<b>Immunosuppression</b>	
<b>Induction Therapy</b>	
Basilixumab + methylprednisolone	33
<b>Maintenance Therapy</b>	
FK + MMF + Pred (1)	23
CsA + MMF + Pred (2)	1
(2)→(1)	8
(2)→(1)→(2)	1
<b>Follow-up (months)</b>	39.9±24.01 Median=30, Min/Max [12, 106]

Minimum (Min.), Maximum (Max.); Tacrolimus (FK), Mycophenolate mofetil (MMF), Prednisolone (Pred), Ciclosporin (CsA).

follow-up time was 39.9±24.01 months (Table 1). In all cases, induction therapy included basilixumab and methylprednisolone. Maintenance therapy included three immunosuppressors: mycophenolate mofetil, prednisolone and tacrolimus or ciclosporin. Patients were divided into four CMV serostatus groups: D+/R- (n=10), D+/R+ (n=19), D-/R+ (n=3) and D-/R- (n=1).

The first twelve months of follow-up saw eighteen patients with CMV infection/ disease (Figure 1): 60% (6/10) of patients from group D+/R- and 63.2% (12/19) from D+/R+.

Five patients had CMV disease. In D+/R- group there were two cases: one with hepatitis, enteritis and exanthema and another with enteritis, leucopaenia and neutropaenia. In D+/R+ group there were three cases of disease: two children with leucopaenia and neutropaenia and one asymptomatic patient with increased transaminases.



**Figure 1** Distribution of renal transplant recipients into groups according to CMV serostatus, positive PCR CMV monitoring and CMV disease during one year follow-up.

Two patients from D+/R- and six patients from D+/R+ had recurrent CMV infections (7 episodes in two D+/R- patients; 14 episodes in six D+/R+ patients; 2-5 episodes/ patient), with no significant difference between groups (Fisher exact test,  $p=0.686$ ).

There was a significant moderate/ weak correlation between the number of human leukocyte antigen (HLA) mismatches and occurrence of CMV infection ( $r_{pb} = -0.368$ ,  $p=0.038$ ), more pronounced in the D+/R+ group ( $r_{pb} = -0.567$ ,  $p=0.014$ ).

Around 75% of first CMV infections in group D+/R+ developed early in the first three months (Table II) with a mean of  $11 \pm 10$  weeks (me=7 weeks). On the contrary, onset of CMV infection in the D+/R- group was significantly different (Mann-Whitney test,  $p=0.018$ ) with a mean of  $24 \pm 13$  weeks (me=26 weeks). Two patients

of D+/R- group had CMV primary infection during prophylaxis (8 and 13 weeks after transplantation).

Mean viral load in group D+/R- was  $9927 \pm 15866$  copies/mL (median 2640 copies/mL) and in group D+/R+ was  $4894 \pm 6319$  copies/mL (median 2760 copies/mL), with no significant difference of viral loads between groups or between infection and disease cases (Mann-Whitney test,  $p>0.05$ ).

Overall there were eleven hospital admissions for CMV infection/ disease (3/11 episodes in D+/R- group and 8/20 episodes in D+/R+ group), related to intravenous antiviral drugs (n=7) or short follow-up period (n=4). The mean time for achievement of negative viral loads was of  $15.8 \pm 14.2$  days in D+/R- patients and  $12.42 \pm 13.28$  days in D+/R+ patients, with no significant difference between groups (Mann-Whitney test,  $p>0.05$ ). There was only one case of antiviral drug resistance to valganciclovir with persistent positive viral loads.

In the study group there were seven patients with  $\geq 1$  acute graft rejection episodes: two cases in patients with CMV infection/ disease (n=18) and five cases in other patients (n=15), with no significant difference between groups (Fisher exact test,  $p>0.05$ ). Mean values for glomerular filtration rate were not significantly different in patients with or without CMV infection/ disease (112 versus 105, 101 versus 106 and

**Table II**

Number of patients with first CMV infection in accordance with time

Time	Group of Patients	
	D+/R+	D+/R-
$\leq 3M$	1 (10%)	9 (47%)
$>3M, \leq 6M$	1 (10%)	2 (10.5%)
$>6M, \leq 12M$	4 (40%)	1 (5.3%)

Months (M). Percentage of affected patients in each serology group are shown in parenthesis.

110 versus 107 mL/min/1.73 m<sup>2</sup>, at six months, one year and three years respectively; Student t test,  $p > 0.05$ ).

There were no significant differences between the patients with ( $n=18$ ) or without ( $n=15$ ) CMV infection/ disease and the number of other infections: bacterial (47 versus 58 episodes), fungal (3 versus 2 episodes) or viral (2 versus 7 episodes). There were no CMV/ Epstein-Barr virus co-infections. During follow-up there were no cases of renal graft loss, lymphoproliferative disease or death.

Beyond the initial twelve months, there was a variable follow-up for each patient, with a mean period of  $39.9 \pm 24.0$  months. During that period there were no new affected patients: the same 6/10 D+/R- and 12/19 D+/R+ patients had CMV infection/disease. Although there was an increase in the number of recurrent infections: four new CMV infection episodes (eight episodes in two D+/R- patients; seventeen episodes in six D+/R+ patients).

## DISCUSSION

CMV Infection during the first year post renal transplant was significant in our patients, with an incidence of 54.5%, including 60% of CMV D+/R- high-risk group. This is in accordance with other series<sup>1,7,9</sup> that report a wide variation in CMV infection incidence related with the existence of different risk factors. Although all the included patients were submitted to triple immunosuppressive regimen, including mycophenolate mophetil which is usually related with a higher incidence of CMV infection<sup>12</sup>, especially in CMV D+/R- patients, this did not seem to increase infection rates in one year follow-up of this group.

The incidence of CMV infection and disease in the D+/R- group was not superior to the incidence of the D+/R+ group. This is probably explained by the use of prophylaxis in the D+/R- group. The only patient of D-/R- group had no reported infections, which supports our management practice of excluding those patients from PCR monitoring.

CMV infection appeared later in the D+/R- group submitted to prophylaxis (24 weeks versus 11 weeks

in the D+/R+,  $p=0.018$ ), as expected<sup>2,8</sup>. This raises concerns about the risk of late and invasive CMV disease associated with mortality<sup>13</sup>, though deferring infection to a period with a less intensive immunosuppressive regimen may improve the clinical outcome. In our setting there were only two cases of CMV disease in D+/R- group and there were no important long-term complications. Late-onset CMV infection was neither more tissue-invasive nor more life-threatening. It is worth noting that all first infections occurred in the first year after transplant, and there were no new affected patients in the rest of follow-up.

The use of prophylaxis may increase the risk of antiviral resistance. Most reported cases are related to ganciclovir and the risk seems to increase with more aggressive immunosuppression and long-term prophylaxis<sup>1,2</sup>. Valganciclovir was developed to overcome the disadvantages associated with ganciclovir<sup>14</sup>, including higher propensity to the development of viral resistance, low oral bioavailability and the need for frequent administration, which can adversely affect patient adherence. In our review only one patient presented valganciclovir resistance, developing CMV disease while on prophylaxis. The use of a therapeutic dosage was not effective, requiring the reduction of the immunosuppressive regimen in order to control CMV viraemia. Despite the fact that no conclusions can be drawn about the comparison of different antiviral drugs, we consider that our results show that either ganciclovir or valganciclovir are effective in cases of CMV infection/ disease. The low number of D+/R- patients affected with recurrent infections (2 out of 10) in our review, may be an important advantage of the antiviral prophylaxis regimen adopted, needing future research.

Corticotherapy of acute graft rejection episodes increases the risk of CMV infection and disease<sup>5,15</sup>. We found no significant difference in the number of acute rejection episodes in patients with or without CMV infection, unlike the findings of other authors<sup>15</sup>. This is probably related with the small study group, comparing with larger populations of multicentric studies. In our review, one of the two graft rejection cases treated with methylprednisolone pulses that occurred in the CMV infection/ disease group ( $n=16$ ), was immediately previous to one CMV infection episode. This fact only underlines the importance of maintaining or initiating antiviral prophylaxis during

treatment of acute rejection, especially in high-risk patients of D+/R- groups. Likewise, antiviral prophylaxis may also decrease the number of acute graft rejections, as it has been demonstrated in some studies that CMV infection might be a trigger of acute rejection<sup>9,16</sup>.

CMV serostatus and infection are also considered important predictors of long-term graft survival. Nevertheless, after three years' follow-up we have not found any significant difference in glomerular filtration rate between patients with or without CMV infection. We also did not verify an increase in the incidence of bacterial, viral or fungal infections in the group with CMV infection as other studies report<sup>4,17</sup>. Both these results must be related with the small dimension of the study group in a retrospective analysis.

Other risk factors for CMV infection are certain HLA-types of the recipient<sup>18</sup> and donor-recipient HLA-mismatch. Some authors report that the adverse impact of CMV disease on graft survival is apparent only in patients with zero HLA-DR matches<sup>19</sup>. Recent experimental data<sup>20</sup> suggests that CMV infection could up-regulate allograft rejection-related surface proteins expression (like intercellular adhesion molecule-1 and HLA class I and class II antigens) in the endothelial cells of renal transplantation recipients. In our setting, we found only an association between HLA mismatch and CMV infection, but other explanatory mechanisms in addition to an increase in acute rejection episodes, should be sought. Though this association was not an independent predictor for CMV infection, it should be further studied in future reviews.

Different HLA alleles have been related with the occurrence and extent of CMV antigenaemia and also the severity of CMV primary infection. One study<sup>18</sup> showed that the presence of HLA-DQ<sub>3</sub>, may be an independent predictor for CMV infection. Also, a recent review<sup>21</sup> showed that HLA-DR<sub>10</sub> and DR<sub>11</sub> may be associated with small or non-production of CMV strain-specific neutralising antibodies, likely leading to uncontrolled severe infection. Other authors point out that the differential presentation of polymorphic CMV peptides by HLA molecules or differential recognition by host CD8+ and CD4+ T lymphocytes, or both, may modulate the immunologic response and CMV pathogenesis in renal transplantation patients.

These findings all together suggest that HLA alleles and match evaluation may play an important role in future CMV prevention strategies.

## CONCLUSIONS

Management of CMV infection in renal transplantation must always take into account risk groups and predictors of infection. Considering our findings of low-infection morbidity and low-invasiveness disease cases, the use of long-term prophylaxis in D+/R- CMV high-risk group and a preemptive therapy regimen in intermediate risk (D+/R+ and D-/R+) groups associated with efficient CMV monitoring assays, might be the optimal CMV prevention management and should be validated in prospective clinical trials. Low-risk patients (D-/R-) may probably be excluded from this prevention strategy, if other risk conditions are absent. Likewise, long-term consequences of CMV infection and side effects of antiviral therapy need to be addressed in future prospective studies. Our series also highlights that the mechanisms of CMV infection and HLA type and matching should be further studied.

**Conflict of interest statement.** None declared.

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