Consequences of Cytomegalovirus Infection in Kidney Transplant Recipients: Data Review 5 Years Later

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Abstract

Introduction: The CMV infection is a very important complication for the kidney transplant recipients. We studied this problem and published our results at 2011, following years other authors have informed their outcomes. Now we want to compare the findings.

Methodology: Descriptive retrospective observational study, health clinical records and evidence collected during the period between 1994 and 2009, of all patients who received a kidney transplant between 1994 and 2005 in the Hospital Universitari i Politècnic La Fe were reviewed.

Results: 996 patients were studied, 541 were male (60%). Clinical follow-up the patient was between 2 and 15 years. CMV serology was positive in 802 donors (83%) and 860 recipients (89%). 193 cases of early-onset infection were detected (19%: 193/996), 24 delayed-onset infection (2,6%: 24/889), 42 of early-onset disease (4,2%) and 18 cases of delayed-onset disease (2%). Early infection and disease were more frequent significantly (p <0,05) in cases of positive receptor /negative donor (D+/R-). Graft survival showed statistical association (p <0,05) with donor serology. There was no difference between the recipients that had presented acute rejection and those who do not, with respect to early infection, late infection or those with early-onset disease (7/180 vs 8/593; p 0.03). History of infection was associated with all-cause mortality (p <0,05, OR de 2,03; IC 95% 1,24-3,31) and history of disease was associated with graft loss (p <0,05, OR 1,97; IC 95% 1,14-3,43). After logistic regression, it remained significant association between graft loss as the dependent variable and age of donor or recipient (p <0,05) and between all-cause mortality, as the dependent variable, and a history of CMV infection (p <0,05).

Conclusion: History of CMV infection was associated with all-cause mortality. Similar results were previously presented and subsequent studies have continued to report on the relationship. Despite the variability between the methodologies of the various studies, the evidence is important. Therefore, it remains of primary importance to advance the study of the influence of CMV in the future of kidney transplant recipient and possibly other diseases with immunosuppression and develop measures to prevent this situation.

INTRODUCTION

The risk of infection is increased in the patient with kidney transplant. Factors favoring infections are renal failure, incompatibility in HLA system, the state of immunosuppression, inflammation and its mediators, exposure to microorganisms, and invasive procedures during surgery and postoperative. Infections can be classified according to the time of debut early, intermediate and late. Cytomegalovirus (CMV), human herpesvirus 5, is characterized by its ability latency, and may affect the patient in any of the three periods [1,2]. The disease can be caused by primary infection or reactivation of the virus itself or reinfestation with another strain in the context of immunosuppressant treatment [3-5].

More than two thirds of patients, donors or kidney transplant recipients, have been exposed to CMV prior to transplantation [4]. CMV infection can produce direct effects by the disease itself and other indirect effects such as reducing graft survival or patient, favor rejection, favor other infections, tumors or atherosclerosis.

In 2010, observing the consequences of infection in our patients with kidney transplant, we decided to measure them in the short and long term. Also, we wanted to identify factors related to its appearance and consequences. Now, 5 years later to publish those data [6], the question is what is the situation regarding CMV infection in patients with kidney transplantation and check whether our results remain valid.

METHODOLOGY

Descriptive retrospective observational study, health clinical records and evidence collected during the period between 1994 and 2009, of all patients who received a kidney transplant between 1994 and 2005 in the Hospital Universitari i Politècnic La Fe were reviewed. Induction immunosuppression therapy received by patients in general was anticalcineurinic (ciclosporina/tacrolimus), plus azathioprine or mycophenolate mofetil and corticosteroids. Patients at high risk for rejection were given thymoglobuline, and patients with risk of delayed graft function received interleukin 2 antagonists (basiliximab.
or daridzumab) and it delayed or reduced the dose of anticalcineurin. Pretransplant CMV serology is determined to donor and recipient. If it was a positive donor / negative recipient, the recipient is administered intravenous globulin. Prophylactic therapy anti-CMV was changed over the years of the study, the first patients received acyclovir and subsequently used ganciclovir or valganciclovir from start improvement in graft function, treatment was continued 90 days. In case of illness, immunosuppression was reduced and ganciclovir and intravenous globulin was administered until clinical improvement and decreased viral load.

Because of the long period of revised monitoring, a diagnostic method were varied over time, with advances in this field, initially with the use of serology, then antigenemia and finally was able to use PCR determination. Isolation in cell tissue depended on whether the patient biopsy was performed.

For this, the diagnosis of CMV infection was by:
- Serology: increased IgG antibody titer or positive IgM (previously negative), usually determined by Enzyme-Linked Immunosorbent Assay (ELISA).
- Isolation by urine culture, blood, throat swab and bronchoalveolar lavage.
- Determination of pp65 antigenemia in peripheral blood leukocytes.
- Quantification of CMV by Polymerase Chain Reaction (PCR) in peripheral blood.

CMV infection was considered the active presence of the virus without laboratory or clinical impact on the function of organs or systems. CMV disease was considered to viral presence and typical clinical or disturbances in blood analysis.

Statistical analysis was performed using SPSS 17. A level of statistical significance of 95% was assumed (a = 5, p >0,05), and the accuracy of estimates was calculated with a confidence level of 95% (IC 95%).

RESULTS

996 patients were studied, of these 107 was missing; 541 were male (60%). Recipients have a mean age of 47 years (17-75) and donors 38 years (3-73). Clinical follow-up the patient was between 2 and 15 years. Prophylactic treatment he received was acyclovir 20 patients (2,4%), ganciclovir 478 (56,8%), valganciclovir 166 (19,7%) and no treatment 178 (21%).

214 patients (24%) lost the graft with a mean graft survival of 55 months, the most frequent causes were chronic allograft nephropathy (n=48) and acute rejection (n=17). They died 77 patients with functioning graft, the most frequent causes of death were neoplasia (n = 24) and cardiovascular disease (n = 22).

CMV serology was positive in 802 donors (83%) and 860 recipients (89%). 193 cases of early-onset infection were detected (19%; 193/996), 24 delayed-onset infection (2,6%;24/889), 42 of early-onset disease (4,2%) and 18 cases of delayed-onset disease (2%). Early infection and disease were more frequent significantly (p <0.05) in cases of positive receptor / negative donor (D+ / R-) (Table 1). Most cases of CMV infection were diagnosed by changes in serology, since patients were asymptomatic and no extraordinary tests were performed. The CMV disease was diagnosed by changes serology in 30%, by detection of antigen in 20%, by PCR detection in 42% and virus isolation in tissue in 5% of cases.

The disease usually presents as fever and viral syndrome in 20 patients, and with affected organs in others, the most common digestive (27), followed by pneumonia (9), allograft dysfunction (2) and retinitis (1). They need a total of 1283 days of hospital stay, with a mean of 27 days per patient, and 183 days of hospitalization in Intensive Care Unit. During early or late CMV disease, 4 patients lost the graft and 6 died, 16.6% of those affected (10/60).

Graft survival showed statistical association (p <0.05) with donor serology, being higher in recipients with negative donor (OR1,54, IC95% 1,01-1,18). The survival time of graft was also higher in recipients of negative donor (D- 71 months, D+ 53 months, p <0,05). Different combinations of donor-recipient serology not associated with graft loss or death.

Early-onset infection depending on the type of prophylaxis was significantly (p <0.05) higher among those who received acyclovir (10/29) and those not receiving prophylaxis (51/178) than ganciclovir (93/477), or valganciclovir (29/166); this is not observed about early or late disease. Mortality was lower in the groups treated with ganciclovir or valganciclovir (p 0.007).

There was no difference between the recipients that had presented acute rejection and those who do not, with respect to early infection, late infection or those with early-onset disease (7/180 vs. 8/593; p 0.03). Regarding treatment with antilymphocyte antibodies or steroid high dose, his administration was not associated with early and late-onset disease (12/305 8/305, 9/158 6/158 p >0.05).

History of infection was associated with all-cause mortality (p <0,05, OR de 2,03; IC 95% 1,24-3,31) and history of disease was associated with graft loss (p <0,05, OR 1,97; IC 95% 1,14-3,43) (Table 2). After logistic regression, it remained significant association between graft loss as the dependent variable and age of donor or recipient (p <0.05) and between all-cause mortality, as the dependent variable, and a history of CMV infection (p <0.05).

DISCUSSION

In 2010, after checking in clinical practice the consequences of CMV infection and disease in our kidney transplant patients, we decided to quantify these facts and reviewed the data of 10 years of follow-up: were published the following year, in 2011 [6]. At that time it was available much information about the cytomegalovirus in kidney transplant recipients, but there was
Infection and early-onset disease were more frequent in the negative recipients receiving a graft of positive donors. These results had already been informed to prior series [3,4,7,11], and continue to be reported in the new series[16,20]. However in most multivariate analyzes, serology recipient and donor does not show significant association with infection or disease [14,19]. Also in our patients, the possibilities to graft survival and the time was lower in patients receiving donor graft +, similar to the results of McGee et al in African-American patients [20], but this association was not maintained in the multivariate analysis of our data. Previous authors had already found the no relationship between serology to donor-recipient pair and graft survival, if the data were adjusted for age, thus is not necessary to assign certain combination of serology CMV couples transplant [7,30].

We observed association between acute rejection and CMV late-onset disease, however acute rejection was not associated with early infection or disease; Santos et al. [21], subsequently confirmed this finding in their study of more than 15,000 kidney transplant. The relationship between acute rejection and CMV can be bidirectional, since the pathogenesis and management of one, could favor the presentation of the other, and vice versa [3,14]. The study of this possible association requires strict control of confounding factors and chronology. In the previous and subsequent literature our study we found contradictory results; generally they report the no association between CMV infection and acute rejection [7,19,20,31], but some authors report increase in acute rejection during treatment of CMV disease, while they reduced immunosuppression [14,32].

Therapy with antilymphocyte antibodies or intravenous steroids high doses was not associated with CMV disease. Before and after our study, other authors published contradictory outcomes [4,16,17,19,20,22,25,33-36].They are needed more powerful studies to clarify this point.

Prophylactic therapy with ganciclovir or valganciclovir was associated with lower early infection and with lower all-cause mortality. No differences were observed for CMV disease. Similar results were known in previous series [4,37,38]. All times different authors have done recommendations to dose reduce or avoid treatment in cases where it is not necessary, given the risk of leucopenia or rejection [13,38,39].

History of CMV infection was associated with all-cause mortality and CMV disease was associated with graft loss. The association CMV infection with all-cause mortality was maintained after logistic regression. Similar results were previously presented [7,11,31]. Subsequent studies have continued to report on the relationship between CMV and mortality or graft loss [15,17,21,24], also they show an association between CMV and arteriosclerosis or cancer [1,6,40]. Despite the variability between the methodology of the various studies, the evidence is important. Therefore, it’s important to deepen the study of epidemiological factors, keep the possible diagnosis of CMV infection and disease present and develop the therapeutic possibilities in order to improve patient survival and renal graft.

REFERENCES


