 Int J Hum Genet, 12(1): 69-71 (2012)

Pre and Post Transplant *Cytomegalovirus* (CMV) Infection and Successful Graft Survival

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KEYWORDS CMV. Graft Survival. Allograft

ABSTRACT Allograft rejection continues to be a major problem and is the leading cause of graft loss in renal transplant recipients. Histocompatibility testing plays an important role in selection of donors for transplantation. A correct assignment of HLA antigens is considered important given that inadequate HLA matching of patient-donor pairs is associated with rejection in kidney transplantation. The present study was to assess a long and successful graft survival in end stage renal failure patients. 50 live related renal transplant patient-donor pairs were selected at random (n=100). Serological HLA A, B and DR typing results were compared to typing results obtained using sequence-specific primers in the polymerase chain reaction. Evidence of CMV infection was also monitored by CMV-PCR and CMV antigenemia pp65 assay on all patients and compared with the occurrence of acute rejection in the post transplant period. 4 patients developed CMV disease with graft dysfunction, during the first 12 weeks post-transplantation, which responded to specific anti-viral therapy and reduction in immunosuppression. Our results reveal that Frequent monitoring of CMV-PCR or CMV pp65 antigenemia and prompt start of treatment in such patients is required. Early diagnosis of CMV antigenemia improves graft and patient survival.

INTRODUCTION

Since the advent of organ transplantation, the transplant centers are aiming at better quality of life with longer graft survival for renal allograft recipients. Host immune response plays the key role in acceptance of the allograft. Detailed immunological investigation can improve the long-term success of transplantation in individual cases of end stage renal failure (Ting 1978). Although the success rate of clinical transplantation has improved in the past two decades, allograft rejection continues to be a major problem and is the leading cause of graft loss in renal transplant recipients. A number of factors, including the use of newer immunosuppressive drugs, pre-transplant blood transfusions, better matching of donor-recipient pairs, organized follow-up care and optimal management of the various post-transplant complications have contributed to the recent improvement in clinical results (Persij 1982; Koka 1990; Yuge 1991).

It has been recognized that the specificity of antigens involved in graft rejection is under genetic control. The HLA system plays a significant role in determining the acceptance or rejection of a tissue transplant (Terasaki 1991). HLA typing by serology is the most commonly used method in routine clinical settings (Dausset 1958; Amos 1966). Serology is a quick and convenient method, but it is hindered in many cases by serological cross reactivity, non-availability of antisera, and decrease in expression of HLA antigens, particularly in immunosuppressed patients (Ray 1979). The present study extends the low-resolution system into a serologically equivalent system. The principle of PCR-SSP is that each individual allele (making up a serological specificity) is amplified by a primer pair exactly matched to that region (Olerup and Zetterquist 1991). The importance of HLA typing was further documented by several reports that pre-existing leukocyte antibodies could induce hyper acute rejection (William 1968; Bradley 1985; Ettiner and Robertson 1987).

Cytomegalovirus (CMV) disease is more frequent in allograft recipients who are seronegative and receive kidneys from seropositive donors. In recent time, CMV infection has been found to have adverse effects on graft function

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(Murray 1994; Yamamoto 1994). Increased incidence of CMV infection could be due to the use of higher immunosuppressive, especially, receptor specific antibodies used for induction therapy or treatment of rejection. This study was undertaken to have a long and successful graft survival in end stage renal failure patients.

MATERIALS AND METHODS

This study comprised of 50 renal failure patients, who underwent live related renal transplantation and their perspective donors. CMV IgG and IgM by ELISA test was performed from serum samples of patients and donors, prior to transplantation. Evidence of CMV infection (Karen 1989) was monitored by the Human Cytomegalovirus Phosphorylated matrix protein (pp65) and related phosphoprotein (pp71) genes. CMV PCR test was performed from DNA samples of patients using Biocore, Korea, and also by CMV antigenemia pp65 lower matrix protein in leukocytes from EDTA blood samples, DiaSorin, Saluggia (VC), Italy, and compared with the occurrence of acute rejection in the post transplant period and graft function. The level of significance was reported in terms of probability (p) value.

RESULTS

Pre and post transplant CMV infection by PCR in Renal Allografts for donors and recipients and compare it with graft function. Fifty renal allograft recipients and their perspective donors are included in the study (N=100). CMV infection was defined by seroconversion of CMV antibody, four-fold increase of serum anti-CMV IgG in successive blood sampling or the presence of anti-CMV IgM antibody. 36 out of 100 transplant recipients and donors were CMV-IgG positive. Five were positive for CMV-IgG and IgM both and 6 were positive for CMV-IgM only. All these patients were given anti-viral drugs, prior to transplantation.

Evidence of CMV infection was also monitored by CMV-PCR and CMV antigenemia pp65 assay on all patients and compared with the occurrence of acute rejection in the post transplant period. One patient's antigenemia preceded the diagnosis of rejection, who responded to reduction in immunosuppression. 4 patients developed CMV disease during the first 12 weeks post-transplantation, which responded to specific anti-viral therapy (Table 1).

Table 1: Pre and post transplant CMV status

CMV	*N=100*
CMV IgG	36
CMV IgM	6
CMV IgG and IgM	5
CMV PCR (post Tx)	4

DISCUSSION

The results of HLA-A, -B and -DR typing using serology were compared to the results of typing with PCR-SSP of all recipient-donor pairs. In different situations, when the expression of HLA antigens on the cell surface is down-regulated, it is impossible to type by serological methods and it is advisable to use molecular typing such as PCR-SSP. In addition, the PCR-SSP technique does not require the viable cells necessary for serological typing and also allows determination of the subtypes of HLA antigens very clearly. CMV infection is ubiquitous in renal transplant patients who are seronegative and receive kidneys from seropositive donors. Most of these infections are due to reactivation and are asymptomatic. Our data reveals that CMV infection also leads to acute deterioration in graft function and it may also result in immunosuppression thus allowing infection by other opportunistic agents. Pre-emptive peroral ganciclovir treatment up to 12 weeks post-transplantation, effectively prevents CMV disease in renal transplant recipients for which frequent monitoring of CMV pp65 antigenemia and CMV-PCR is required (Sagedal 2000).

CONCLUSION

Our data reveals that CMV infection also leads to acute detoriation in graft function and it may also result in immunosuppression thus allowing infection by other opportunistic agents. Pre-emptive peroral ganciclovir treatment up to 12 weeks post-transplantation, effectively prevents CMV disease in renal transplant recipients for which frequent monitoring of CMV pp65 antigenemia and CMV-PCR is required.

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