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Positive donor and negative recipient cytomegalovirus status is a detrimental factor for long-term renal allograft survival

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Abstract In 524 allogeneic cadaveric kidney transplants, the impact of cytomegalovirus (CMV) donor/recipient status on the incidence of CMV infection, CMV disease, early and long-term graft, and patient survival have been analyzed with respect to rejection episodes. Most CMV infections (59%) and diseases (17%) were found in CMV-negative recipients of CMV-positive kidneys. The 1-year function rate of CMV-positive kidneys (75%) dropped about 10% below that of CMV-negative organs (85%), and in the case of CMV-negative recipients an additional graft loss of more than 10% happened within the 4th and 5th years (5-year graft survival pos./neg.: 56%). This detrimental effect was exaggerated if it coincided with antibody-treated rejection episodes.

Key words Kidney transplantation
Follow-up studies · Cytomegalic inclusion disease · Risk factors
Survival analysis

Introduction

Cytomegalovirus (CMV) infection has a high morbidity and increased mortality in immunocompromised patients. Because there are experimental and clinical indications for a detrimental influence on long-term organ function [3, 6], we tried to examine the long-term effect of CMV infection in cadaveric renal transplantation with respect to the donor/recipient CMV status and the influence of rejection episodes.

Patients and methods

Study population

A retrospective analysis of the long-term results in 524 patients undergoing kidney transplantation at our center in the years 1987–1991 with known donor/recipient CMV status was carried out, dividing them into four groups: CMV-negative patients who received CMV-positive organs (pos./neg.); CMV-positive recipients with positive donors (pos./pos.); seropositive patients with negative donors (neg./pos.); CMV-negative organs in negative recipients (neg./neg.).

Because 308 CMV-positive and 216 CMV-negative organs were allocated in the 5-year period, the largest numbers of patients (167 and 141) are found in the groups with pos./neg. and pos./pos. CMV status. In the last two groups, 101 and 115 transplants with a neg./pos. and neg./neg. combination were examined. We detected the incidence of serologically confirmed CMV infection as well as of clinically diagnosed CMV disease in the four different groups.

Other factors of potential influence on long-term graft function showed no significant difference between the four cohorts; in particular, the percentage of patients with rejection episodes did not correlate with the CMV risk (Table 1). The 1–5-year patient and graft survival was analyzed with respect to the donor/recipient CMV status and rejection episodes. Statistical analysis was performed with the chi-square and Students *t*-test for comparing survival probabilities, the log rank test was used. *P* values less than 0.05 were considered significant.

Table 1 Basic data and risk factors in the different donor/recipient cytomegalovirus (CMV) constellations

CMV donor/recipient:	pos./neg.	pos./pos.	neg./pos.	neg./neg.
Renal transplants ($n=524$)	167	141	101	115
Mean follow-up (years)	3.9	3.9	3.7	3.7
Donor age	37	36	33	33
Recipient age	45	46	47	44
PR antibodies	7%	9%	11%	10%
Retransplants	18%	23%	29%	25%
HLA mismatches	1.8	1.8	1.9	1.6
ATN incidence	53%	55%	46%	49%
Patients with rejection episodes	44%	52%	42%	43%
CMV infection	59%	48%	18%	7%
CMV disease	17%	7%	2%	2%

Immunosuppressive protocol

Patients received triple-drug induction therapy (cyclosporin A, azathioprine, steroids) in the case of a first transplant and panel-reactive antibodies not exceeding 30%. Otherwise, a quadruple-drug induction therapy with an additional 7 days of antibody treatment was instituted. The maintenance therapy consisted of cyclosporine alone in the majority of our patients.

In the case of rejection, defined in this study as any episode of anti-rejection treatment, a 3-day steroid bolus treatment was the first therapeutical step. Following histologically, confirmed rejection, patients were treated with a 7-day course of poly- or monoclonal antibodies.

CMV prophylaxis and therapy

CMV-negative patients receiving organs from CMV-positive donors, as well as those taking antibody treatment against rejection, received prophylactic doses of CMV hyperimmunoglobulin 50–100 U/kg body weight at 14-day intervals, whereas in the case of CMV disease 100–200 U/kg b.w. were given for 5 consecutive days [10]. DHPG was not available during the study period.

Results

As expected, a strong correlation was found between positive donor CMV status and recipient infection as well as CMV disease. More than half of all diseases were diagnosed in the pos./neg. group (Table 1). No significant increase of CMV disease in steroid-treated rejections could be found, whereas in the case of antibody-treated rejection episodes, the risk of CMV disease is two- to threefold higher than in recipients who did not reject CMV-positive organs.

The 1-year graft function of CMV-negative organs is about 85%, whereas both groups with CMV-positive organs have function rates of 75%. This deterioration in graft function increases in the 4th and 5th years in the group of CMV-negative recipients of positive organs, so that a significantly decreased long-term function of 56% after 5 years is found for this group of patients at risk (Fig. 1).

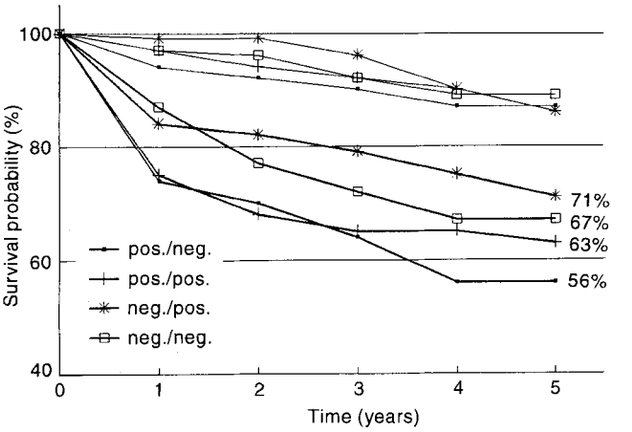

Fig. 1 Patient and graft survival with respect to donor/recipient CMV status

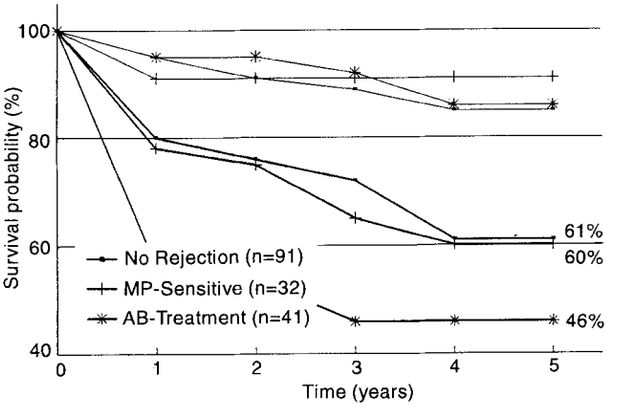

Fig. 2 Patient and graft survival for pos./neg. CMV status with respect to rejection episodes

The patients' survival rates did not differ significantly, although it should be mentioned that the only two cases of CMV-associated lethal complications in the whole study population occurred in this group with pos./neg. CMV status. In the group of patients with the highest risk of

primary CMV infection (pos./neg.), the coincidence with antibody-treated rejection is most detrimental, as demonstrated in Fig. 2. More than half of the organs are lost within the first 3 years, whereas a significant impact on patient survival cannot be detected.

Discussion

The incidence of CMV infection and disease as well as the patient and graft outcome related to the donor/recipient CMV status vary widely in the literature concerning cadaveric renal transplantation. There are publications including multicenter data from tissue typing registries that show no significant impairment of graft and patient survival [1, 4, 5], whereas other studies, also including multicenter trials, reveal a marked influence on graft and/or patient outcome [2, 8, 9, 11].

In a first long-term follow-up our data emphasize that there is indeed a detrimental effect of CMV-positive kidneys on early graft function and an additional significant decrease of long-term function in the case of CMV-negative recipients. This deterioration seems to be brought about via manifestation of the CMV disease and is exaggerated if it coincides with acute rejection episodes. These results may show some improvement in the near future because of new diagnostic and therapeutic tools which we did not have at our disposal during the study period. If not, CMV matching would be justified [7, 12].

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