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Early detection of primary cytomegalovirus infection after heart and kidney transplantation and the influence of hyperimmune globulin prophylaxis

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Abstract. A randomized study of prophylaxis with hyperimmune globulin (HIg) was performed in 28 cytomegalovirus (CMV)-seronegative heart and kidney recipients with CMV-seropositive donors who were extensively monitored for active CMV infection and CMV disease. Detection of CMV antigen in peripheral blood granulocytes (antigenemia) was the first sign of primary CMV infection, generally occurring several weeks before IgM or IgG anti-CMV antibodies were detected and before positive cultures appeared. A correlation was found between rejection treatment with OKT3 or ATG, severity of CMV disease, and graft loss. Rejection treatment had no influence on incidence of CMV transmission. Primary CMV infection occurred most often in older patients with older donors. No beneficial effects were seen with HIg prophylaxis, which was administered from week 1 until week 7 after transplantation. Incidence of primary CMV infection was equal in both groups (50%) and no influence on the severity of primary CMV infection was seen. The only effect that was seen was on the time from transplantation to detection of active CMV infection, which was prolonged by HIg prophylaxis.

Key words: CMV, hyperimmunoglobulin prophylaxis – Hyperimmunoglobulin prophylaxis, CMV – Kidney transplantation, CMV – Heart transplantation, CMV

Active cytomegalovirus (CMV) infections frequently occur after organ transplantation. In kidney transplantation, CMV disease is related to low allograft survival [25] and in heart [7, 18] and heart/lung transplantation [11] to increased patient mortality. Primary CMV infections after transplantation usually have a higher incidence of development of CMV disease than recurrent CMV infection in CMV-positive recipients [19]. Passive immunization with hyperimmune globulin (HIg) prevented CMV disease in CMV-seropositive kidney transplant recipients studied by Steinmuller et al. [21]. However, these results could not be confirmed in other studies [14]. Therefore, it has been recommended that HIg treatment be restricted to nonimmune patients receiving organs from CMV-seropositive donors [13, 14]. In this setting, prophylaxis with HIg after transplantation reduced CMV disease in kidney [4, 20], heart [6], and liver transplantation when combined with acyclovir [22]. Incidence of primary CMV infection was not reduced by HIg prophylaxis in heart transplantation [15].

In kidney transplantation, CMV is not always transmitted from a CMV-seropositive donor to a CMV-negative recipient. Incidence for kidney transplantation has been reported to range from 58% up to 83% [1, 9, 10, 18, 25] and for heart transplantation from 83% up to 89% [16, 26]. Factors influencing transmission can be of patient origin (age, rejection therapy) or of donor origin, as it was shown in pairs of recipients from one kidney donor that CMV was transmitted either to both patients or to neither of them [3].

To determine the frequency of primary CMV infection and CMV disease after heart and kidney transplantation, we extensively monitored 28 pretransplant, CMV-seronegative patients with CMV-seropositive donors. Half of these patients were selected to receive high-dose HIg prophylactically in a randomized trial. Also analyzed were other factors influencing the occurrence of primary CMV infection and CMV disease, such as age, number of mismatches, and rejection treatment.

Patients and methods

Patients

Patients who entered the randomized hyperimmune globulin trial. The study population for the anti-CMV hyperimmune globulin (HIg) trial included CMV-seronegative patients receiving a heart or kidney transplant from CMV-seropositive donors. Patient characteristics are cited in Table 1. In half of these patients, HIg (Cytotect, Biotest Pharma, Frankfurt, FRG) was administered prophylactically at 1, 2, 3, 5, and 7 weeks after transplantation, 1 ml/kg body

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Table 1. CMV-seronegative patients with CMV-seropositive donors

	HIg prophylaxis		No prophylaxis	
	Heart	Kidney	Heart	Kidney
Number	3	11	3	11
Male/female	3/0	7/4	3/0	4/7
Age: average (years)	49	35	44	32
range (years)	45–56	12–62	33–54	5–65

Table 2. Primary CMV infection and CMV disease in relation to HIg treatment

	Total (heart/kidney) transplant recipients	HIg prophylaxis	
		With	Without
No primary infection	14 (1/13)	7 (1/6)	7 (0/7)
Asymptomatic or mild symptoms	9 (5/4)	4 (3/1)	5 (2/3)
CMV disease	5 (0/5)	3 (0/3)	2 (0/2)
Total	28 (6/22)	14 (4/10)	14 (2/12)

weight intravenously, in a randomized setting. Cytotect was chosen because of its high CMV-neutralizing capacity in vitro. Protein content of the HIg was 100 mg/ml. Treatment was instituted 1 week after transplantation, when the CMV serology of the donor and recipient were known. The last dose was given 7 weeks after transplantation since primary CMV infection (or disease) is usually manifest within 7 weeks after transplantation. The dosage schedule was also based on monitoring of IgG anti-CMV serum levels in eight patients. In these patients the serum IgG-anti-CMV levels remained positive by ELISA (serum dilution 1:400) during the whole period of prophylaxis. Two kidney recipients received a kidney from a living related donor (LRD); one of these recipients received HIg prophylaxis.

All patients were closely monitored for active CMV infection weekly from week 2 until week 7 after transplantation; from then on it occurred every 2 weeks until at least 3 months after transplantation. Symptomatic CMV infections were treated with ganciclovir (2.5–5 mg/day) for 2 weeks.

Rejection treatment

Maintenance immunosuppressive therapy consisted of cyclosporin and low-dose steroids or imuran and low-dose steroids in the kidney recipients and of triple therapy with cyclosporin, imuran, and steroids in the heart transplant recipients.

Rejections were treated with high-dose steroids (HDS; 200 mg dexamethasone or 1000 mg methylprednisolone) in both the heart and kidney recipients. Severe and persistent rejections that did not resolve after HDS treatment were treated with OKT3 (Orthoclone, Ortho Pharmaceuticals, Raritan, N.J.) or ATG (National Institute for Public Health and Environmental Protection, Bilthoven, The Netherlands).

Definition of active CMV infection and CMV disease

Primary, active CMV infection was defined as antigenemia and/or positive cultures, together with or followed by CMV seroconversion.

CMV disease was diagnosed when active CMV infection was present and when the patients were suffering at the same time from fever (38.5°C for at least 2 days) and leukocytopenia or elevated hepatic enzyme levels (mild CMV infection) that were not due to other causes. Serious CMV disease with organ involvement included kidney dysfunction and kidney loss, retinitis, and pneumonia. CMV disease in six patients was treated with ganciclovir, 5 mg/kg twice a day for 7 or 15 days, if necessary, adapted to kidney function.

Detection of active CMV infection

Detection of CMV antigenemia. For detection of active CMV infection in peripheral blood, polymorphonuclear leukocytes (PMNs) were isolated by ficoll density centrifugation to remove mononuclear cells. The bottom fraction was enriched for PMNs by dextran sedimentation. Residual erythrocytes were lysed and cytospin preparations were made from the PMNs (1.5×10^5 cells/cytospin). From each blood sample, at least two cytospin preparations were incubated with a combination of two monoclonal antibodies (C10 and C11; Biotest, Dreieich, FRG) against CMV antigen (pp65). One control cytospin preparation was incubated with diluent. Specific binding was visualized by incubation with goat anti-mouse IgG labelled with peroxidase (TAGO, Burlingame, Calif.), followed by incubation with 3-amino-9-ethylcarbazole and 0.012% H_2O_2 in citric acid buffer as substrate. Positive nuclear staining was defined as antigenemia [17].

Cultures of urine, saliva, and buffy coat cells

Quick cultures of urine, saliva, and buffy coat cells were performed on fetal fibroblasts in 96-well plates. The same cells were used for buffy coat cultures as for the cytospin preparations. Samples were diluted in culture medium containing 10% fetal calf serum and were inoculated on the fetal fibroblasts, six wells per sample. After 2 h of incubation, the plates were washed and incubated for another 2 days with fresh culture medium. CMV infection in the fetal fibroblasts was detected by using monoclonal antibodies against CMV immediate early antigen (IEA; Biosoft clone E-13, Paris, France) and fluorescence staining [8]. Positive cultures of buffy coat cells were defined as viremia, positive cultures of urine or saliva as CMV excretion.

CMV serology

Specific anti-CMV IgG and IgM antibodies in serum were measured using a commercially available ELISA (Sorin Biomedica, Saluggia, Italy).

Statistical evaluation

Statistics were calculated using Fischer's exact test [F] to determine differences between patient groups or the paired or unpaired Student's *t*-test [S] for comparison between two means.

Results

Primary CMV infection in relation to HIg treatment

Primary CMV infection occurred in 9 of the 22 (41%) kidney and 5 of the 6 (83%) heart transplant recipients who were CMV-seronegative before transplantation and who had a CMV-seropositive donor (Table 2). HIg prophylaxis had no influence on the incidence of primary infection, occurring in 7 of the 14 patients with HIg prophylaxis and in 7 of the 14 patients without treatment.

CMV disease in relation to HIg treatment

HIg treatment also did not influence the severity of CMV disease; CMV disease occurred in three patients with and in two patients without HIg prophylaxis (Table 2). Severe CMV disease was only seen in kidney transplant reci-

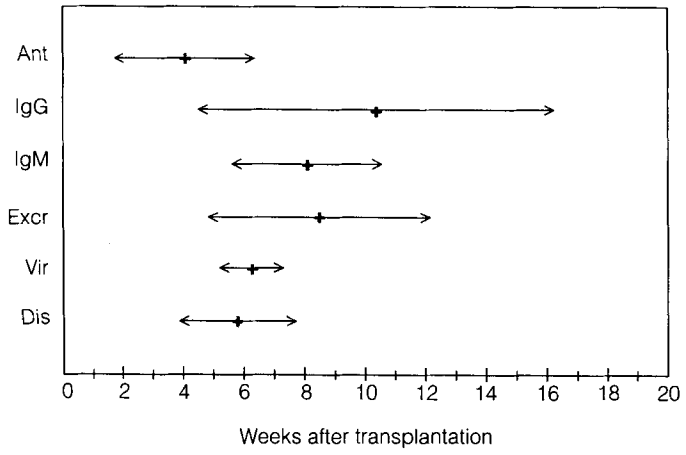

Fig. 1. Time sequence of detection of primary infection. Ant, Antigenemia ($n = 14$); IgG, IgM, detection of anti-CMV IgG and IgM antibodies ($n = 14$, $n = 13$); Excr, CMV excretion in urine or saliva ($n = 10$); Vir, viremia ($n = 4$); Dis, CMV disease ($n = 10$). Antigenemia was detected significantly earlier after transplantation than positive IgG, IgM, or CMV excretion ($P < 0.01$ [S]). *Arrows* indicate the standard error

pients. Asymptomatic and mild symptomatic primary CMV infections were seen in nine patients, four of whom had prophylaxis with HIg. On the average, CMV disease occurred 5.8 ± 2.0 weeks after transplantation, both in patients who received HIg prophylaxis and in those who did not.

Ganciclovir treatment was given to five kidney recipients with severe CMV disease and to one heart transplant recipient. Two kidney recipients who received kidneys from the same CMV-positive donor both developed CMV disease; in one patient pneumonia developed and in the other, who had received HIg, retinitis. In another patient pneumonia developed, one patient had renal dysfunction, and in yet another fever, leukocytopenia, and hepatic dysfunction were seen. Two kidney recipients had persistent infection and needed repeated ganciclovir treatment.

Ganciclovir was also administered to one heart transplant recipient with *Pneumocystis carinii* pneumonia who had, at the same time, primary CMV infection.

Graft survival was significantly lower in the patients who had CMV disease (four out of five lost their kidney) than in those having no primary infection or mild infection (graft loss in 3 out of 20, $P < 0.01$ [F]). There was no relationship between HIg treatment and graft loss.

Detection of primary CMV infection and HIg treatment

Primary CMV infection was initially detected by antigenemia in 12 of the 14 patients. In two patients, both heart transplant recipients, CMV excretion and IgM antibodies were the first signs of CMV infection, which was followed by antigenemia. The sequence of detection of primary CMV infection with the different methods is shown in Fig. 1. Antigenemia was detected significantly earlier than IgM ($P < 0.01$ [S]), IgG ($P < 0.01$ [S]), and CMV excretion ($P < 0.01$ [S]). Viremia was only detected in four patients, on the average 6.3 ± 1.9 weeks after transplantation; one of those had CMV disease.

Three of the four patients without CMV excretion were treated with ganciclovir when only antigenemia was present. In six of the seven patients prophylactically treated with HIg, antigenemia was detected 4 weeks or later after transplantation, whereas in those not treated with HIg, antigenemia was detected earlier (within 4 weeks after transplantation in six out of seven patients; $P = 0.01$ [F]). No influence of HIg treatment on the appearance of IgM, IgG, or CMV excretion was observed, except in one patient with HIg prophylaxis, in whom no anti-CMV IgM antibodies were detected. In all other primary infections IgM was present.

Rejection treatment

Maintenance immunosuppressive therapy did not differ between patients with or without HIg prophylaxis.

Rejection treatment with OKT3 was instituted in 11 patients within 6 weeks after transplantation. Five of these patients received HIg prophylaxis. Primary CMV infection occurred both in patients who were treated for rejection within 6 weeks after transplantation and in those not treated for rejection (Table 3). Time of rejection treatment had no influence on the occurrence of primary CMV infection. Four patients were treated with OKT3 immediately after transplantation; two of these patients became primarily infected with CMV. Another seven patients were treated 1–5 weeks after transplantation; of these patients, three had a primary CMV infection. Other patients were treated later on. However, rejection treatment did influence the severity of infection in patients in whom primary CMV infection occurred. Severe CMV disease was more often present in patients with primary CMV infection who were treated with OKT3 or ATG ($P = 0.02$ [F]). Treatment with HDS did not influence the severity of CMV disease.

Age

Recipient age was, on the average, 29 ± 16 years in the patients in whom no primary CMV infection occurred; donor age in this group was 32 ± 16 years. Recipient age was significantly higher in patients in whom asymptomatic or mild symptomatic primary CMV infection occurred

Table 3. Early rejection treatment and influence on CMV infection

	Number (heart/kidney transplantation)	Steroids		OKT3 or ATG	
		Yes	No	Yes	No
No primary infection	14 (1/13)	10	4	7	7
Asymptomatic or mild symptoms	9 (5/4)	5	4	1	8[a]
CMV disease	5 (0/5)	3	2	4	1[a]

[a] More OKT3 or ATG rejection treatment given in patients who developed CMV disease, $P = 0.02$ [F]

(48 ± 13 years, $P < 0.01$); donor age in this group was 47 ± 4 years. CMV disease occurred in both young kidney recipients ($n = 2$) and older patients ($n = 3$); in this group, recipient age was 32 ± 20 years, donor age 37 ± 25 years.

Other factors

No relationship was found between occurrence of primary CMV infection or CMV disease and the number of HLA-A, -B, -C and -DR mismatches.

Ischemia time and perfusion liquid (Euro-Collins, University of Wisconsin, or HTK solution) had no influence on whether or not primary infection occurred or on the severity of CMV disease.

Discussion

In kidney [7, 11, 18, 25] and heart and lung transplantation [11, 18] it has been shown that CMV disease, especially in primary infections, is associated with low graft survival. In kidney recipients, primary CMV disease diminished from 60% to 21% after prophylactic HIg treatment [4, 20]. In heart transplantation, beneficial effects of HIg prophylaxis on primary CMV disease have also been seen [6, 14, 15]. In liver transplantation, primary CMV disease diminished from 71% to 24% [22] in CMV-seronegative recipients receiving prophylaxis with HIg combined with acyclovir. These effects of HIg prophylaxis are probably due to direct neutralization of CMV by the antibodies in the hyperimmune globulin treatment.

In CMV-positive recipients, cellular immune responses are important for the prevention of active CMV infection [2]. Cellular immunity to CMV is absent in CMV-negative recipients of CMV-positive donors. Other mechanisms of action of HIg prophylaxis may include the enhancement of cellular immunity by antibodies, e.g., antibody-dependent cellular cytotoxicity. Like CMV neutralization, this may also influence the incidence and severity of CMV infection in patients at risk for primary infection.

In our study, however, no beneficial effects of HIg prophylaxis were seen on the frequency of primary CMV infection or on the severity of CMV disease. The dosage regime used was chosen because primary CMV infections (or disease) usually become apparent between 1 and 7 weeks after transplantation and because the CMV serology of the donor and recipient are known 1 week after transplantation. The schedule was comparable to that in other studies [14, 15, 22]. CMV disease in the HIg-treated group was indeed present during prophylaxis. Within 7 weeks of prophylaxis, we detected an IgM and IgG anti-CMV response in all patients who had a primary CMV infection. Therefore, it seemed useless to continue administration of prophylaxis with HIg after 7 weeks.

There are several possible reasons why we did not see any beneficial effects of the HIg prophylaxis. In the first place, the time of administration of the first dose may be an important factor; in our study this was relatively late, 1 week after transplantation. Second, larger numbers of patients may be necessary for positive effects to occur in a statistically significant fashion. Third, the cost effectiveness of HIg prophylaxis has been shown to be highly dependent on the risk of development of serious CMV disease [24]. In our study, the overall incidence of serious CMV disease in the CMV-negative recipients from CMV-positive donors was low, only 5 out of 28 (18%).

Rejection treatment with OKT3 or ATG had a pronounced effect on the severity of CMV disease. Graft survival was significantly less in the patients in whom severe CMV disease had developed, despite ganciclovir. Others have also shown that graft survival did not improve despite ganciclovir therapy given after CMV disease had developed [5]. Early treatment or prophylaxis with ganciclovir may prevent severe CMV disease and improve graft survival in patients with primary CMV infection who need strong rejection treatment.

Incidence of primary CMV infection in CMV-seronegative kidney recipients with CMV-positive donors was low in our study: 41% compared to the 58%–83% mentioned in other studies [1, 9, 10, 18, 25]. In the heart transplant recipients, primary infection was found in 83% of the patients, comparable with 83% and 89% in other studies [16, 26]. Incidence was not influenced by HIg prophylaxis, something that was also shown by Metselaar et al. [15] for heart transplantation. In addition, in our study, rejection treatment with OKT3 or ATG did not influence the occurrence of primary CMV infection, nor did the number of HLA mismatches. This suggests that allogeneic reactions in the donor kidney or heart and the immunosuppressive status (HIg prophylaxis and rejection treatment) of the recipient are not important for transmission of CMV but do have some influence on the severity of CMV infection.

Other factors might be more important in determining whether or not CMV is transmitted with the donor organ. Perhaps CMV is not always present in the donor organ or not able to reactivate from the donor organ. Donor factors are important, as it was shown in CMV-negative recipient pairs from the same CMV-seropositive kidney donor that either both recipients became primarily infected with CMV or neither of them did [3]. Some CMV strains may be more infectious and pathogenic than others. Also, infection with multiple CMV strains is possible [12, 23] and so the chance of transmission with a donor organ may be higher with multiply infected donors. Indeed, we observed severe CMV disease in two patients receiving kidneys from the same donor.

Although donor and recipient age did not influence severity of CMV disease in our study, relatively more primary CMV infections were seen in older recipients with older donors. We found no relationship between CMV transmission and organ preservation.

Another interesting finding was that primary CMV infection was first detected by antigenemia in 12 of the 14 patients. This indicated that not only in secondary CMV infections [2] but also in primary CMV infections this method is the first to detect active CMV infection. Antigenemia occurred significantly earlier than IgM, IgG seroconversion and CMV excretion. Primary CMV infection detected with antigenemia was somewhat delayed in patients who received HIg prophylaxis, but that did not influence the frequency or the severity. It is remarkable that

in seronegative recipients of kidneys from seropositive donors, the first detection of active CMV infection was by antigenemia and not by CMV excretion in the urine. This suggests that granulocytes pick up CMV antigen in the donor kidney and remain in circulation. It has been shown that CMV is present in endothelial cells in tissues and kidneys of healthy donors [23]. Alternatively, CMV infection spreads to the bone marrow undetected and infects myeloid cells, which may give rise to antigen-positive PMNs detected in peripheral blood. It is still unclear whether PMNs can support the spread of CMV throughout the body.

We conclude that no beneficial effects of HIg prophylaxis were seen in our study. Incidence and severity of primary CMV infection were comparable in both treated and untreated patients. The only effect observed was that HIg prophylaxis delayed detection of antigenemia. CMV disease was associated with increased allograft loss. Patients especially at risk for development of CMV disease had primary CMV infections and were treated for rejection with OKT3 or ATG. The transfer of CMV with the donor organ is not dependent upon the immune status of the recipient (HIg or rejection treatment with OKT3). Other factors, like donor and recipient age and CMV strain, may also influence whether or not CMV is transmitted.

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