CYTOMEGALOVIRUS INFECTIONS AFTER RENAL TRANSPLANTATION: EFFECT OF PROPHYLACTIC HYPERIMMUNOGLOBULIN

E-H Scheuermann, P-B Bechstein, W Schoeppe, W Fassbinder
Zentrum Innere Medizin, Universitätsklinik, Frankfurt, FRG

Summary

Incidence and clinical symptomatology of CMV infection was investigated in 83 patients, who received cadaveric renal transplants in 1982 and 1983. CMV-antibody status was determined using an ELISA technique. Forty-three of the 83 patients (52%) were seronegative, and 40 (48%) seropositive for CMV before transplantation. Seroconversion (i.e. primary CMV infection) or an increase in titre (i.e. reactivation or re-infection) was found in 18 cases (42% and 45%, respectively) in both groups. Eighty-nine per cent of all infections occurred within the first three months. Clinical symptomatology was much more severe in the group with primary CMV infection; all cases with atypical pneumonia (n=8) and both fatal cases belonged to this group. Preformed CMV antibodies thus appeared to prevent severe syndromes associated with CMV infection. Therefore, a randomized controlled study was started in 1984 in order to investigate the efficacy of an intravenous CMV hyperimmunoglobulin (HIG). Twenty-nine patients received 5,000 units HIG (10g IgG), and 23 control patients 10g polyvalent IgG immediately prior to transplantation, and on days 18, 38 and 58 thereafter. Infection rates were not affected by this type of prophylaxis, but clinical symptomatology of the infection was much less severe in both groups receiving immunoglobulins, particularly in patients with HIG. Only one full blown, life-threatening CMV syndrome was observed, this case in the control group. Fatal cases occurred in neither group. Thus both preparations were not capable of preventing CMV infections (or reactivation), but prophylactic HIG – and to a minor degree polyvalent IgG – were able to protect the patients against the occurrence of severe CMV syndrome post-transplantation.

Introduction

Cytomegalovirus (CMV) infection remains a serious problem after successful renal transplantation. Not only does the virus cause clinical syndromes of its
own, such as fever, leuco- and thrombocytopenia, hepatitis, pneumonia, chorio-
retinitis, gastrointestinal ulceration, pancreatitis, immunohaemolytic anaemia,
but it also increases the likelihood of bacterial, protozoan and fungal super-
infections [1].
CMV is the most common form of infection identified in renal transplant
recipients, being demonstrable in 60–96 per cent of patients in the first year
post-transplant [1]. Two epidemiological patterns of CMV disease have been
noted. One is primary CMV infection in which the transplant recipient has
had no previous exposure to this virus (and is seronegative for CMV before
transplant). The other is secondary CMV infection, where the patient is sero-
positive for CMV before the transplant. Here, reactivation of latent, endogenous
virus is responsible for most cases, but reinfections with exogenous virus, intro-
duced in the same ways as in primary infections, may also occur [2].
There is no recommended treatment for CMV infection, and prophylaxis
with active vaccination, interferon or hyperimmunoglobulin is investigational
[3]. This report describes the frequency and symptomatology of primary and
secondary CMV infections in our renal transplant population, before a pro-
spective study with prophylactic CMV hyperimmunoglobulin was begun, and
summarizes our first results of this study.

Materials and methods

The first study included all 86 patients who had received cadaveric renal allo-
grafts in our unit between January, 1982 and December, 1983. Three patients,
transferred to other centres with functioning grafts within the first post-operative
month, and who did not have any signs of CMV infection at the time, were
excluded. In the remaining 83 patients, complete follow-up was possible until
the time of evaluation of this study (June, 1985).
In 1984 a prospective, randomized, controlled study was begun to investigate
the efficacy of prophylactic CMV hyperimmunoglobulin in renal transplanta-
tion. Patients received either 10g (i.e. 5,000U) hyperimmunoglobulin (Cyto-
text®, Biotest-Pharma, Dreieich, Germany) in the treated group, or 10g of IgG
prepared from random donors (Intraglobin®, Biotest) in the control group.
Both preparations were given as short intravenous infusions (1) immediately
before transplantation and peri-operatively blood transfusions, and (2) at days
18, 38, 58 and 78 post-transplantation. To date, 52 patients have been under
observation for more than three months, 23 are in the control group, and 29 in
the hyperimmunoglobulin group.
Azathioprine and prednisone were used as the basic therapy in all patients.
Rejection crises were treated initially with two to four bolus dosages (1g each)
of methylprednisolone; in steroid resistant rejections, plasmapheresis or anti-
thymocyte globulin (ATG) therapy was instituted, depending on the histological
type of rejection. Standard dosages and our anti-rejection regimen have been
described in detail elsewhere [4].
All patients received two units of buffy-coat rich packed red cells, 0–4 hours
prior to the transplant procedure, as peri-operative blood transfusions [5].

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Cytomegalovirus antibodies (IgG and IgM) were determined by the enzyme-linked immunosorbent assay (ELISA). Commercially available microttitre plates (Enzygnost-Zytomegalie®; Beringwerke, Marburg/Lahn) were used. Details are described elsewhere [6].

Determinations of CMV antibodies were performed routinely (1) immediately prior to transplantation; (2) twice monthly during the first three post-operative months, and (3) in monthly intervals thereafter.

Primary CMV infection was identified by detection of CMV antibodies in a patient, who was seronegative before transplantation. Secondary CMV infection (reactivation or re-infection) was defined by a four-fold or greater increase in the CMV titre in a patient, who was seropositive before transplantation. A CMV syndrome [7] was diagnosed, if two or more of the following clinical features were present in patients with serological evidence of active infection: (a) unexplained fever (>38.5°C) for at least three days; (2) leucopenia (white cell count <3,000/mm³) and/or thrombopenia (<80,000/mm³) on three or more consecutive days after cessation of azathioprine treatment; (3) elevated SGOT or SGPT (>40U/L) or bilirubin (>1.5mg/dl) in the absence of serological evidence for hepatitis A or B infection; (4) radiological signs of interstitial pneumonitis without another discernible cause.

In order to compare these CMV symptoms, the patients were scored according to severity of disease. For the observation of each of the symptoms: fever, leucocytopenia, thrombocytopenia, elevated SGPT (or SGOT) activities one score point was given, and this was multiplied by the factor, 2, 3 or 4, if the symptom persisted for 2, 3 or 4 weeks at least. Two score points were accorded to the observation of the symptoms of icterus or atypical pneumonia, and this was multiplied by two, if the symptom persisted for at least two weeks.

Results

Incidence of CMV infections after renal transplantation

Before transplantation, 43 of the 83 patients were seronegative (52%), and 40 were seropositive (48%). In the seronegative group, seroconversion (i.e. primary CMV infection) was observed in 18 cases (42%); in the seropositive group an increase in titre of at least four-fold (i.e. secondary CMV infection) was found in 18 cases (45%).

Eighty-nine per cent of all primary infections occurred within three months of transplantation. Seroconversion occurred with approximately equal frequency in the first, second and third months post-transplantation; in all these cases, initially IgM antibodies were found. Only two infections were seen after the first three months; in one of these IgM antibodies were not detected.

In the patients who were seropositive before transplantation, an increase in titre of at least four-fold was found most often in the second or third month post-transplantation, and less frequently in the first month or after the third month. In 10 of the 18 patients (56%) with ‘secondary CMV infection’ a reappearance of IgM antibodies could be demonstrated.
Clinical course and symptomatology of CMV infection post-transplantation

CMV infection post-transplantation is associated with a wide spectrum of clinical syndromes, ranging from asymptomatic seroconversion to fatal disease with disseminated infection of nearly all organs of the recipient. Most often, the infection is associated with a self-limited disease (‘CMV syndrome’), which presents itself as a period of prolonged fever together with leucopenia, some degree of liver damage and impairment of graft function.

In general, symptomatology of CMV infections was less severe in secondary than in primary infection; 16 of 18 cases with primary infections, but only seven of 18 cases with reactivation (or re-infection) developed a CMV syndrome. Details are described elsewhere [6]. Fever, impairment of graft function, liver damage and leucopenia were the most frequent symptoms in both groups. In nearly half of the patients with primary infection the most dangerous complication, i.e. interstitial pneumonia, was observed, whereas none of the seropositive patients experienced this potentially lethal complication. Two patients with primary infection and no patient with secondary infection died. In both fatal cases, disseminated infections, including atypical pneumonia and encephalitis, and fungal superinfections were observed.

First experiences with prophylactic CMV hyperimmunoglobulin

At the time of evaluation (June, 1985), 52 patients have entered the study and have been observed for at least three months post-transplantation (23 control patients and 29 treated patients). Both immunoglobulin preparations (Intraglobin® and Cytoject®) were well tolerated; adverse reactions were not observed. Forty-nine of the 52 (94.2%) grafts are still functioning to date.

CMV infections occurred in 16 of the 23 control patients (69%), and in 22 of the 29 patients with hyperimmunoglobulin prophylaxis (76%). Thus the frequency of infections was obviously not reduced by this type of prophylaxis. But in seronegative recipients the clinical symptomatology of the (primary) infection was much less severe in both immunoglobulin groups, particularly in the patients with hyperimmunoglobulin (Table 1). Only one full blown CMV syndrome with life-threatening interstitial pneumonia and secondary infections (pneumocystis-pneumonia and staphylococcus-septicaemia) was observed; this case belonged to the control group. No fatal cases occurred in either group.

Six patients in the hyperimmunoglobulin group experienced a primary CMV infection. In three cases an asymptomatic seroconversion was observed, whereas the other three cases developed a transient, mild CMV syndrome.

In the patients who were seropositive at the time of transplantation, the administration of polyvalent immunoglobulin or hyperimmunoglobulin did not further reduce the severity of the observed CMV syndrome; in all these cases the symptoms were usually mild (Table 1).

Discussion

Our data show that CMV infection contributes significantly to morbidity and mortality after primarily successful renal transplantation. Therefore, measures
to prevent the infection or to mitigate at least some of its most severe consequences are urgently needed.

We could demonstrate that symptomatology of CMV infection is much less severe in patients with preformed CMV antibodies, even though infection rates were about the same in seropositive as in seronegative recipients. This observation prompted us to investigate the efficacy of a specific hyperimmunoglobulin passively administered immediately prior to the transplant procedure in an attempt to reduce the severity of CMV infections post-transplantation. Meanwhile, positive results in the prevention of CMV infections by hyperimmunoglobulins have been obtained after bone marrow transplantation in the USA [8] and in Germany [9]. Only by intravenous administration are high antibody titres obtainable immediately. Since 90 per cent of all CMV infections we have observed were within the first three months following transplantation, passive immunization was continued for this length of time.

The passive immunization was not capable of preventing CMV infection (or reactivation), but clinical symptomatology of the infection was much less severe after the prophylactic administration of CMV hyperimmunoglobulin. Life-threatening CMV syndromes were not observed in this group. Our figures are as yet too small to draw any final conclusions from these observations. As no adverse effects were observed with this type of prophylaxis, the study is being continued.

References
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