Successful Treatment for Active Cytomegalovirus Infection by Cytomegalovirus Antibody-Enriched Immunoglobulin in a Renal Transplant Recipient

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Abstract

Active cytomegalovirus (CMV) infection was treated successfully by only CMV antibody-enriched immunoglobulin (CMV-IG) in a renal transplant recipient. CMV-IG was injected at 86 mg/kg iv twice a day for a total of 16 days (4 plus 12 days, interrupted by a pause of 4 days), followed by weekly iv injection of 86 mg/kg (7 weeks). Active CMV infection was diagnosed on the basis of DNAemia in plasma, by a newly developed CMV polymerase chain reaction (PCR) test (AMPLICOR® CMV). The disappearance of CMV from plasma was confirmed by this PCR test. It seems that single CMV-IG therapy is worth consideration for the treatment of CMV infection.

Introduction

Cytomegalovirus (CMV) infection is a frequent cause of morbidity and mortality in transplant recipients who suffer from serious complications such as interstitial pneumonia, retinitis, gastrointestinal disease, hepatitis, and other visceral disease. Ganciclovir has been shown to be effective in improving or halting the progression of those CMV diseases[1)], and has been used alone or in combination with CMV antibody-enriched immunoglobulin (CMV-IG)[1,2)].

The problem is that a major side effect associated with ganciclovir is myelosuppression, causing leukocytopenia in transplantation patients[3)]. In addition, the transplantation patients are normally treated with immunosuppressants like cyclosporine (CsA), tacrolimus, or others. These drugs also sometimes cause myelosuppression, resulting in leukocytopenia[4,5)]. Therefore, clinicians working on transplantation often encounter a situation in which ganciclovir is hard to administer for CMV disease.

We report here the first case in which active CMV infection was treated successfully by only CMV-IG in a renal transplant recipient. After this treatment with CMV-IG, disappearance of CMV from the patient's plasma was confirmed by a polymerase chain reaction (PCR)-based assay. The test is qualitative but was used semiquantitatively.

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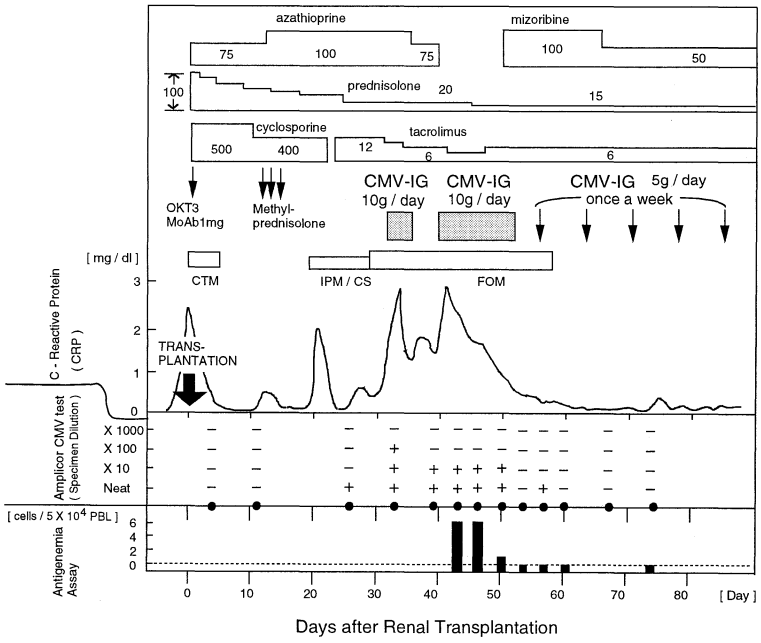
Fig. 1 The Clinical Course.
A 64-year-old Japanese man underwent renal tansplantation. CMV infection was monitored sequentially by the PCR-based AMPLICOR® CMV test (using plasma as source material) and antigenemia asay. AMPLICOR® is a qualitative test, but was used semiquantitatively by preparing a series of dilutions of each plasma specimen with human plasma that was pooled in advance and was proved CMV-negative by this kit: +, positive; −, native. The results of antigenemia assay are expressed as positive cells per 50,000 peripheral blood leukocytes. (PBL). CTM, cefotiam; IPM/CS, imipenem/cilastatin: FOM, fosfomycin; MoAb, monoclonal antibody; CMV-IG, cytomegalovirus antibody-enriched immunoglobulin. These antibitics, CMV-IG, OKT3 MoAb, and methylprednisolone were administered intravenously. Azathioprine, mizoribine, prednisolone, and tacrolimus were given per os and the numbers shown are the volume of the medicine (unit, mg).



Case

A 64-year-old Japanese man (weight 58 kg, height 165 cm) with endstage renal failure secondary to chronic glomerulonephritis had undergone 20 months of three times weekly hemodialysis. After living renal transplantation from his younger brother, he received induction therapy with OKT3 (1 mg) followed by administration of CsA, 500 mg/day, prednisolone (100 mg/day), and azathioprine (75 mg/day) (Fig. 1). Both recipient and donor were IgG seropositive for CMV.

Plasma specimens (EDTA) from this patient were collected during the clinical course for monitoring DNAemia of CMV using a PCR-based assay kit (AMPLICOR® CMV, Roche Diagnostics Systems, Branchburg, NJ). The PCR test requires 50 μl of plasma for sample preparation and uses 5 μl of plasma-equivalent DNA per PCR. We evaluated the possibility of using this kit semiquantitatively, by preparing a series of dilutions of each plasma specimen with human plasma that was pooled in advance and proved CMV-negative. Figure 1 shows the clinical course of this renal transplant recipient. At day 11, rejection was suspected and methylprednisolone therapy (1 g/day) was

given. At day 20, C-reactive protein (CRP) increased and antibiotic (intravenous) therapy was started. Furthermore, an increase in the serum creatinine level (from ~1.5 to ~3.5 mg/dl) and a decrease in urine volume (from ~3000 to ~600 ml/day) made us diagnose rejection and change the immunosuppressant from CsA to tacrolimus (12 mg/day). At day 25, CMV DNAemia was found in the plasma by PCR. However, treatment for CMV was not started because of the low CRP level. Several days later, unexplained low fever, an increase in the CRP level, and CMV DNAemia detected by PCR made us diagnose active CMV infection and initiate CMV-IG therapy (86 mg/kg iv twice a day) for 4 days plus 12 days after a pause of 4 days. Since the leukocyte count was low, $\sim 2.8 \times 10^9$/l, ganciclovir was not used because of its myelosuppressive effect. CMV pp65 antigenemia assays were performed at the same time as PCR assay from day 44 of the clinical course, using monoclonal antibody C10/C11 recognizing pp65[6]. This patient's diagnosis was "active CMV infection", not "CMV disease", because of lack of evidence of clinical CMV disease such as interstitial pneumonia or gastrointestinal disease[7]. At day 53, both PCR and antigenemia were negative. Daily CMV-IG therapy was discontinuted, and was replaced by weekly injection (86 mg/kg). After that the CRP level was almost 0 mg/dl and the rejection was controlled properily. Weekly CMV-IG therapy was not used again by day 98, when the patient was discharged and followed as an outpatient.

Discussion

One group stated that single therapeutic use of CMV-IG is not recommended, although its combination with ganciclovir was hopeful[8].

Some clinicians suspected that using CMV-IG alone might have been effective against CMV infection. However, there were no data to support this, because CMV infection has been hard to diagnose to date. Viral culture took several days to yield results. Direct CMV antigen detection (antigenemia assay) resolved the problem of time, but its snesitivity still remained insufficient, ~87.5%[9]. Therefore, even if CMV infection was followed by the antigenemia assay during the therapeutic course, whether CMV has really disappeared or not still remained to be unanswered.

PCR assay detecting a low CMV DNA load in plasma or leukocytes resolved the problem with its sensitivity of nearly 100%[10]. However, its specificity was still insufficient, ~65%, due to the frequent false positives[11,12]. When PCR was carried out as originally described by Saiki et al.[13], false positives could not be avoided[11,12]. The PCR technique also requires some molecular biological skills and is not suitable for a routine laboratory test as it stands. In collaboration with Roche Molecular Systems (Brainchburg, NJ and Alameda, CA), we had an opportunity to use a PCR-based kit for CMV detection, which was newly developed, to resolve all the above problems. The use of dUTP instead of dTTP and uracil-*N*-glycosylase in PCR amplification helped to reduce the false-positive problems[14]. By using this PCR assay, the disappearance of CMV from the patient's plasma was confirmed during the course of single CMV-IG therapy.

The standard therapeutic procedure is a combination of ganciclovir and CMV-IG, in which the dose of CMV-IG is, for example, 500 mg/kg iv every other day[1,2], much larger than that in this report. Our patient suffered from "active CMV infection", not "CMV disease"[7]. Therefore, were are not sure whether single CMV-IG therapy with this small dose (86 mg/kg iv twice a day) is effective for apparent CMV disease. Nevertheless, it seems that single CMV-IG therapy is worth considering for the treatment of CMV infection.

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腎移植患者におけるサイトメガロウイルス感染症に対して抗サイトメガロウイルス抗体高力価グロブリン製剤のみによる治療が奏功した1例

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要　旨

腎移植患者に併発したサイトメガロウイルス感染症に対して，抗サイトメガロウイルス抗体高力価グロブリン製剤(CMV-IG)のみによる治療が奏功したので報告する．(CMV-IG)は，1日2回，86mg/kgで16日間(休止日をはさんで，4日間と12日間)点滴静注投与された．その後，86/kgで週1回，計7週間投与された．サイトメガロウイルス感染症は，新開発のサイトメガロウイルス診断PCRキット（AMPLICOR® CMV）によって血漿中のウイルス血症を証明することにより，診断された．このキットを使うことにより，患者血漿中よりサイトメガロウイルスが消えていく様子を明瞭にモニターすることができた．