Efficacy and safety of lowering immunosuppression to treat CMV infection in renal transplant recipients on valaciclovir prophylaxis: a pilot study

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Abstract

Background. Routine cytomegalovirus (CMV)-pp65 antigenaemia monitoring shows that some patients will develop pp65 antigenaemia during valaciclovir prophylaxis or after cessation of treatment. The aim of this pilot study was to evaluate the safety and efficacy of lowering immunosuppression in kidney transplant recipients who exhibit mildly symptomatic CMV infections while on valaciclovir prophylaxis.

Methods. We selected 12 patients who experienced mildly symptomatic CMV infections defined as a positive CMV-pp65 antigenaemia test associated with either neutropenia, asthenia or arthralgia, but no fever. All of them received prophylaxis with valaciclovir for at least 3 months. Testing for CMV-pp65 antigenaemia was performed weekly for 6 months.

Results. The mildly symptomatic infections occurred at a median interval of 69 days after transplantation—during prophylaxis in eight cases and after valaciclovir discontinuation in the other four cases. All of them were effectively managed by lowering immunosuppressive therapy, leading to the disappearance of symptoms and CMV antigenaemia reduction. No immunological complication or recurrence of CMV infection or disease was noted. I.v. ganciclovir never became necessary.

Conclusion. The mildly symptomatic CMV infections occurring in valaciclovir-treated patients may be managed efficiently and without immunologic complication by lowering immunosuppressive therapy.

Keywords: cytomegalovirus; immunosuppression; kidney transplantation; preemptive therapy; valaciclovir

Introduction

Cytomegalovirus (CMV) disease remains a significant cause of morbidity and mortality in kidney transplantation [1]. A 3-month prophylaxis against CMV infection with valaciclovir has been reported to be safe and effective in kidney transplant recipients [2]. However, during prophylaxis, CMV-pp65 antigenaemia develops in some patients. This CMV infection may be either asymptomatic or mildly symptomatic (without fever). In kidney transplant recipients, intensive monitoring of pp65 antigenaemia and early treatment of CMV infection, namely preemptive therapy, has been reported to be a safe alternative to prophylaxis. In the literature, however, the modulations of immunosuppression that may accompany preemptive therapy usually are not described in detail, and their influence on viral clearance is not evaluated.

The purpose of this pilot study was to evaluate the safety and efficacy of the isolated lowering of immunosuppression in 12 kidney transplant recipients who exhibited a mildly symptomatic CMV infection while on valaciclovir prophylaxis.

Materials and methods

In our unit, to prevent CMV infection, valaciclovir prophylaxis is administered to all CMV-seropositive recipients and to all recipients from seropositive donors. Valaciclovir is given according to their renal function, starting on the first day after transplantation and continuing for at least 3 months. Among the 221 patients transplanted during the study period (July 1998 to June 2001), 116 patients were given prophylaxis with valaciclovir (52.5%). Among the latter, only one patient experienced a CMV disease during prophylaxis (positive pp65 antigenaemia associated with the presence of at least one concomitant febrile illness). After cessation of prophylaxis, five developed a CMV disease,
patients presented with asymptomatic infection (defined as the detection only of virus replication without clinical symptoms or neutropenia) and 12 with a mild symptomatic infection (without fever). These 12 patients were included in our pilot study.

All the patients (seven females, five males, mean age = 45 ± 14) included in this study had received either a kidney transplant \( (n=10) \) or a kidney–pancreas transplant \( (n=2) \) and were treated with valaciclovir as anti-CMV prophylaxis. Testing for CMV-pp65 antigenaemia, was performed weekly for 6 months after transplantation. Four patients had a D+R- status and eight patients were R+ whatever the CMV status of the donor. The patients were selected because they experienced a mildly symptomatic CMV infection defined as a positive CMV-pp65 antigenaemia associated with either neutropenia \( \text{white blood cells (WBC)} <4000/mm^3; n=10 \), asthenia (three of 12) or arthralgia (two of 12), but no fever. Immunosuppressive treatment consisted of calcineurin inhibitors (ciclosporine \( n=9 \), tacrolimus \( n=3 \)) together with low-dose steroids and azathioprine \( (n=3) \) or mycophenolate mofetil \( (n=9) \). Cyclosporine was given at an initial dosage of 6mg/kg/day adapted to trough levels ranging from 150 to 250 ng/ml. Tacrolimus was given at an initial dosage of 0.15 mg/kg/day adapted to trough levels ranging from 12 to 15 ng/ml. Induction was used in 11 patients (Thymoglobuline\(^\text{C213}^\)) for 10 days at doses adjusted according to lymphocyte monitoring. Time-to-event data are summarized as median and range. Safety and efficacy data were recorded during the 6 months post-transplantation.

Results

These 12 patients experienced a mildly symptomatic infection at a median interval of 69 days after transplantation (range 13–156 days). At the time antigenaemia was detected, their median daily dose of cyclosporine was 200 mg/day (range 150–300 mg/day, \( n=9 \)) with trough levels ranging from 65 to 190 ng/ml (median 105 ng/ml). The median daily dose of tacrolimus was 9 mg/day (range from 6 to 10 mg/day, \( n=3 \)) with trough levels of 7, 12 and 16 ng/ml. The median daily dose of mycophenolate mofetil (MMF) was 2 g/day (1–3 g, \( n=9 \)) or 100 mg/day for azathioprine (75–125 mg). The median daily dose of prednisone was 10 mg/day (ranged from 7.5 to 35 mg/day). Valaciclovir prophylaxis was given for 129 ± 25 days. Infection occurred during prophylaxis in eight cases and after valaciclovir discontinuation in the other four cases. In the latter cases, CMV infection occurred at a median interval of 35 days after valaciclovir withdrawal (range 8–49 days). At the time of infection, 11 of the 12 patients presented with leukopenia with a median WBC count of 3000/mm\(^3\) (900–3900). The mean maximum CMV-pp65 antigen count was 204 positive cells per 200 000 (range 3–500). All of these mildly symptomatic infections were effectively managed by lowering immunosuppressive therapy: reduction of MMF in six cases, withdrawal of MMF in three cases, withdrawal of azathioprine in two patients, decrease of cyclosporine or tacrolimus dose in three cases. Immunosuppressive therapy was reduced at a median interval of 92 days after transplantation. A single immunosuppression reduction was implemented in eight patients while two modifications were done in four patients. After lowering immunosuppressive therapy, clinical symptoms or leukopenia, or both, quickly disappeared and CMV-pp65 antigenaemia decreased. However, achievement of negative antigenaemia status was often delayed (median time to reversal: 56 days). Finally, i.v. ganciclovir was never necessary in these mildly symptomatic forms of CMV infection. Reducing immunosuppressive treatment did not result in any immunological complication, i.e. acute rejection. No recurrence of CMV infection or disease was noted.

Discussion

In this pilot study, the isolated reduction of immunosuppression allowed a safe and steady resolution of CMV infection in patients with mildly symptomatic CMV infections.

The two major strategies to prevent CMV infection and disease in transplanted patients are prophylaxis (with either valaciclovir or oral ganciclovir) or preemptive treatment [2–10]. The latter relies on the monitoring of CMV infection (pp65 antigenaemia or PCR) and the use of ganciclovir as soon as CMV infection is detected [8–10]. Preemptive therapy, although widely used, has been evaluated less extensively than prophylaxis. More importantly, the modulation of immunosuppression that may be started at the same time that the antiviral agent is given has never been evaluated, so that the respective efficacies of modulating immunosuppression and antiviral therapy is unknown.

It can be argued on the one hand, that in our study the ‘natural’ courses of the CMV infections would have been similar without immunosuppressive modulation. On the other hand, that the course of CMV infection could have been shortened by using antiviral therapy without immunosuppressive modulation. In this preliminary experiment, reducing immunosuppression was safe, probably because it was started rather late in the post-transplantation period, at a time of lower incidence of acute rejection. We avoided using either i.v. or oral ganciclovir, thus reducing both the morbidity associated with it and its cost. Finally, reducing immunosuppression allowed the resolution of the CMV infection without any instances of recurrence.

The preliminary data suggest that, in patients with a mildly symptomatic CMV infection, the isolated reduction of immunosuppression is safe and efficient. It should therefore be compared in prospective trials with preemptive therapy without immunosuppressive modulation in order to determine the most cost-effective strategy.

Conflict of interest statement. None declared.
References


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