Invited Comment

Prophylaxis of cytomegalovirus infection in renal transplantation: new data for an old problem

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Introduction

New reports in the literature about the effective use of valacyclovir (Zelitrex®, Valtrex®, Glaxo Wellcome) as prophylactic treatment for cytomegalovirus (CMV) infection in renal transplantation, have prompted us to update our recent Editorial Comment (Nephrol Dial Transplant 13: 3012–3016, 1998) on this interesting topic. Valacyclovir not only reduces the incidence of active CMV infection and CMV disease in renal transplant patients, but it also seems to exert a beneficial effect on the incidence of acute allograft rejection, other herpesvirus infections and non-viral infections.

These additional properties of valacyclovir warrant a critical analysis of the published data in the light of the old and new available information about ganciclovir prophylaxis in renal transplantation.

Valacyclovir trials

Valacyclovir is an amino acid ester prodrug of acyclovir that is rapidly and almost completely hydrolysed to acyclovir and has an oral bioavailability of 54% compared to 20% for acyclovir. The plasma AUC of acyclovir attained with high oral dosage of valacyclovir (2 g q.i.d.) approximates that of intravenous acyclovir administration at 10 mg/kg every 8 h [1]. Valacyclovir in low dose has proven to be as effective as acyclovir in the treatment of first and recurrent episodes of genital herpes simplex virus (HSV) infection but with a more convenient dosing strategy than the latter.

Lowance et al. recently reported the results of a large prospective placebo-controlled trial on the use of oral valacyclovir as prophylaxis for active CMV infec-

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Conventional or shell-vial cultures of blood and urine were used to confirm the presence of CMV. Viral antigen detection (pp-65 antigen) or CMV-DNA-PCR (polymerase chain reaction) methods were not employed; it is not clear whether immunohistochemical techniques were applied for identification of intranuclear viral inclusion bodies in organ biopsy specimen. Standard treatment of an episode of CMV disease consisted of intravenous ganciclovir or foscarin; it is not mentioned for how many days this therapy was given. Secondary end-points were renal allograft rejection, graft function and survival, patient survival, the occurrence of HSV infections, varicella-zoster disease and non-herpesvirus infections. The use of medical resources was also evaluated.

The incidence of laboratory-confirmed CMV disease during the prophylaxis period among the sero-negative recipients was 45% in the placebo group versus only 3% in the valacyclovir group. After 6 months follow-up the incidence remained unchanged in the placebo-treated group at 45% and increased to 16% in the valacyclovir treated group; the incidence of CMV end-organ disease (tissue invasive CMV disease) in these two groups was 25% and 4%, respectively. Recurrent disease was rare; five relapses in the sero-negative placebo group and two in the sero-negative valacyclovir group.

Among the sero-positive recipient groups, the incidence of CMV disease was lower as expected: 9% in the valacyclovir group versus 6% in the placebo group at 90 days and 1% and again 6%, respectively, 3 months later. Recurrent disease was absent in both sero-positive patient groups and only four recipients in the placebo group had evidence of tissue-invasive disease. CMV-related mortality was very low in this study; one patient succumbed as a result of CMV disease.

The cumulative rate of biopsy-proven acute rejection after 6 months was 52% in the sero-negative placebo-treated group compared to only 26% in the valacyclovir-treated group. In the sero-positive groups this difference in acute rejection rate was not statistically significant anymore (36% vs 30%, P = 0.40). The incidence of chronic allograft rejection and both graft function and graft survival as well as patient survival did not differ between the study groups at any time during follow-up.

The risk of clinical HSV infection was significantly reduced in both sero-negative and sero-positive valacyclovir treated groups compared to placebo-groups; also the rate of non-herpesvirus infections (e.g. Candida, Staphylococcus) was lower in the sero-negative patients that received valacyclovir.

As a consequence of a lesser rate of CMV disease, valacyclovir-treated patients used overall less inpatient medical resources than did the placebo-treated control patients. Adverse events pertaining to the central nervous system were significantly more frequent in the valacyclovir-treated patient groups. Hallucinations and confusion occurred in a total of 15.7% (48/306) in the latter groups compared to 3.2% (10/310) in the placebo groups. These drug-related neurological side-effects were considered mild and reversible after dose adjustment. Overall compliance with the protocol was greater among the patients that received valacyclovir.

The impressive results of this study have to be interpreted in the light of current clinical practice. The comparative high incidence of CMV infection (45%) and tissue-invasive CMV disease (25%) in the sero-negative placebo group are in part, the result of the overall frequent use of induction therapy with OKT3, anti-lymphocyte globulin or anti-thymocyte globulin in the study population (more than 50% of the patients). It is not clarified in this paper exactly when in relation to the CMV infection the acute rejection episodes occurred that made treatment with antilymphocyte antibodies necessary. As significantly more patients in the sero-negative placebo group received monoclonal or polyclonal antibody therapy (29/55) for acute rejection, this chronological relation is important for the interpretation of the results. Differences in susceptibility for CMV infection among renal transplant recipients are of course not only the result of differences in immunosuppressive drug therapy. More and more experimental evidence becomes available to support a multi-causative model of CMV disease development. Several influential factors come into play: TNF-α, IFN-γ, gene polymorphism of TNF-α and IL-1 receptor antagonist genes, genetic heterogeneity of cytomegalovirus, coinfection with HHV6, CMV-induced changes in the surface expression of LFA-3 of infected cells, CMV-enhanced endothelial ICAM-1 expression, host HLA-type, ....

Also, when comparing the results of this trial with those of other trials, one has to pay attention to the definition of CMV disease that is employed. "CMV disease" as described in this study is the equivalent of "CMV syndrome" or "active CMV infection" in other trials. Except in the instances where symptoms of organ involvement are accompanied by the positive identification of the virus in the relevant clinical specimen, one cannot speak of CMV disease. Instead the authors use the term ‘tissue-invasive CMV disease’ to signify proven organ involvement and so this term is the equivalent of CMV disease.

Recurrent CMV disease was very infrequent in this study and occurred only in the sero-negative patient groups (7/208). This finding is in sharp contrast with a recent report describing CMV disease recurrence in 31% (103/332) of kidney and simultaneous kidney-pancreas transplant recipients treated with i.v. ganciclovir therapy for CMV disease followed by 10 weeks of oral acyclovir as secondary prophylaxis. The most significant clinical risk factors for recurrence in multivariate analysis were a cadaver organ source and treatment for acute rejection [4]. Recurrence of CMV disease had no effect on the 5-year graft survival and patient survival in this study.

The finding of a high rate of biopsy-confirmed (52%) and relative steroid-resistant (52.7%, 29/55) acute rejections in the sero-negative placebo group indirectly points towards an immunological high-risk population. Furthermore, the fact that only a small proportion of
these patients were available for comparative analysis at 6 months (33.9% for CMV disease and 21.6% for biopsy-confirmed acute rejection) remains unexplained.

The authors conclude that their study population was representative of typical renal transplant recipients. However, in the European [5] and Tri-continental Mycophenolate Mofetil Study [6] the incidence of biopsy-proven rejection at 6 months (Grade I, II and III using the Banff criteria) in the control group was respectively, 46.4% (dual therapy with CsA and steroids) and 35.5% (triple therapy with CsA, steroids and azathioprine). In the European [7] and American Tacrolimus study [8] the incidence of biopsy-proven rejection (‘borderline’ biopsies excluded) at 12 months in the control group was respectively, 35.9% (CsA steroids and azathioprine) and 40.0% (CsA, steroids, azathioprine and anti-lymphocyte antibody preparation). These figures compare relatively favourable with the incidence of acute rejection found in the sero-negative placebo-group in this study, especially when one takes into account the fact that the majority of these patients were receiving a triple-drug immunosuppressive treatment together with induction therapy in more than half of them. The mechanism underlying the potential anti-rejection effect of valacyclovir remains unclear. The fact that no difference in acute rejection incidence was seen between the sero-positive placebo group and the sero-positive valacyclovir group suggests that valacyclovir as such, has no important intrinsic immunosuppressive effect. The authors imply that the prevention of CMV disease and acute rejection may be related. Upholding this explanation proves difficult regarding the fact that the efficient use of other prophylactic anti-CMV drugs is not associated with a significant reduction of the acute rejection rate.

The substantial reduction of the acute rejection rate in the valacyclovir treated group remains a remarkable result that warrants to perform in the future analogous trials in which new immunosuppressive drugs like tacrolimus, MMF and rapamycine are used.

The diminished host defense induced by CMV infection is indirectly illustrated by the fact that valacyclovir therapy also reduced the incidence of non-herpesvirus infections. The independent role of CMV as a risk factor for invasive fungal disease was recently also confirmed in the setting of orthotopic liver transplantation [9]. The CMV-mediated induction of TGF-β production was shown in a rat model and might contribute to the CMV-related state of immunosuppression [10]. Roughly one out of every six valacyclovir treated patients suffered from neurological side-effects, mostly hallucinations or confusion. This rather high frequency of central nervous system symptoms is of course related to the high dosage of the drug required in order to obtain adequate plasma-levels. Therefore, future trials testing a reduced dose of valacyclovir (1 g t.i.d.) are underway and will probably attain improved results in this respect.

In a letter to the editor, Himmelmann and his colleagues presented two renal transplant patients in whom low-dose oral valacyclovir (1 g t.i.d.) was successfully employed as pre-emptive therapy for CMV infection in the first patient, and as oral treatment of a CMV recurrence in the second patient. Therapy was guided by quantitative pp65-antigenaemia detection. The pp65-antigen test became negative after 3 and 6 weeks of therapy, respectively, and was preceded by the resolution of all clinical symptoms and without recurrence after stopping valacyclovir therapy [11]. In a study of 153 pp65-antigen-positive renal transplant recipients Yang et al. showed that all patients with low-grade CMV infection (n = 62) had a spontaneous remission without antiviral therapy. Among the patients with a high-grade CMV infection, the subgroup with the greatest risk for CMV disease comprised those patients that received OKT3 treatment without ganciclovir prophylaxis; all of them developed active disease (n = 6). All other patients with a high-grade CMV infection had a low incidence of CMV disease [12]. Sagedal et al. confirmed that almost 2/3 of all CMV infections detected by way of a positive pp65-antigen assay in renal transplant recipients at risk for CMV (D+), go in spontaneous remission. The CMV infection tended to last longer in those recipients (1/3) in need of ganciclovir therapy (mean 28 vs 14 days) [13]. These findings emphasize the caution one has to observe when interpreting treatment 1 results and using the pp65-antigen detection method as therapeutic 2 guidance.

**Ganciclovir trials**

More scientific evidence has recently become available on the use of oral ganciclovir prophylaxis in renal and other solid organ transplantation. In heart, lung and liver allograft transplantation, oral ganciclovir prophylaxis has also proven to be effective [14–16].

Other reports reveal less successful application of ganciclovir prophylaxis in immunologic high-risk renal allograft recipients with a D+/R− CMV-status [17]. In this study patients that were considered to have a high immunologic risk (re-transplantation, delayed graft function, acute rejection) were switched from azathioprine to MMF therapy as part of a triple immunosuppressive drug scheme (CsA microemulsion, steroids). They were matched by D+/R− controls without high immunologic risk. CMV prophylaxis of 3 weeks of i.v. ganciclovir followed by 9 weeks of oral low-dose acyclovir or ganciclovir, was not sufficient to prevent CMV syndrome in 53% of these high risk patients (vs 10% in the control group) and tissue-invasive CMV infection in 12% (vs 0% in the control group). The authors suggest a possible role of MMF in this failure of CMV prophylaxis. These data, however, confirm that re-transplantation and acute rejection are risk factors for primary CMV infection. In the high-risk group almost half of the patients had a steroid-resistant acute rejection episode but it is not clear whether anti-lymphocyte antibody (ALA) preparations were used as treatment. And if so what type
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of CMV-prophylaxis was administered during this anti-rejection therapy. The same authors reported in a previous article that i.v. GCV prophylaxis is effective in preventing CMV infection in D+/R− recipients and in CMV-positive recipients treated with ALA [18]. It therefore cannot be concluded on the basis of these results that MMF is an independent risk factor for CMV infection although other multi-centre trials point in that direction.

In another retrospective study of patients on triple immunosuppressive therapy with azathioprine, cyclosporin A and steroids (no ALA), it was pointed out that CMV prophylaxis could only be justified for CMV high-risk (D+/R−) recipients because half of them will develop CMV infection and because they are responsible for the majority of CMV-related hospital days when left untreated [18]. For the other transplant patients (D+/R+; D−/R+) the cost to benefit ratio of the prophylactic strategy was unfavourable. The authors agree however that these findings cannot be extrapolated to other situations in which more potent immunosuppressive drug protocols are used.

Jassal et al. published clinical practice guidelines for CMV prophylaxis based on a review of the available literature [19]. For patients at risk for primary CMV infection (and therefore also for CMV disease) they advocate prophylactic treatment without specifying the type of drug. Furthermore, all patients treated with anti-lymphocyte antibodies should receive ganciclovir prophylaxis regardless of their risk for CMV infection (except D−/R−). The prophylactic strategy for the CMV medium-risk patients (D+/R+; D−/R+), without ALA therapy, is left at the discretion of the physician in charge.

Conclusion

These recent studies confirm the efficacy of antiviral drug prophylaxis for CMV infection in renal transplant recipients that are at risk because of donor/recipient CMV status or because of concomitant immunosuppressive drug therapy. The fact that this goal can be achieved using oral antiviral therapy constitutes a major progress in clinical transplantation practice. Therefore currently oral CMV prophylaxis during 12 weeks is still advised in all transplant recipients at risk for CMV infection. This position may have to be revised when future prospective controlled trials comparing prophylaxis with either pre-emptive or deferred therapy prove that the latter strategy is more cost-effective, especially for patients at moderate risk for CMV (D+/R+; D−/R+). CMV prophylaxis during administration of ATG or OKT3 as induction or as anti-rejection therapy remains mandatory.

The first valacyclovir study in renal transplant patients has shown promising results and this drug will be a valuable alternative in the future. New studies with valacyclovir will have to focus on the feasibility of lower dose regimens (e.g. 3 × 1 g/day) in order to reduce central nervous system side-effects while maintaining efficient CMV prevention. The beneficial effect of valacyclovir on acute allograft rejection must be further substantiated by additional prospective controlled trials in which newer immunosuppressive drugs like MMF, tacrolimus and rapamycin are studied.

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References


