Viral Infections in Renal Transplantation:  
A Clue to Excessive Immunosuppression

Infecções Virais no Transplante Renal:  
Uma Pista para Imunossupressão Excessiva

Daniel L. Bohl, Matthew J. Koch, Daniel C. Brennan

1 Instructor of Medicine, Washington University School of Medicine in St. Louis; 2 Assistant Professor of Medicine Washington University School of Medicine in St. Louis, 3 Professor of Medicine - Washington University School of Medicine in St. Louis, Director, Transplant Nephrology, Barnes-Jewish Hospital

Funding Sources: This work was supported in part by NIH 1 K24-02886 (DCB) and NKF 22 3062 38053 (DLB), the 2004 Amgen Renal Fellowship Award, and the NIH Loan Repayment Program. MJK is supported by the NIH Loan Repayment Program.

ABSTRACT

Viral infections are common after transplantation and may be biomarkers of excessive immunosuppression. Monitoring for reactivation of viral infections such as CMV and BK should be routine. Molecular techniques including PCR are the monitoring tests of choice. Immune activating viruses like CMV produce bi-directional effects that predispose to rejection and poor outcomes. Non immune-activating infections like BK can produce inflammation that may lead to poor allograft function or graft loss. When specific antiviral treatment is available, it should be considered for treatment of even asymptomatic infections such as CMV, as these can be associated with mortality and allograft dysfunction. Preemptive immunosuppression reduction may prevent progression from viremia to nephropathy for BK. The risk versus benefit of resuming prior immunosuppressive agents or doses following clearance of a viral infection remains unknown.

Keywords: Viral infection. Renal transplantation. Polyomavirus. Cytomegalovirus. Epstein Barr virus. Immunosuppression.

RESUMO

As infecções virais são comuns após o transplante e podem se constituir em biomarcadores de imunossupressão excessiva. A monitorização da reativação das infecções virais, tais como CMV e BK, deveria ser uma rotina. As técnicas moleculares incluindo o PCR são as preferidas. Viruses ativadores imunológicos, tais como CMV, produzem efeitos bidirecionais que predispõem a rejeição e evolução ruim dos enxertos. As infecções com ativação não imunológica, como as causadas pelo vírus BK, podem promover inflamação com função inadequada ou perda do enxerto renal. Em caso de disponibilidade de um tratamento específico antivírus, este deveria ser considerado, mesmo quando as infecções forem assintomáticas, tais como CMV, visto que estas se associam com mortalidade e disfunção do enxerto. A redução antecipada ou “preemptive” da imunossupressão pode prevenir a progressão de viremia para nefropatia pelo vírus BK. O risco versus benefício de se retomar com os medicamentos imunossupressores ou com as doses utilizadas antes da depuração viral permanece desconhecido.

INTRODUCTION

Infection occurs in 2/3 of renal transplant recipients in the first year after transplantation and is associated with morbidity, mortality and graft-loss after transplantation. Too little immunosuppression is associated with rejection and graft loss and too much immunosuppression is associated with infection and malignancy. Thus, a delicate and immeasurable balance exists between these two extremes (Figure 1).

Typical symptoms and signs of infection or over immunosuppression may be addressed in the review of systems. Constitutional symptoms include fatigue, malaise, fever, chills, sweats, rigors, and weight change. Skin symptoms and signs include rash, jaundice, and nail changes. Head, eyes, ears, nose and throat (HEENT) symptoms include headache, photophobia, otalgia, sore throat, and neck stiffness. Cardiopulmonary symptoms include cough, dyspnea, chest pain, and edema. Gastrointestinal symptoms include nausea, vomiting, abdominal pain and diarrhea. Genital and urinary symptoms include dyspareunia, urinary frequency, dysuria, nocturia, incontinence, bladder neck obstructive symptoms, and symptoms of nephrolithiasis. Neurologic and psychiatric signs include tremors, insomnia and disorientation.

Specific hematologic signs of infection may discriminate bacterial infections from viral infections or parasitic infections. Bacterial infections tend to be associated with increases in the total white blood cell (WBC) count, particularly in the polymorphonuclear (PMN) count. Viral infections are often associated with a decrement in the WBC, due, for the most part, to a relative lymphopenia. Viral infections may also be accompanied by a relative monocytosis. Parasitic infections may be manifested by a relative eosinophilia. Not only are these signs helpful for diagnosis, but they provide clues to the underlying pathophysiology, immunology, and treatment. Both bacterial and viral infections are associated with an inflammatory response but the impact differs. Parasitic infections are relatively uncommon in the U.S. They may frequently occur in other geographic regions, but their diagnosis, treatment and implications are not the subject of this review.

Bacterial infections tend to be extracellular and produce damage to cells through release of toxins, cytokines and inflammatory molecules without cellular incorporation. Bacterial infections are controlled by ingestion and elimination of the bacterium by the innate immune system through PMN’s without elimination of recipient cells. Bacterial infections are clearly foreign and the innate immunity provided by the PMN’s and use of appropriate antibiotics limits the infection and results in minimal acute cellular inflammation if detected and treated early. The acute inflammation is characterized by PMN’s and minimal residual fibrosis of the affected tissue without significant “collateral damage.” Recurrent bacterial infections, however, are a sign of an impaired innate immunologic response and warrant investigation for predisposing factors such as hypogammaglobulinemia. Mild to moderate hypogammaglobulinemia is often related to antimetabolite use. In the setting of recurrent bacterial infection, reduction of immunosuppression, particularly reduction of the antimetabolite should be considered, since calcineurin inhibition is more closely associated with immunosuppression of the T cell response. In contrast, antimetabolites are more broadly immunosuppressive and affect the innate and adaptive immune response.

Viral infections, in contrast, are typically intracellular infections incorporating into, or redirecting through episomes, the cellular genome to become mechanisms of viral production. Viral infections are controlled by innate immunity provided by natural killer (NK) cells and adaptive immunity by cytotoxic T cells. The humoral response is adjunctive and may not be neutralizing. Thus, control of viral infections is accomplished by elimination of the infected cell and the pathogen together, but not the pathogen alone. Elimination of the pathogen requires an appropriate cellular and humoral response that may indirectly affect the allogenic response. Regardless, eradication of the virally infected cell results in increased inflammation and fibrosis as the body eliminates the infected cells and replaces the empty damaged tissue space with chronic inflammatory cells, e.g., lymphocytes and scar or fibrotic tissue. Viral infections may also masquerade as self, or...
slightly altered self, further limiting an appropriate response to “foreign” antigen. Since transplant rejection focusses on elimination of self or altered self, viral infections may manifest as rejection and induce a conundrum of management. Viral infections may also initiate “heterologous immunity” in an additive fashion. It is our interpretation from the data available (vide infra) that active viral infection be a sign of or an “in vivo bioassay” of “excessive immunosuppression” associated with inflammation and potential allograft failure. Viral infections are often accompanied by allograft dysfunction and allograft pathology that may appear histologically consistent with rejection. The treatment for viral infections, immunosuppression reduction, is directly opposite to enhanced immunosuppression for treatment of rejection.

Whether viral infection and rejection can co-exist is a matter of controversy. In the absence of specific antiviral therapy, the treatment of choice is decreased, rather than increased immunosuppression. This scenario occurs in the setting of BK nephropathy. Although reduction of the calcineurin inhibitor for viral infection seems reasonable, given the effect on cytotoxic T cells which respond to viral infections, reduction of the antimetabolite has been associated with control of several viral infections, including CMV and BK, without significantly increasing the incidence of acute or chronic rejection. Viral infection is also associated with an inflammatory cytokine response that is more intense than that seen with acute rejection. By blocking interleukin-2 (IL-2) and other secondary signaling molecules, calcineurin inhibition continuance has a greater potential to down-regulate a potentially harmful cytokine response than elimination of the antimetabolite. An alternative strategy to immunosuppressive reduction for viral infection with signs or symptoms of rejection, however, is to treat inflammation initially with steroids. This strategy is similar to that for patients with AIDS and Pneumocystis jiroveci (formerly carinii-PCP). Thus, steroids may be used initially to reduce inflammation and then reduced immunosuppression is used subsequently to control BK virus. However, we, and others, believe that viral infection in the transplant recipient represents excessive immunosuppression and in the absence of available specific antiviral therapy, the first response should be immunosuppressive reduction rather than augmentation.

When specific antiviral therapy is available, concomitant antiviral and continued appropriate maintenance immunosuppressive therapy may be used with monitoring of the viral load to ascertain clearance of infection. This is especially true when, based on epidemiologic, HLA, or other characteristics, the perceived risk of significant rejection outweighs the perceived risk of long-term effects from viral infection. Although hepatitis A, B, and C, and papilloma viruses are common and associated with significant morbidity among kidney transplant recipients, currently, the most concerning viruses causing morbidity in kidney transplant recipients are the family of human herpes viruses (HHV) and BK among the polyomaviruses. Among the HHV viruses, the most concerning viruses in transplantation are CMV, which is HHV-5, and Epstein Barr Virus (EBV), which is HHV-3 (Table 1). Although there are rare case reports of JC and SV40 causing nephropathy, these are very rare and the most concerning polyoma virus is BK. Both the HHV and polyoma viruses are DNA viruses that are latent or “permissively replicative” and may be reactivated within the immunosuppressed recipient or introduced by the donor kidney.

Cytomegalovirus

Cytomegalovirus is the “classic” transplant associated viral infection. It causes fever, malaise, leucopenia, thrombocytopenia, and allograft dysfunction. Even asymptomatic infection with CMV is associated with renal allograft dysfunction, mortality, and graft loss, despite early detection and treatment of asymptomatic infections. Poor outcomes are associated with poor HLA matching and may reflect increased immunogenicity, inflammatory response, or failure to clear CMV. Cytomegalovirus is commonly associated with leukopenia, and so it is common to discontinue the antimetabolite as part of the therapy. We routinely discontinue the antimetabolite upon the diagnosis of CMV, even in the absence of leukopenia. This allows for more rapid clearance of the virus and improves the patient’s ability to mount an appropriate humoral response. Although we have shown that weekly monitoring for CMV and a preemptive approach was as effective as routine prophylaxis, we found that the preemptive approach was too impractical outside of a clinical trial setting. Thus, we routinely use CMV prophylaxis in the initial post transplant setting. We treat subsequent asymptomatic or minimally symptomatic CMV disease with oral valganciclovir 900 mg bid (adjusted for renal function) until viral clearance, assessed with weekly PCR. We treat invasive CMV initially with intravenous ganciclovir until there is evidence of clinical improvement and then we convert to oral valganciclovir. We do not routinely reinstitute the antimetabolite, but if we do, it is in patients deemed at
high risk for rejection. We also assess an appropriate humoral response by measuring CMV IgG. If this is appropriately elevated, we may cautiously reintroduce the antimetabolite and monitor the blood for CMV by polymerase reaction (PCR) biweekly for 1-2 months, as this is the typical time for reactivation after augmentation of immunosuppression.

**Epstein Barr Virus**

Epstein Barr Virus has been associated with post transplant lymphoproliferative disease (PTLD). Monitoring for EBV can be performed but the interpretation is complex. Viral loads greater than 5,000 copies/mL in the blood are associated with PTLD. Despite clearance, potentially related to antiviral agents such as acyclovir or ganciclovir, PTLD may progress. High EBV loads probably indicate a “net state of over immunosuppression” manifested as a reactivation of lytic EBV infection. Reactivation is associated with expression of a viral thymidine kinase which is responsive to antiviral agents such as ganciclovir. When EBV is oncogenic, however, it is in a latent state rather than a lytic state and, thus, not responsive to antiviral agents.

Recently the use of arginine butyrate to convert the latent state to a lytic state followed by ganciclovir has been investigated in patients with lymphoid malignancy including PTLD patients. Ten of 15 patients achieved a response. Two patients with PTLD achieved a complete response and two a partial response, while 2 had no response. Though encouraging, this therapy should still be considered investigational.

**Polyoma virus (BK)**

The BK virus is the most recently recognized viral pathogen affecting renal transplant recipients. It was originally reported in 1971. Its impact was limited, however, until the introduction of new potent immunosuppressive medications such as tacrolimus and mycophenolate mofetil. In the current era of immunosuppression, BK virus causes nephropathy in up to 8% of recipients, and frequently results in allograft loss or permanent dysfunction. It presents as an asymptomatic gradual rise in creatinine with a tubulointerstitial nephritis that mimics rejection on biopsy and produces a treatment dilemma.

The diagnosis and severity of BKV infection correspond to our understanding of the pathogenesis of BKV nephropathy. Thus, viral replication begins early after transplantation and progresses through detectable stages – viruria, then viremia, then nephropathy. Detection of BKV DNA in the plasma, or viremia, may be a better indicator of nephropathy than detection in the urine by cytology or PCR. Threshold values of 10,000 copies/mL in the blood have been suggested to predict BKV nephropathy, but considerable overlap of these values exists among recipients without BKV nephropathy, active BKV nephropathy, and resolved BKV nephropathy.

Our group has found that a preemptive strategy that includes frequent BK monitoring during the first year after transplantation (monthly for the first 6-months and at months 9 and 12) and in the subsequent evaluation of renal dysfunction after the first year, with discontinuation of the antimetabolite upon detection of BK viremia, is an effective way to manage BK infection. Our monitoring and treatment strategy are shown in Figure 2.

Alternatively, one can monitor by screening urine with decoy cells or PCR. A retrospective analysis of our randomized, controlled trial showed that although screening of urine was highly sensitive, it had a poor positive predictive value (<20%) of progression to sustained viremia, and thus the potential for development of BK nephropathy. Thus, we prefer to monitor blood rather than urine for evidence of active BK infection. Using this strategy, we have had only one patient develop BK nephropathy in the last 7 years among greater than 1000 patients, and this has been associated with an acceptable rate of acute rejection of less than 5% at one year and 10% at two years.

There is no known effective antiviral treatment for BK infection. A number of potentially therapeutic agents have been tried and include: cidofovir, leflunomide, intravenous immunoglobulin, and quinolones as we recently reviewed. All of these potentially therapeutic
agents have been used in combination with immunosuppression reduction and the role of these agents remains unclear. Reduction of immunosuppression remains the cornerstone of management.

Whether immunosuppression should be introduced after clearance of BK is unclear. With the recognition that BK nephropathy is associated with inflammation and poor patient and graft outcomes and that many patients may not require “triple immunosuppression”, it seems prudent to reduce the immunosuppression—preferably by eliminating the antimetabolite and monitoring for rejection.

Recently, an assay that measures adenosine triphosphate (ATP) release of magnetically sorted-phytohemagglutinin (PHA)-stimulated peripheral CD4+ cells has been advocated in an attempt to define the net state of immunosuppression. This assay is known as the Cylex-Immuknow assay and is available, commercially, in the U.S. Levels of 225-525 ng/mL were generally seen in patients with stable allograft function, levels >525 ng/mL among those experiencing acute rejection and levels less than 225 ng/mL and usually less than 100 ng/mL were seen among those with active viral infection including those with HCV, CMV, or BK infection. These data support the thesis that active viral infection is associated with excessive immunosuppression. However, the viral infection itself may also be immunosuppressive. In either case the rational treatment approach is reduction in immunosuppression. Decreases in immunosuppression in the face of active viral infection have been associated with an increased ATP level. Thus, the assay has been used to titrate initial immunosuppression reduction and its subsequent increase, in patients with viral infection after transplantation.

**SUMMARY**

Viral infections are common after transplantation. Viral infections appear to be biomarkers of excessive immunosuppression. Monitoring for reactivation of viral infections like CMV and BK should be routine. Molecular techniques including PCR are the monitoring tests of choice. Immune activating viruses like CMV produce bi-directional effects that predispose to rejection and poor outcomes. Non immune-activating infections like BK still produce inflammation that may lead to poor allograft function or loss. Specific antiviral treatment should be given for the treatment of asymptomatic CMV infections, as these are associated with increased mortality and allograft dysfunction. Preemptive immunosuppression reduction can prevent progression from viremia to nephropathy for BK and other viruses. If, when, and how to increase immunosuppression after clearance of a viral infection is unknown. Prospective studies are needed to answer this important question.

**REFERENCES**


