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Future directions in the treatment of BK virus nephropathy

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BK polyomavirus-associated nephropathy (BKVAN) is an important cause of allograft renal dysfunction after kidney transplantation. Recent evidence has suggested associations of BK infection with urological malignancies and the development of de novo donor specific antibody (DSA). Despite recent advances in kidney transplantation knowledges, management of BKVAN has remained challenges. Recent evidence has suggested that BK-specific T-cell responses, but not neutralizing antibodies, is important in clearance of BK viremia. In this article, we present future directions in prevention and treatment of BKVAN.

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Editorial

BK polyomavirus-associated nephropathy (BKVAN) is an important cause of allograft renal dysfunction after kidney transplantation (1), up to 10% of kidney transplant patients (2,3). In addition, recent evidence has suggested associations of BK infection with urological malignancies (4) and the development of de novo donor specific antibody (DSA) (5,6), resulting in antibody mediated rejection and allograft loss.

Although a few screening methods for BK virus have been applied, transplanted kidney biopsy is still the gold standard for diagnosis of BKVAN (7,8) and intra-nuclear viral inclusions-SV40 positive staining (or in situ hybridization for BK virus) is pathognomonic (8,9). However, SV40- negative inflammation with viremia can be found in 22.8% of cases, prior to subsequent pathological confirmation of BKVAN, which could be due to 1) missed disease from sampling error or 2) viral reactivation following T cell rejection (10). This ongoing issue causes challenges and difficulties in diagnosis and management of BKVAN.

Current treatments of BKVAN

Despite recent advances in kidney transplantation knowledges, management of BKVAN has remained challenges. Although a few medications that have been proposed and used as adjunctive therapies for BKVAN (Table 1), clinical benefits of these adjunctive therapies are currently controversial. Thus, careful immunosuppression reduction/modification remains the mainstay treatment for BKVAN (11). However, reducing immunosuppression may put patients at risks for rejection (3). Moreover, as mentioned prior, SV40-negative inflammation with viremia can often be found leading to the difficulties in differentiation in diagnosis of BKVAN, rejection, or concurrent rejection and BKVAN. This ongoing problem results in significant use of bolus corticosteroids in this setting. However, recent evidence suggested deleterious effects of bolus corticosteroids on a higher rate of graft loss in patients with BK infection (12). Brincidofovir, a novel agent for treatment of BK virus infection (Table 1), has been developed to reduce adverse effect and increase the efficacy of cidofovir (13,14). Some case reports/case series demonstrated its efficacy for treatment of BKVAN (13,14). However, the recent data on brincidofovir for treatment of cytomegalovirus (CMV) infection unfortunately showed that brincidofovir was not found to be more effective than placebo, and the rate of CMV infection was higher after drug discontinuation (15,16). In addition, brincidofovir also has worrisome gastrointestinal side effects, mimicking graft-versus-host disease (GVHD) (17).

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Table 1. Proposed Adjuvant therapies for BKVAN

Adjuvant therapies	In vitro activity	Clinical benefit for BK infection
Cidofovir	Yes	Yes/No (case reports, retrospective studies, meta-analysis) (11); + Cost-effective (26)
Brincidofovir	Yes	N/A (case reports, case series and phase II NCT00793598) (18)
Leflunomide	Yes	No (Clinical trials) (18)
Fluoroquinolone	Yes	No (clinical trials) (27,28)
mTor inhibitors	Yes	No (retrospective studies) (18)
Intravenous immunoglobulin	Yes	Yes (retrospective studies) (18,20)

Future directions

In patients under immunosuppressive or immunomodulatory therapy including kidney transplant recipients, lacks of BK-specific T cell response and/or neutralizing antibodies have been proposed as underlying pathogenesis of high BK viral replication and cytopathic damage, leading to BKVAN development (18). In-vitro, intravenous immunoglobulin (IVIG) provided the inhibitory effect on BK virus replication via BK virus neutralizing antibodies (19). Despite a need of multicenter randomized trial confirming its clinical benefits, retrospective studies have shown potential benefits of combination treatment with reduced immunosuppression an IVIG on clearing BK virus infection (18-20).

Recent evidence has suggested that BK-specific T-cell responses, but not neutralizing antibodies, is important in clearance of BK viremia (21). Thus, T cell adoptive therapy has been proposed as potential novel treatment of BK infection (22) by transferring T cell that recognizes the BK virus antigen to BK virus-infected recipients. Very recently, Papadopoulou et al (22) transferred viral-specific T cell to 7 hematopoietic stem cell transplant recipients with BK viremia. Investigators report successful treatment response without significant serious adverse effects. Future studies of this novel adoptive T cell therapy for BK virus infection are required in kidney transplant setting.

Prevention of BKVAN and individualization of BKVAN risk

To date, a number of risk factors for BK virus infection have been proposed including donor-, recipient-, and transplant-associated risk factors, which some factors are modifiable (3,23). Within recent years, pre-transplantation donor–recipient pair seroreactivity against BK virus has been found to a strong predictor of BK viremia and BKVAN after kidney transplantation (24). Pre-transplantation BK serological testing of potential donors and recipients may help stratify patient risk for BK infection after kidney transplantation. Since different types of immunosuppression result in different risks for BK infection (25), future studies are required if the use of pre-transplantation BK serological testing of potential donors and recipients in prediction model for BKVAN development can help choose appropriate immunosuppression for each recipient in order to reduce BKVAN while weighing rejection risk.

Authors' contribution

All authors had access to the data and a role in writing the manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no conflicting interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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