Transplant Nephrology

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The progressive rise in the number of kidney transplant recipients in the last 2 decades is reflective of the technological advances in the field. Nephrologists are responsible for providing long-term longitudinal care to these patients. It is pertinent that nephrologists understand the various nuances of aspects such as immunosuppression, opportunistic infections, and identification of causes associated with graft dysfunction.

Key Words: BK, immunosuppression, infections, Transplant

Transplant nephrology is a broad topic to cover when preparing for the Nephrology board exams; however, there are some general domains that many board examination questions may be based on.

- Infections in kidney transplant recipients, typical timing of each infection following transplant, prevention and identification, diagnosis, and treatment (eg, cytomegalovirus [CMV] reactivation and BK nephropathy).
- Understanding of immunological risk and the identification and treatment of allograft rejection (human leukocyte antigen [HLA] typing, antibody-mediated rejection, and T-cell-mediated rejection).
- Mechanism of action of immunosuppressive medications (tacrolimus, mycophenolate, and belatacept) and monitoring of immunosuppression.
- Side effects of specific classes of immunosuppression, eg, calcineurin inhibitors (CNIs), antimetabolites, and corticosteroids.
- Longer-term complications of kidney transplantation include malignancy post-transplant (most commonly nonmelanoma skin cancers) and post-transplant lymphoproliferative disease.

CASE 1

A 55-year-old male, with a past medical history of deceased donor kidney transplant 6 months ago, end-stage kidney disease secondary to biopsy proven diabetic nephropathy, hypertension, nonobstructive coronary artery disease, is found to have BK viremia of 7155 IU/mL on routine surveillance screening. Following are his labs:

White cell count: 5.6 $\times$ 10^9/L.

Hemoglobin: 11 g/dL, Platelets: 350,000/mcL.

Sodium: 134 mmol/L, Potassium: 4.7 mmol/L, Blood urea nitrogen: 23 mg/dL.

Creatinine: 1.5 mg/dL (122 μmol/L)

Urinalysis: No microscopic hematuria or proteinuria.

His immunosuppressive regime includes tacrolimus 4 mg twice a day (BID) (goal 5-8 ng/mL), mycophenolate mofetil (MMF) 500 mg BID, and prednisone 5 mg.

What is the next step in management with regard to new-onset BK viremia?

A. Continue current immunosuppressive regimen and repeat BK levels in 4 weeks
B. Discontinue prednisone
C. Reduce MMF to 250 mg BID and repeat BK levels every 2 weeks
D. Pursue kidney transplant biopsy
E. Reduce tacrolimus goal to 3-5 ng/dL.

The correct answer is C.

BK virus was first detected in a kidney transplant recipient at a hospital in London in 1971.[1] BK virus is a small, nonenveloped, icosahedral, closed circular, double-stranded DNA virus and member of the Polyomaviridae family.[2] Kidney transplant recipients experience infection via reactivation of latent infection or transmission of new infection from the donor kidney. The infection occurs in the following chronological stages—viruria, viremia, and allograft nephropathy. Viruria and viremia are detected in approximately 30% and 12% of kidney transplant recipients, respectively.[3] Nearly 50% of kidney transplant recipients develop viremia (BKV) during a period of 2-6 weeks after the onset of viruria, with a similar proportion of viremic patients developing BK viral-associated nephropathy (BKVAN) in the aforementioned time period.[4] Risk factors for development of BKV/BKVAN include the following.

- Intensity of immunosuppression: This is the most important factor associated with BKV/BKVAN. The high incidence of disease in the early post-transplant period is owing to this risk factor.
- Donor-associated factors: BK viruria prior to transplant and attenuated response to the virus.
- Recipient-related factors: Diabetes, older age, and certain HLA-C alleles.[5]
- Transplant-associated factors: ABO incompatibility, HLA mismatch, donor seropositive and recipient seronegative for BK virus, delayed graft function, ischemia

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or rejection of transplant kidney, and placement of urinary stent.[6]

Given the first post-transplant year is associated with high incidence of the virus, screening protocols for early detection have been developed. Although the frequency of screening differs across transplant centers, the Kidney Disease: Improving Global Outcomes and the American Society of Transplantation Infectious Diseases Community of Practice guidelines recommend monthly screening for the first 6 months post-transplantation and then every 3 months for the next 18 months.[7,8]

Plasma BK polymerase chain reaction (PCR) is the recommended test for the purpose of screening for BKV and BKVAN. Urine BK PCR is not the recommended test for screening given its lack of specificity—almost 50% of patients with viruria will not develop viremia and a plasma PCR is a requisite for confirmation. Urine cytology demonstrates the classic "decoy cells"—tubular epithelial cells with ground glass nuclear inclusions surrounded by a condensed rim of chromatin (other variations include multinucleation, clumped chromatin, and "owl eye inclusions").

Kidney transplant biopsy is the gold standard for diagnosis of BKVAN. The following features are required for pathologic confirmation.[9]. First, enlarged hyperchromatic nuclei and "ground glass" intranuclear inclusions within tubular epithelial cells. Second, immunohistochemistry confirmation utilizing antibodies directed against BK virus or cross-reacting SV40 large T antigen (the latter does not distinguish between BK and JC virus) [Fig 1].

CLINICAL SUMMARY

- It is imperative to understand infectious and metabolic complications associated with immunosuppression in kidney transplant recipients (myriad of adverse of adverse effects associated with tacrolimus are discussed).
- Monitoring, recognition and management of infections and rejection is nuanced and nephrologists should be acquainted with these aspects (management of BK viremia, T-cell mediated rejection, and antibody mediated rejection is discussed).
- Switching of mycophenolate mofetil to azathioprine should be done at least 6 weeks prior to attempting conception in kidney transplant recipients.

Treatment primarily involves modification of the foremost risk for BKV/BKVAN—intensity of immunosuppression. The following is a recommended approach once viremia is detected:

- Proceed with reduction of antimetabolite (MMF or azathioprine) dose in half (continue same doses of CNI and/or prednisone), with monitoring of renal function and plasma BK PCR every 2 weeks.
- Complete cessation of antimetabolite if viral loads increase or have continued to plateau.
- If the above interventions have not led to reduction in viral load, reduce CNI goals balancing with risk for rejection.

Adjunctive therapies such as cidofovir, quinolones, and leflunomide have no role in treatment of BKV/BKVAN.[10] Intravenous immunoglobulin could be considered as an adjunct given its promising results in multiple observational trials.[11–13] Lastly, patients experiencing graft loss as a result of BKVAN should be considered for retransplantation given high rates of subsequent allograft survival.[14]

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Q2. A 63-year-old female with a deceased donor kidney transplant done 2 months ago, end-stage kidney disease secondary to autosomal dominant polycystic disease (right native nephrectomy done at the time of kidney transplant), hypertension, and diet-controlled type 2 diabetes presents with mild tremors of upper limb for the past 2 days. Her medications include tacrolimus 4 mg BID, MMF 500 mg BID, prednisone 5 mg, and nifedipine 30 mg daily. Her labs demonstrated the following:

Sodium: 134 mmol/L.

Potassium: 6 mmol/L, Bicarbonate: 18 mmol/L, Glucose: 130 mg/dL (7.2 mmol/L), Blood urea nitrogen: 40 mg/dL. Creatinine: 1.8 mg/dL (baseline creatine 1.4-1.6 mg/dL)

Urinalysis: Trace glucose, negative protein, blood, ketones, leukocytes, and nitrites.

What is the likely cause for this patient's clinical presentation and laboratory abnormalities?

A. Antibody-mediated rejection
B. Supratherapeutic tacrolimus levels
C. MMF toxicity
D. Diabetic ketoacidosis
E. Obstructive uropathy

The correct answer is B.

Tacrolimus was derived from the soil fungus *Streptomyces tsukubaensis*. Its mechanism of action for T cell inhibition is via binding to an immunophilin FK-binding protein. The ensuing tacrolimus-FK-binding protein complex inhibits dephosphorylation of calcineurin, thereby preventing nuclear translocation of nuclear factor of activated T cells, subsequent transcription of interleukin-2 and activation/proliferation of T-cells.[15]

There is a myriad of multisystemic adverse effects associated with tacrolimus (and cyclosporine), as discussed below:

- Nephrotoxicity: Both acute and chronic kidney impairment are associated with tacrolimus. Acute kidney injury usually occurs in the context of supratherapeutic tacrolimus levels and is a consequence of vasoconstriction. Histologically, this manifests as isometric

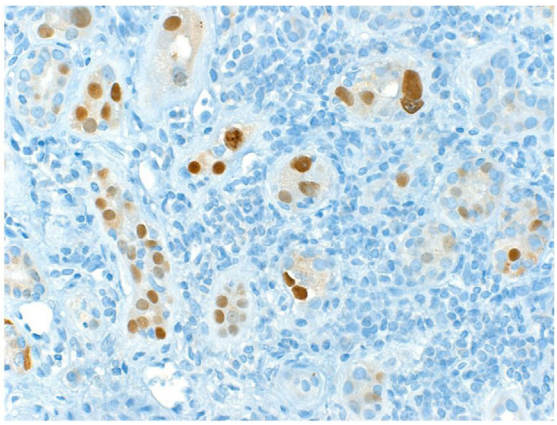

Figure 1. Positive SV40 stain in tubular cell nuclei (160× magnification). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

vacuolization of proximal tubules (Fig 2), along with necrosis and early hyalinosis of individual smooth muscle cells in afferent arterioles.[16] In addition, tacrolimus is also associated with thrombotic microangiopathy (TMA) even with therapeutic levels.

Chronic kidney disease from long-term tacrolimus exposure occurs as a consequence of direct tubular and hemodynamic effects. The classic histological manifestation is focal interstitial fibrosis associated with macrophage influx and tubular atrophy termed as striped fibrosis. Other features include focal and global segmental glomerulosclerosis, ischemic collapse or glomerular scarring, and damaged medial smooth muscle cells in afferent arterioles replaced by beaded medial hyaline deposits that bulge into the adventitia.[16]

- Electrolyte derangement: Tacrolimus is associated with multiple electrolyte disorders, most commonly including hyperkalemia, metabolic acidosis, and hypomagnesemia.

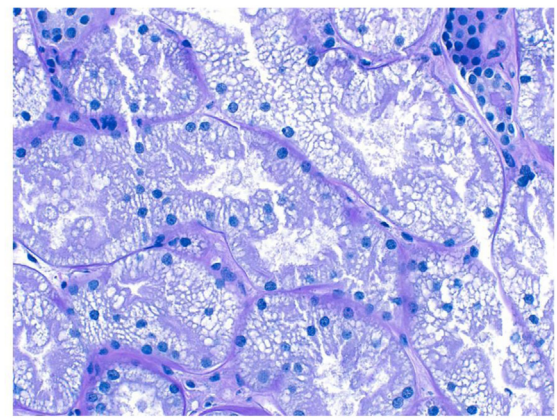

Figure 2. Tubular isometric vacuolization periodic acid schiff (PAS) stain (160× magnification). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The incidence of hyperkalemia in patients treated with CNIs is 5-40%.[17] The mechanism of development of hyperkalemia and metabolic acidosis in the setting of tacrolimus includes activation of the sodium-chloride co-transporter and reduction of transcriptional activity of mineralocorticoid receptor.[18,19] Persistence of metabolic acidosis is associated with increased risk of graft loss, death-censured graft failure, and mortality.[20,21]

The incidence of hypomagnesemia in kidney transplant recipients on tacrolimus is over 40%, with it being an independent predictor of development of new-onset diabetes after transplantation.[22] Hypomagnesemia occurs as a result of renal magnesium wasting from downregulation of the tubular magnesium transported TRPM6.

- Neurotoxicity: Tremors are the most common neurological symptom associated with tacrolimus (with other less frequent symptoms such as peripheral neuropathy and neuralgia).[23] Severe manifestations of neurotoxicity include hallucinations, psychosis, seizures, ataxia, dysarthria, vision loss, and posterior reversible encephalopathy syndrome.[24]
- Cardiovascular effects: It is well recognized that cardiovascular disease is the leading cause of mortality in kidney transplant recipients.[25] The development of common cardiovascular risk factors such as hypertension, hyperlipidemia, and diabetes (new-onset diabetes after transplantation) are associated with tacrolimus use.

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CASE 3

A 29-year-old female with a history of living-related kidney transplant 3 years ago and end-stage kidney disease secondary to IgA nephropathy, presents to the clinic for a routine follow-up. She is considering pregnancy in the near future and was seeking advice regarding this in the setting of her kidney transplant. She uses oral contraceptives currently, has optimal home blood pressure readings, and has had an uncomplicated clinical course since kidney transplantation. Her medications include tacrolimus 4 mg BID (goal 4-6 ng/mL), MMF 500 mg BID, and prednisone 5 mg. Her labs are as follows:

White cell count: 7.7×10^9/L.

Hemoglobin: 13.2 g/dL, Platelets: 245,000/mcL.

Sodium: 139 mmol/L, Potassium: 4.2 mmol/L, Blood urea nitrogen: 25 mg/dL.

Creatinine: 1 mg/dL (88 μmol/L)

Urinalysis: No microscopic hematuria or proteinuria.

What would be the appropriate recommendations with regard to pregnancy at this stage post-transplantation?

A. Proceed with switching MMF to azathioprine at least 6 weeks prior to attempting conception

B. Recommend against pregnancy
C. Lower tacrolimus goals to 2-4 mg/dL
D. Recommend waiting time for another year prior to pursuing pregnancy
E. Obtain 24-hour ambulatory blood pressure monitoring

The correct answer is A.

The American Society of Transplant consensus guidelines recommend that pregnancy be avoided in the first year post-transplantation, and it only be pursued in the setting of stable maintenance immunosuppression, no rejection in the past year, serum creatinine <1.5 mg/dL (122 mmol/L), and minimal/no proteinuria.[26]

It is recommended that changes in immunosuppression be instituted prior to conception. CNIs and steroids are listed as category C in the Food and Drug Administration pregnancy safety classification and can continue safely during pregnancy with close monitoring of levels. While antimetabolites (MMF and azathioprine) are listed as category D, azathioprine can be used safely in pregnancy with a recommendation to switch from mycophenolate at least 6 weeks prior to attempting conception.[27]

Hypertension (new-onset and worsening of existing) and pre-eclampsia are the most common complications associated with pregnancy in kidney transplant recipients.[28] Risk factors for development of pre-eclampsia includes chronic hypertension, previous preeclampsia, and elevated serum creatinine (1.7 mg/dL or 150 mmol/L) at the commencement of pregnancy.[29] The initiation of low-dose aspirin between 12 and 18 weeks of pregnancy is helpful in preventing and delaying the onset of pre-eclampsia.[30] Labetalol and nifedipine are more efficacious than methyldopa for reducing the risk of severe hypertension.[31] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in pregnancy given the risk of fetal kidney injury.[32]

With regard to risk of rejection during pregnancy (Table 1), higher serum creatinine, suboptimal levels of immunosuppression, and prior rejection correlate with higher risk.[33] Suboptimal fetal outcomes have been reported with higher risk of small for gestation and low birth weight offspring in kidney transplant recipients.[34] The incidence of preterm delivery is higher in kidney transplant recipients in comparison to the general population, with maternal hypertension and high serum creatinine (1.7 mg/dL or 150 mmol/L) noted as risk factors.

Table 1. Complications Associated With Pregnancy in Kidney Transplant Recipients

Maternal Complications	Fetal Complications
Hypertension	Low birth weight
Preeclampsia	Stillbirths
Gestational diabetes	Preterm delivery
Miscarriage	Neonatal death
Allograft rejection	Birth defects

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CASE 4

A 48-year-old lady received a 1:1:1 mismatch allograft from her mother as a living-related donor kidney transplant 6 months ago. Prior to transplant, she had been on peritoneal dialysis for 2 years without complications. Her primary cause of end stage kidney disease (ESKD) was autosomal dominant polycystic disease. Her maintenance immunosuppression regime included tacrolimus 4 mg twice daily, mycophenolate 500 mg twice daily, and prednisolone 5 mg once a day. She was also taking co-trimoxazole, valacyclovir, calcium, vitamin D, and 5 mg of amlodipine for hypertension. She presents to a routine follow-up visit and reports feeling unwell—she has had nausea and vomiting for 1 week. She admits to suboptimal compliance with her immunosuppressive medications over the past month since her last visit. Laboratory investigations revealed:

White cell count: 8.7×10^9/L.

Hemoglobin: 13.2 g/dL, Platelets: 145,000/mcL.

Sodium: 137 mmol/L, Potassium: 4.7 mmol/L, Blood urea nitrogen: 25 mg/dL.

Creatinine: 6.8 mg/dL (600 μmol/L), Urinalysis: microscopic hematuria and proteinuria.

Ultrasound reveals a slightly echogenic allograft without hydronephrosis; subsequently kidney biopsy was performed, which revealed the following (Figs 3 and 4) :

What is the most appropriate initial management of this patient?

A. Intravenous Piperacillin-Tazobactam for allograft pyelonephritis.

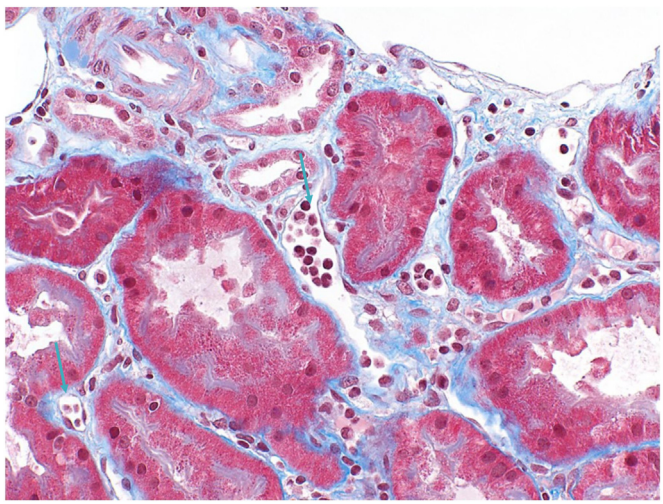

Figure 3. Arrows denoting peritubular capillaritis (trichrome stain; magnification 160×). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

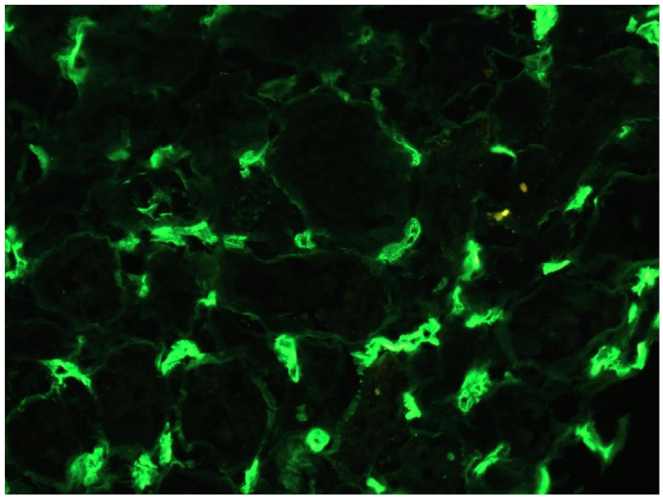

Figure 4. Diffuse linear immunofluorescence stain for C4d in peritubular capillaries.

B. Methylprednisolone 500 mg intravenously daily x 3 days, increased tacrolimus and mycophenolate doses.
C. Methylprednisolone 500 mg intravenously daily x 3 days, increased tacrolimus and mycophenolate doses, plus antithymocyte globulin.
D. Methylprednisolone 500 mg intravenously daily for 3 days, increased tacrolimus and mycophenolate doses, plus plasmapheresis.

The correct answer is D.

Acute rejection is classified according to the Banff criteria, which is regularly updated.[35] Overall, allograft rejection in the first year following kidney transplant has become less common given advances in immunological risk assessment and the efficacy of contemporary immunosuppressive medication regimes.[36] These regimes consisting of mycophenolate, tacrolimus, and corticosteroids are associated with a lower risk of acute rejection with a consequent increase in the risk of diabetes mellitus type 2 post-transplant.[23]

There are two principal forms of acute allograft rejection; acute T-cell-mediated rejection (TCMR), which was previously referred to as cellular rejection, and acute antibody-mediated rejection (ABMR). HLA typing prior to transplant allows for the identification of a threshold of acceptable HLA mismatching ranging from zero mismatches to complete mismatch.[37] This is an essential step since the recognition by recipients T cells of a foreign HLA will trigger an immune response leading to allograft rejection.[37] HLA mismatching tends to have a linear adverse relationship with allograft survival.[36] However, some of this risk may be obviate by the effectiveness of contemporary immunosuppressive regimes.[36]

The degree of recipient's sensitization to HLA antigens in the form of pre-existing antibodies to those antigens is assessed prior to transplant, which allows for an estimation as to the degree of incompatibility with HLA antigens in the respective donor population known as the level of panel reactive antibody (PRA). The PRA is expressed as a percentage, which refers to the percentage of potential donor antigens that the recipient has raised preformed antibodies against. Antibodies that may generate a positive cross-match assessment and likely lead to allograft rejection are known as donor-specific antibodies.[37] Rarely, an antibody responsible for the generation of allograft rejection is not related to an HLA antigen and is known as a non-HLA antibody, meaning that the antigen that generated the antibody was not HLA in origin.[38] In certain circumstances, a patient may need to undergo desensitization prior to transplant if they have a high PRA or known donor-specific antibodies, and in circumstances where de-sensitization is not appropriate, recipients at high risk of allograft rejection may enter a pooled kidney paired exchange program.[39] Allograft rejection can also manifest more chronically or subacutely and may be referred to as transplant glomerulopathy or subclinical rejection. When allograft rejection arises out of poor recipient compliance with immunosuppressive medications, the prognosis for graft function is poor.[40]

While the Banff criteria is used for classifying the type of rejection and severity and used as a guideline for decisions around intensification of immunosuppression, the treatment ought to be individualized by the transplant nephrologist incorporating other clinical factors.[8] These factors will include the severity of presentation, the degree of potential reversibility based on kidney biopsy findings, the type of allograft rejection present (TCMR vs ABMR vs co-existing TCMR and ABMR), and the overall comorbidity index of the patient and the level of pre-existing exposure to immunosuppression up to that point.[41]

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CASE 5

An 18-year-old man with a background history of ESKD due to severe IgA nephropathy, and hypertension received a deceased donor allograft 2 weeks prior. His native IgA was proven by biopsy at age 16 with poor prognostic MEST-C score. He progressed rapidly to ESKD and commenced peritoneal dialysis, which he received for 1 year prior to transplant. HLA mismatch was 1:2:1. After initial immediate graft function, he developed acute allograft dysfunction over 5 days and allograft biopsy demonstrated acute TMA. He did not have manifestations of a systemic microangiopathic hemolytic anemia, hemoglobin 14.8 g/dL, blood film did not display schistocytes, and serum lactate dehydrogenase is normal.

He was screened for complement disorders through genetic testing and testing for autoantibodies to complement regulator proteins, which were negative. Serum complement was normal. Consensus opinion after consultation with hematology and immunology services was that the renal-limited TMA was CNI-induced even though serum trough levels were not out of target range. The deceased

donor was a 60-year-old road traffic accident victim. Donor viral serological screening was negative for hepatitis C, HIV, and hepatitis B; however, he was Epstein Barr virus (EBV) seronegative and CMV seropositive. The recipient was also EBV seropositive but was CMV seronegative. Please answer the following two questions.

What change to this patient's maintenance immunosuppression regime would you advise?

A. Corticosteroids maximize MMF and hold CNI
B. Corticosteroids and MMF and replace CNI with cyclophosphamide.
C. Consider the addition of Belatacept to replace the CNI in the maintenance immunosuppression regime.
D. Repeat doses of induction immunosuppression with interleukin-2 antagonists.

The correct answer is C.

What factors in a patients' history would make you concerned about the use of Belatacept?

A. EBV seropositive recipient and EBV seropositive donor.
B. EBV seronegative recipient and EBV seropositive donor.
C. EBV seronegative recipient and CMV seropositive donor.
D. CMV seropositive recipient and EBV seropositive donor.

The correct answer is B.

Belatacept is a fusion protein comprised of human IgG1 fc fragment and the extracellular domain of Cytotoxic T Lymphocyte-Associated Antigen 4, which inhibits T cell activation through costimulatory blockade.[42,43] It is administered intravenously, and its predominant indication is in individuals who are intolerant of CNIs due to toxicity; however, some transplant programs also preferentially use Belatacept as maintenance immunosuppression in order to minimize the adverse effects associated with long-term calcineurin use.[44] Belatacept is contraindicated in recipients who are seronegative for EBV, where the donor is EBV seropositive due to the risk of EBV-associated post-transplant lymphoproliferative disease.[45]

Randomized controlled trials assessing the switch in immunosuppression from calcineurin-based regimes to Belatacept based regimes appear to indicate more frequent biopsy-proven rejections; however, allograft function appeared superior in the Belatacept group, and allograft survival was similar to those assigned to continue calcineurin.[46,47] Some studies have suggested improved long-term graft survival with Belatacept.[48] CNIs cause direct hemodynamic changes in the kidney, with vasoconstriction of both efferent and afferent arterioles leading to a reduction in glomerular filtration rate (GFR) acutely.[49] In addition, CNIs are also associated with dose-related fibrosis and deterioration in kidney function over the long term.[50] Since CNIs exert a direct hemodynamic effect to reduce GFR, switching to other immunosuppressive agents tends to be associated with improved GFR or lower serum creatinine values.

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SUMMARY

It is pertinent that nephrologists be adept at managing immunosuppression, along with identification and mitigation of complications in kidney transplant recipients. Immunosuppression is frequently associated with myriad of issues such as acute tubular injury (tacrolimus), infections, and cancer. Counseling of kidney transplant recipients regarding alteration of immunosuppression and potential complications in the context of pregnancy is imperative.

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