Polyoma virus in transplant recipients

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Renal transplant patients must receive immunosuppressants for a long time to prevent graft rejection; these medications make them susceptible to infections and neoplasms, which still are an important morbimortality cause in patients receiving solid organ transplants.[1]

Recently, the BK virus, which belongs to the polyoma family and has a special affinity for the urinary tract, has been recognized as an agent that may cause loss or dysfunction of the kidney graft.[2-4] Polyoma viruses are icosahedral 40-nm big viruses with an approximately 5,300 base pairs long DNA.

BK (BKV) and JC (JCV) viruses were initially named upon the initials of the patients in whom they were described for the first time: BKV was found in the urine of a renal transplant patient that had urethral stenosis [5] and JCV in the brain of a patient with progressive multifocal leukoencephalopathy.[6] BKV and JCV share 75% homology in their nucleotide sequence. The simian virus 40 (SV40) also belongs to the polyoma virus family and may infect humans, and shares 70% homology in the nucleotide sequence with BKV.[7,8]

The BKV genome is functionally divided into three regions: 1) a non-codifying regulatory region; 2) an early region codifying for proteins t and T, which are transcribed before virus replication; and 3) a late region codifying for the agnoprotein and the capsid proteins VP1, VP2, and VP3, which are transcribed after virus replication.[9,10]

CLINICAL MANIFESTATIONS

Primary infection by BKV occurs during the childhood either through the gastrointestinal or respiratory tracts, is generally asymptomatic, although it may occasionally produce upper respiratory or urinary symptoms. After the primary infection, the virus remains latent at different locations inside the host, mainly within the urinary tract (kidneys, bladder, prostate, cervix, vulva, testis) and within the hemato-lymphoid tissues (tonsils, peripheral blood mononuclear cells), and may be reactivated by immunosuppressive events. Eighty to ninety percent of the adult population is BKV-seropositive,[11,12] whereas in children the seropositivity rate reaches 80%-90% at 10 years of age.[13,14]

In bone marrow transplants, BKV presents as hemorrhagic cystitis, whereas in kidney transplant patients it may produce hematuria, urethral stenosis and/or tubulointerstitial nephritis with the risk for progression to graft loss. Patients receiving transplantation of other solid organs and those immunocompromised for any other reason (acquired immunodeficiency syndrome, systemic lupus erythematous) may also present with polyoma-induced nephritis.[15-18]

Most of polyoma-induced nephrites occur within the first year post-transplantation, although 25% of the cases are diagnosed later on.[19] Graft-loss rates vary 10%-80% according to the different series, and it seems to be lower in those centers with active surveillance programs. BKV accounts for most of the cases of cystitis and nephritis, although JCV has also been reported,[18] and occasionally SV40.[20]

In pediatric patients with renal transplant there is a special interest for BKV since this population is more likely to present a primary infection, and the virus may be quiescent within the urothelium of the donated graft. Viruria has been confirmed in 20%-50% of pediatric patients and nephritis in 2%-8%.[13,21,22] In a prospective multicenter study carried out in our country, it has been observed that pediatric patients have a two-fold virus replication rate in the urine as compared with adults within the first 6 months after renal transplant.[23]

Risk factors for post-transplantation infection

The risk factors that have been reported include factors inherent to the donor, the recipient, the graft, and the type of immunosuppression regimen.[24-26] So that the factors relating to the donor include: the presence of active BKV infection, cytomegalovirus (CMV) infection, BKV seropositivity —which has been implicated in the development of viruria, viremia, or nephritis in the pediatric and adult transplanted populations—, the absence of HLA-C7, as well as dead donor *versus* living donor.[25,27] On the other hand, recipient-related risk factors include: older age, male gender, CMV infection, diabetes mellitus, recipient's seronegativity for BKV, absence of HLA-C7, and Caucasian origin. The graft-related risk factors include: organ collection-related damage, time of cold ischemia, and late onset of graft function. One of the issues commonly cited as the risk factors favoring BKV infection is

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immunosuppression, especially maintenance therapy with the combination tacrolimus-mofetil mycofenolate, as well as the use of anti-lymphocytic therapy for managing acute rejection.[28,29] The real impact of the type of immunosuppressants, and particularly their combinations, is clearly studied in a prospective study by Brennan and coworkers, whose data point out that it is the *intensity* of immunosuppression, more than the *type* of immunosuppressant, what confers the highest risk for BKV infection, and thus for BKV-associated nephritis (BKVN).[26] The analyses carried out in that study indicate that the selection of a calcineurin inhibitor or of the adjuvant immunosuppressant did not independently affect BKV viruria or viremia levels. However, the highest viruria ranges were observed with the combination tacrolimus-mofetil mycofenolate and the lowest ones with cyclosporin-mofetil mycofenolate. In addition the study specifically shows how monitoring and early withdrawal of the anti-metabolite agent upon detecting the viremia was associated to viremia resolution and absence of BKVN without occurrence of acute rejection events or graft loss. With no doubt, the type and intensity of immunosuppression exceed whatever risk factor —individual or combined— and represent the most easily modifiable ones among all mentioned. It is evident that a strategy of this nature requires a follow-up with viral markers.

DEFINITIONS AND DIAGNOSIS

Polyoma virus infection.- Evidence of exposure to the virus without differentiating between latency and active replication.[24]

Polyoma virus replication.- Evidence of viral multiplication (lytic or active infection) detected by viral culture, polyoma particles by electron microscopy, polyoma structural proteins by immunohistochemistry, expression of messenger RNA of late virus genes (e.g. VP1); viral DNA at non-quiescent sites (e.g., plasma); cytological (lure cells) or histological evidence of polyoma replication.[24,30]

The infection may be primary of secondary depending on whether replication is detected in a seronegative or seropositive individual, respectively.

Polyoma virus disease is defined as the histopathological or ultra-structural evidence of virus-induced cytopathic and organ damage.

Direct visualization techniques have the drawback of not being able to differentiate between the three types of polyoma virus that infect humans (JCV, BKV, and SV40), in addition to the potential mistake with other virus such as cytomegalovirus and adenovirus.[31] Detection in the urine of lure cells (fig. 1) indicates active replication of the polyoma virus within the genitourinary tract, and although it is a simple method with a 100% sensitivity rate, its specificity for BKVN diagnosis is rather low (71%); even though, it is recommended as the screening method.[32]

The major limiting aspect of the methods based on viral DNA detection is that they cannot differentiate between quiescent infection and reactivation. The use of real-time PCR studying mRNA instead of DNA in cells from the urine sediment has been described as an accurate and non-invasive method for establishing the presumption diagnosis of BKVN in adult kidney transplant patients. By using the cut-off value of 6.5×10^5 copies of the BKV VP1 region per nanogram of total RNA in urine, nephritis may be predicted with 93.8% sensitivity and 93.9% specificity.[33] We may say that the use of urinary sediment RNA has been successfully used for diagnosing acute renal graft rejection[34] and the technique of urine collection has been described in detail.[35]

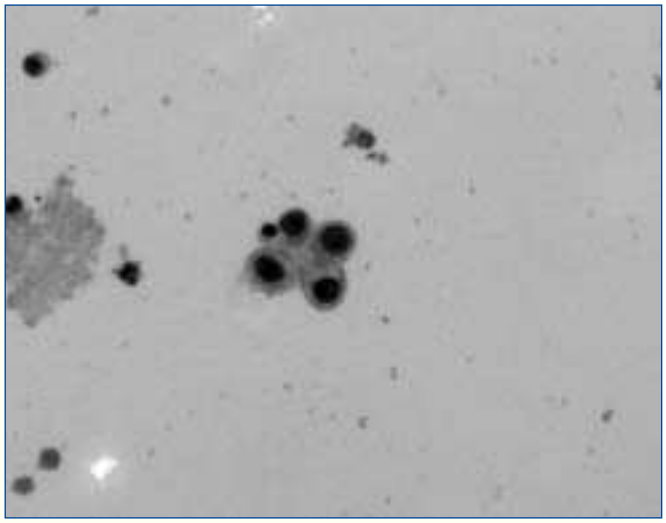

Figure 1. Lure cells in the cytology of the urinary sediment.

HISTOPATHOLOGY

The gold standard for diagnosing viral nephritis still is detailed evaluation of the renal biopsy. According to the recommendations of Banff's classification,[36] two tissular sections must be examined, which must contain medullary parenchyma in order to increase the sensitivity. The histopathological findings include intranuclear inclusion bodies within the epithelial cells, tubular cytopathic changes, and interstitial infiltrate (figs. 2-3).[32] The infiltrate may be mistaken with allograft rejection and with drug-induced nephro-

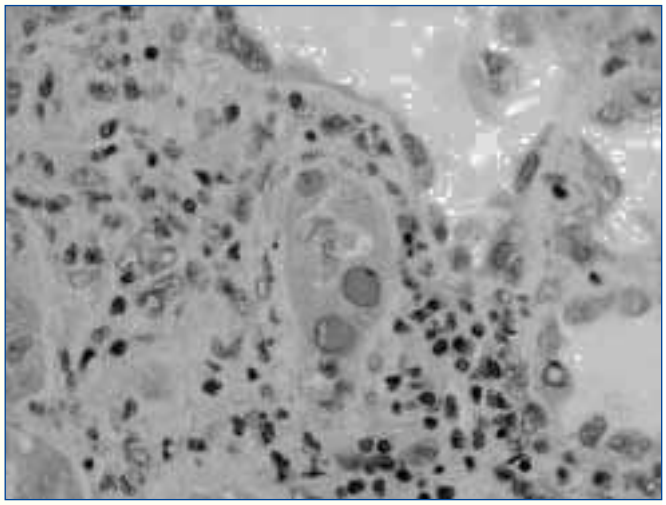

Figure 2. Célls from the tubular epitelium with cytopathic changes (HE 40x AO).

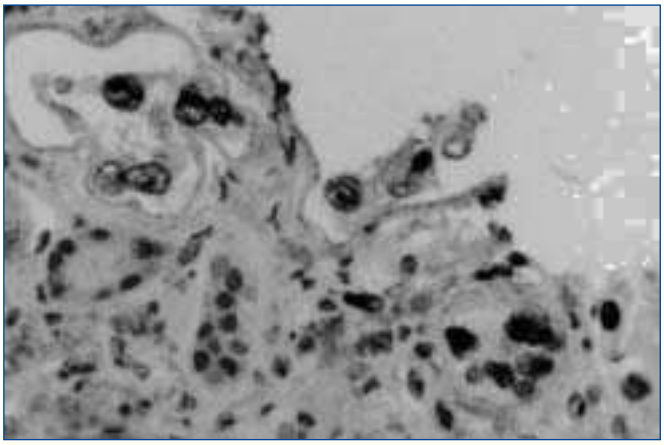

Figure 3. Positive staining for SV40 by immunohistochemistry.

toxicity. Renal tissue assessment by electron microscopy[37] or the use of immunohistochemistry firmly establishes the diagnosis (fig. 4). Given that BKVN may be focal, there is the potential for sampling errors and a negative biopsy should not completely rule out the possibility of BKV-induced nephritis. In those cases in which BKV is suspected, with replication levels above the cut-off values, it is recommended to perform immunohistochemistry, and if negative a new renal biopsy.

It has been proposed that the histopathology report should include the following items:

1) Semi-quantitative assessment of cytopathic viral changes and their location, either at the cortex or the medulla, and assessment of interstitial fibrosis, tubular atrophy and inflammation according to Banff's classification (table I).
2) Classification of the semi-quantitative assessment by nephritis patterns: A, early or limited stage; B, blown or developed stage; and C, late stage (table II).

The differential diagnosis should be made with acute graft rejection and with drug-induced nephrotoxicity; both conditions may be present simultaneously. It may be very difficult to differentiate the tubulointerstitial infiltrate of rejection (Banff type I) from BKV-induced nephritis.[38,39] If endarteritis, fibrinoid vascular necrosis and glomerulitis are present (Banff types II and III), as well as C4d deposition within the peritubular capillaries, then there is no doubt about the coexistence of acute rejection.

Once established, BKVN may lead to renal graft loss in 10%-80% of the cases according to the different series.[4,40] This is why there has been an emphasis on new diagnostic strategies allowing for early identification of this condition.

It has been observed that the greater the immunosuppression levels the higher the frequency of viruria.[41,42]

MANAGEMENT

BKVN management is not completely satisfactory because of two reasons: we still do not count on a uniformly effective anti-viral therapy, and there have not been controlled prospective studies conclusively showing the best treatment strategy.[40,43]

In most of the nephrology centers, the first approach is to decrease the immunosuppression level, although it has also been suggested to discontinue treatment with tacrolimus and

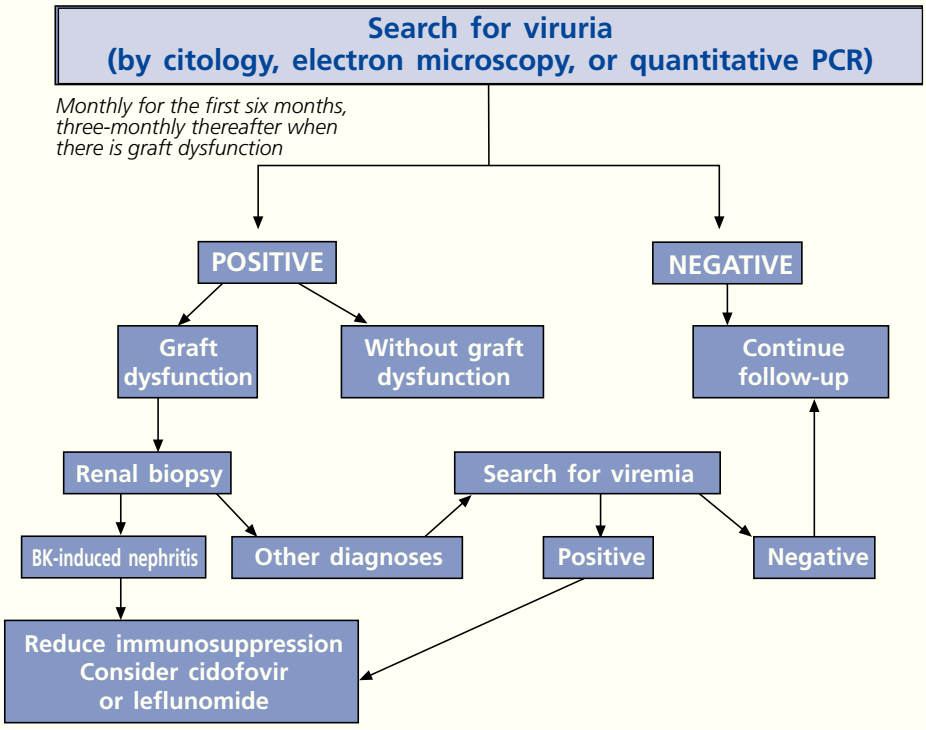

Figure 4. Screening recommendations for adequately detecting the BK virus in patients with kidney transplant.

Table I. Semi-quantitative assessment of renal biopsy

Polyoma virus-induced changes	Cualification according to Banff[36]			
	Viral cytopathic changes[a]	Inflammatory infiltrate[b]	Tubular atrophy	Fibrosis
None	*C* 0			
Minimal	*C* 1. Tubular involvement ≤ 10% of Bx	i 0: Insignificant (≤ 10% of Bx)	ta 0: Insignificant	f 0: Insignificant < 5% of Bx
MIld	*C* 2. Tubular involvement ≥ 10% and ≤ 25% of Bx	i 1: Inflammatory changes in 10-25% of Bx	ta 1: Tubular atrophy in ≤ 25% of Bx	f 1: Fibrosis in 6-25% of Bx
Moderate	*C* 3. Tubular involvement ≥ 26% and ≤ 50%	i 2: Inflammatory infiltrates in 26-50% of Bx	ta 2: Atrophy in 26-50% of Bx	f 2: Fibrosis in 26-50% of Bx
Severe	*C* 4. Tubules infected in > 50% of Bx	i 3: Inflammatory infiltrates in > 50% of Bx	ta 3: Tubular atrophy in > 50% of Bx	f 3: Fibrosis in > 50% of Bx

a: indicates the location at the renal parenchyma, the cortex, or the medulla; *b:* indicates the type of cells: polymorphonuclear leukocytes, plasma cells, eosinophils; *c*: cytopathic changes, i: inflammatory infiltrate, ta: tubular atrophy, f: fibrosis. Bx: Renal biospy. Modified from Hirsch et al.[25].

start on sirolimus.[44] Some groups have used cidofovir as anti-viral therapy, with the drawback of being a nephro- and hepatotoxic drug.[45,46]

BKVN management is bi-faceted: on the one hand, immunosuppression reduction in order to restore the anti-viral immunity, and on the other hand, specific anti-viral therapy.[47]

Modification of immunosuppression

Modification of immunosuppressive therapy has been the main therapeutic strategy even before the development of anti-viral therapy.[24] This strategy has been focused on immunosuppression reduction when making the diagnosis of BKVN on the one hand, and continuous surveillance from the moment of transplantation and modification of immunosuppressive therapy upon detection of viral replication in plasma and urine.

About modification of immunosuppression upon making the diagnosis of BKVN we must comment on the study performed by Vasudev and coworkers.[48] They included 41 adult patients receiving a renal transplant (36 cases) or combined renal-pancreas transplant (five cases), diagnosed with BKVN confirmed by characteristic histological and immunohistochemical findings (staining for SV40 by the peroxidase method) in the renal biopsy. Most of the patients were on triple therapy with prednisone, tacrolimus, and mofetil mycofenolate. The time elapsed from transplantation to diagnosis of BKVN was 318 days on average (variation of 48-1,356 days). Reduction of immunosuppressive therapy (reduction of the dose of immunosuppressants or switch from triple to double therapy) allowed decreasing the renal function loss rate from a creatinine clearance value of 4.8 mL/min/1.73 m^2/month before the diagnosis of BKVN to 0.7 mL/min/1.73 m^2 during the control following the diagnosis. However, graft loss was observed in 46% of the patients studied, which shows the negative impact of BKV infection on patients with renal transplant. Upon reducing immunosuppression, three patients presented acute rejection, two of them loosing the function of the renal graft.

In the study mentioned, better stabilization of renal function was observed with reduction or discontinuation of the therapy with calcineurin inhibitors, relative to global reduction of immunosuppression. The authors[48] mentioned that, although it may be difficult differentiating between the immunosuppressive effect and the nephrotoxic effect of calcineurin inhibitors, in this study they observed that the favorable effect of discontinuation or dose reduction was not observed immediately, as it would have happened had the arteriolar vasoconstrictor effect be the only effect to be suppressed. In this regard, it has been suggested that calcineurin inhibitors may have a permissive effect on viral replication because of their toxic effect on the renal epithelium.[43]

In a study carried out in children, Hymes and coworkers[49] observed that 20 (16%) out of 122 patients receiving a renal transplant developed a positive reaction with the polymerase chain reaction (PCR) for serum viral DNA at an average of 467 days (variation 23-1,410 days) post-transplantation. By comparing the immunosuppression regimens (all children received induction therapy with basiliximab and maintenance therapy with tacrolimus, prednisone, and mofetil mycofenolate or azathioprine or sirolimus) that the patients received, either they developed viral DNA positivity or not, the authors did not find differences between both groups of patients. In all cases immunosuppression reduction was indicated, and seven out of eight children that presented BKVN upon examination of the renal biopsy received in addition therapy with cidofovir. Thirteen (65%) of the treated patients remained PCR-positive, renal function was kept stable in 16 (80%) of them at 13 ± 6 months after initiating the therapy; the four remaining patients (20%), all with BKVN, presented progressive renal function deterioration.

Recently, Trofe and coworkers[50] have presented a summary of the strategies followed in several studies aimed at redu-

Table II. Histological patterns and clinical stages polyoma-associated nephropathy

Histological finding	Clinical correlation
Pattern A Minimal to mild cytopathic changes (*C*1-C2), common at the medulla. Minimal evidence for tubular necrosis and denudation of the basement membrane. Minimal inflammatory interstitial infiltration, tubular atrophy and fibrosis (< i1, ta < 1, f < 1).	**Early or limited stage** W/o graft dysfunction. The detection of lure cells at a routinary exam should lead to early viremia or viruria quantification; nephritis diagnosis must be confirmed by renal biopsy. Favorable prognosis.
Pattern B Viral inclusion bodies in more than 25% of the tubules at both the renal cortex and the medulla. Tubular necrosis and conspicuous basement membrane denudation (*C*2-*C*4). Significant interstitial inflammation (i1-i3). Mild fibrosis and tubular atrophy (ta ≤ 2, f ≤ 2).	**Blown or developed stage** Progressive renal function decrease. The renal biopsy must performed immediately. Differential diagnosis must be made with acute rejection and calcineurin inhibitors toxicity. The graft-loss rate may exceed 50%. .
Pattern C Cytopathic changes and extent tubular damage found at the renal cortex (*C*1-*C*4). Interstitial inflammation (i1-i3). Tubular atrophy and moderate-to-severe fibrosis (ta 3, f2-f3) .	**Late stage** Severe graft dysfunction. Likely graft loss.

Modified from Liptak P et al. and Hirsch et al.[25,39].
C: cytopathic changes, i: inflammatory infiltrate, ta: tubular atrophy, f: fibrosis, see table II for staging.

cing immunosuppression in recipients of renal transplant diagnosed with BKVN (table III).

If acute graft rejection occurs as a result of reduction of immunosuppressive therapy, it is recommended to administer methylprednisolone at a dose of 500 mg/day or 10 mg/kg/day i.v. for three days, and then initiating reduction of the corticosteroid therapy p.o.. In these cases, treatment with anti-lymphocytic preparations is not recommended because it induces a more severe immune dysfunction, which may promote reactivation of the polyomavirus. On the other hand, it has not been observed that treatment of acute graft rejection with corticosteroids may favor the recurrence of BKVN.[26,51]

The second strategy in immunosuppression reduction has been recently described by Brennan and coworkers[26] in a prospective study carried out in 200 patients receiving a renal transplant. All the patients received induction therapy with rabbit anti-thymocyte globulin, and then treatment with tacrolimus or cyclosporin, prednisone and azathioprine or mofetil mycofenolate. The patients were prospectively assessed to detect replication of BKV in plasma and urine by means of PCR. In patients with BKV viremia, azathioprine or mofetil mycofenolate therapy was discontinued; were this insufficient to render the viremia negative, it was indicated to reduce the dose of calcineurin inhibitors. Twenty-three (11.5%) patients developed BKV viremia and 70 (35%) presented viruria. In twenty two out of 23 patients the viremia became negative with reduction of immunosuppression: seven responded to discontinuation of only azathioprine/mofetil mycofenolate, two to discontinuation of only the calcineurin inhibitor, seven to both therapeutic procedures, and the remaining seven to the usual post-transplantation reduction of immunosuppression. However, in only five out of 23 patients the viremia became negative. Reduction of immunosuppression was accompanied by an episode of acute rejection.

In the study described[26] there were no cases of renal biopsy-proven BKVN, although this procedure was only performed in the presence of graft functional impairment, so that it may possible that mild cases of intrarenal viral replication were not diagnosed.

A new strategy recently described is based on *ex vivo* manipulation of T cells to increase the specific immunity against BKV.[52] This would make possible to provide specific immunity against the virus preventing the risk for acute rejection associated to reduction of immunosuppression.

Specific antiviral therapy

Cidofovir

Cidofovir is cytosine analogue nucleotide that inhibits viral DNA synthesis.[53,54] Many of the clinical experience comes from managing cytomegalovirus infection. Cidofovir is cleared mainly by the kidney and its main adverse effect is nephrotoxicity, and patients with renal dysfunction require lower doses. For this reason, the doses used in BKVN management are lower than those used in managing CMV infection. By contrast with the treatment for patients with CMV retinitis, cidofovir in BKVN patients has not been associated to the use of probenecid. Probenecid inhibits renal tubular excretion of cidofovir and allows increasing the plasma levels with lower administered doses. However, in BKVN patients, the lower intratubular excretion of cidofovir may potentially reduce the drug concentration at the tissue carrying the highest viral load in this disease.[55] In this regard, it has been observed that given its intrinsic nephrotoxicity, cidofovir is used in BKVN patients at a dose representing 10%-25% of the effective dose used to treat CMV retinitis. *In vitro* studies have shown that at the doses used in renal transplant, the serum peak concentration is approximately one tenth of the *in vitro* effective level and one twentieth of the 50% inhibitory concentration.[50]

There are reports published on the favorable effect of treating BKV-induced nephritis with cidofovir at a dose 0.25-1 mg/kg i.v., every one to three weeks, with previous hy-

Table III. Reduction or modification of immunosuppressive therapy in BKVN patients

Strategy	Intervention	Commentaries
A. Reduction of immunosuppression		
TAC	Keep levels < 6 ng/mL	Reduction of CI is usually done with MMF reduction
CyA	Keep levels 100-150 ng/mL	
MMF	Dose < 1 g/day (< 600 mg/m²/day)	
AZA	Dose < 100 mg/day (< 1,4 mg/kg/day)	
B. Modification of immunosuppression		
TAC → CyA	Keep levels 100-150 ng/mL	Consider reduction pf MMF levels by CyA
TAC → SIR		In patients with evidence of CI-induced nephrotoxicity
MMF → LEF	keep LEF levels > 40 µg/mL	Indicated in patients with leukopenia or concurrent CMV infection
C. Discontinuation		
of TAC or CyA or MMF	Continue with double therapy	In patients having not responded to strategies A or B

TAC: tacrolimus; CyA: cyclosporin A; MMF: mofetil mycofenolate; AZA: azathioprine; SIR: sirolimus; LEF: leflunomide; CMV: cytomegalovirus; CI: calcineurin inhibitor. Modified from Trofe and coworkers.[49].

dration to reduce the nephrotoxic effects.[43,45,56] In a study carried out in children, Hymes and coworkers[49] prescribed cidofovir at a dose of 0.3 mg/kg fortnightly for eight weeks. In another pediatric study, Araya and coworkers[57] have used «intermediate» doses at 0.75-1.0 mg/kg/dose, for five doses administered fortnightly, without probenecid and no evidence of nephrotoxicity. Kuypers and coworkers used cidofovir at a dose of 0.5 mg/kg weekly for 4-10 weeks in 8 adult patients; after an average follow-up of 24 months no patient lost the graft for this reason.[58]

In treated patients it has also been reported a reduction in the dose of immunosuppressants; thus, it has been argued that it is difficult to differentiate the antiviral effect of treatment with cidofovir from that obtained by improving the host immune response.[43] On the other hand, in some patients treated with cidofovir renal interstitial fibrosis has been observed, as well as worsening of renal dysfunction.[43]

In spite of all this, cidofovir is currently considered as being a therapeutic alternative in BKVN patients having not responded to reduction of immunosuppression and showing evidences of progressive renal function deterioration.[24,55]

Leflunomide

Leflunomide is metabolized to its active metabolite A771726, which inhibits pyrimidine synthesis; besides, its inhibitory effect of protein phosphorylation may be responsible of its antiviral effect.[59]

In a recent study, Williams and coworkers[60] reported on the evolution of 17 BKVN patients treated with leflunomide; viremia negative conversion and a reduction of the viral load were observed in seven patients and eight additional patients, respectively; in these 15 patients, stabilization or improvement in serum creatinine levels was observed. The collateral effects observed were leukopenia, skin rash, and hair loss.

In another study, Josephson and coworkers[61] reported on leflunomide therapy in 26 BKVN patients, in seven of them associated to cidofovir. After six months of therapy, the BKV viral load in the blood and urine was significantly lower than the baseline level in both groups of patients; the virus was undetectable in the blood of 11 patients; in eight of them, viruria also became negative. After 40 months of follow-up, graft loss was observed in four patients, all of whom had showed advanced levels of inflammation and renal damage at baseline renal biopsy. No serious adverse events from the therapy were observed in this study.[61]

In adults, leflunomide has been used at a dose of 100 mg/day for five days, being further reduced to 20-60 mg/day, trying to keep blood levels at 50-100 µg/mL.[47] Prolonged therapy (for more than six months) and maintaining minimal blood levels (not lower than 40 µg/mL) is required; on the other hand, the drug pharmacokinetics may vary considerably between the different patients.[46,50,55]

The immunosuppressant FK 778, a leflunomide derivative, has been recently investigated, showing *in vitro* activity against BKV.[50]

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is used to treat patients with immunodeficiencies, as well as those with other autoimmune or inflammatory diseases;[62] in renal transplant patients, it has been used to treat steroid-resistant rejection, in desensitization protocols, and as a maintenance immunosuppressant.[63-65] The mechanism of action is complex and transcends antibodies transference, including modulation and expression of Fc receptors, inhibition of complement-mediated damage, interference with the inflammatory cytokines network, effects on activation, differentiation and effector function of dendritic cells, macrophages, and T and B lymphocytes.[66,67] The immunomodulatory effects of IVIG might prevent rejection occurrence by decreasing the immunosuppressive therapy. The titer of neutralizing antibodies against the BK virus in IVIG-containing preparations is 2,048 hemagglutination units on average (variation of 2,048-4,096), much lower than the levels presented by BKVN patients that have on average 8,192 hemagglutination units (variation 2,048-65,536).[68]

There exist several reports on BKVN patients treated with IVIG, either as single therapy or associated to antiviral agents.

Wadei and coworkers reported on 55 BKVN patients, twelve of whom received IVIG therapy, two doses of 1.25 mg/kg administered 48 hours apart, ten received cidofovir in addition; the authors did not find differences in renal function worsening at 30 months in the IVIG-treated group *vs* patients without IVIG.[69]

Sener and coworkers reported on eight BKVN patients treated with IVIG 2g/kg at divided doses to two or five days and reduction of immunosuppression by 50%; after an average follow-up of 15 months, 88% showed stable renal function.[70]

Quinolones

It has been shown that quinolones may inhibit the BK virus replication *in vitro*.[71] In a pilot study presented by Josephson and coworkers,[55] gatifloxacin (400 mg/day p.o.) was prescribed for 10 days, in 10 patients with renal transplant that presented on two occasions "lure" cells in the urine. The immunosuppression regimen was not modified. Seven out of 10 treated patients showed viremia reduction greater than 80% and in all of them disappearance of lure cells in the urine was observed. The authors mention that gatifloxacin use was decided given its *in vitro* potency against polyomavirus and also because it concentrates at and clears through the kidney; in this way, tubular renal cells, where viral replication takes place, are exposed to high levels of the quinolone.

Similarly, the use of a fluoroquinolone, ciprofloxacin, in patients with hematopoietic cells transplant has been associated to reduction in the incidence of BKV viruria.[72]

Re-transplant

It has been described in the literature 15 patients receiving a new renal transplant after having lost their graft due to BKVN; infection recurrence was observed in two patients (13%). Most of the patients (11; 73%) received the same immunosuppressant regimen than the one used in the first transplant; nephrectomy of the first transplant was done in 11 patients, although this did not protect from further development of BKVN.[40] In theses cases, it has been recommended to reduce the immunosuppression intensity and avoid re-transplantation in the presence of BKV replication.[73]

On the other hand, Womer and coworkers[74] have recently performed re-transplantation concurrently with nephrectomy of the first transplant in two patients, with adequate renal function of the re-transplanted graft within one year of follow-up. However, it is still suggested that it is more appropriate to reduce immunosuppression (in order to promote the development of an antiviral immune response) before performing a new renal transplant.[74]

SCREENING FOR APPROPRIATE DETECTION OF BK VIRUS INFECTION IN PATIENTS WITH RENAL TRANSPLANT

Regular screening searching BK virus replication is recommended in renal transplant patients with viruria determination, either through cytology for lure cells or by electronic microscopy, and preferably through quantitative PCR, or through viremia according to the resources of each transplantation center, monthly for the first 6 months post-renal transplant, and then quarterly or whenever graft dysfunction is detected (fig. 4). In case of a positive viremia, performing a renal biopsy should be considered, mainly in those cases with graft dysfunction. If there is evidence of BKV-induced nephritis, immunosuppression should be decreased and therapy with leflunomide or cidofovir be considered.

As previously discussed, the advantage of the follow-up with viremia determination is that it brings the opportunity of assessing the impact on viral load reduction by reducing immunosuppression and administering antiviral therapy.

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