The role of Sirolimus in management of BK Virus infection after kidney transplantation

Background

Polyomavirus BK nephropathy remains an important cause of early graft dysfunction and graft loss in kidney transplantation. Inapparent spread of infection occurs early in childhood and seroprevalence among the general population is high (~80%) (1, 2).
The mainstay in the management of affected patients is the reduction or conversion of triple immunosuppression (3). Other treatment options include the use of fluoroquinolones, intravenous immune globulines, leflunomide or cidofovir. The lack of specific targeted therapies has prompted a pre-emptive active surveillance strategy with routine screening intervals post transplantation for viral replication using PCR assays (4).

Cellular and Molecular perspectives

Sirolimus inhibition is rapid and effective up to 24h post infection during viral early gene expression. The mTORC-1 kinase inhibitor torin-1 showed a similar inhibition profile, supporting the notion that early steps of BKPyV replication depend on mTOR activity. Cyclosporine A also inhibited BKPyV replication, while tacrolimus activated BKPyV replication and reversed sirolimus inhibition. FK binding protein 12kda (FKBP-12) siRNA knockdown abrogated sirolimus inhibition and increased BKPyV replication similar to adding tacrolimus. Thus, sirolimus and tacrolimus exert opposite effects on BKPyV replication inrenal tubular epithelial cells by a mechanism involving FKBP-12 as common target. Immunosuppressive drugs may therefore contribute directly to the risk of BKPyV replication and nephropathy besides suppressing T cell functions (5).

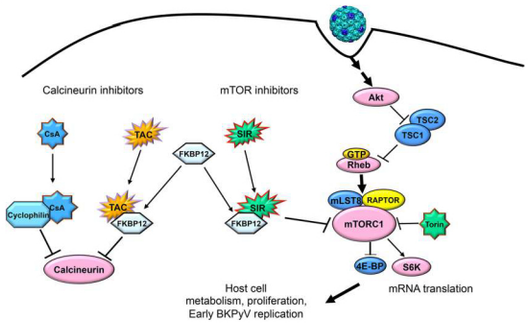

Figure 1: Effects of calcineurin inhibitors and mTOR inhibitors on BKPyV replication. Akt, plasma membrane located, inositol- activated serine-threonine kinase; BKPyV, BK polyomavirus; CsA, cyclosporine A; FKBP, FK binding protein; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; SIR, sirolimus; S6K, S6 kinas; TAC, tacrolimus; TSC, tuberous sclerosis factor; 4E-BP, translation inhibitor 4E binding protein.

Clinical perspectives

Aim of study

The aim of this study were to determine whether a calcineurin inhibitor (CNI) - sparing immunosuppressive regimen is associated with a lower incidence of BK viremia compared to a CNI - based regimen, and to compare peak viremia and time to resolution of BK viremia between the 2 regimens (6).

Methods

A single-center retrospective review was conducted on 180 patients who received a kidney transplant between 2008 and 2011 (6).

Table 1

Inducation theraphy with ATG for high immunologic risk patients Basiliximab for all other patients		
1st Group (Tac Group)	2nd Group (CNI-Sparing Regimen, Sir Group)	3rd Group (Steroid-Free Regimen)
Tacrolimus MMF Prednisone	▪ At or after 3 months: Sirolimus MMF Predinsone	Tacrolimus MMF (This group was excluded from the study.)

- Mean duration of follow-up was 36 months.
- Patients were eligible to be in the Sir group if they were<62 years of age, had calculated panel reactive antibodies (cPRA) of<20%, and did not have an acute early rejection (within 3 months after transplant).
- Maintenance dose of MMF was 1g twice daily.
- Sir was introduced with a single oral loading dose of 6 mg followed by daily maintenance dosing.
- The target trough used for Tac was 8-12 ng/mL during the first 3 months after transplant, 6-10 ng/mL at 3-6 months, and 5-8 ng/mL after 6 months.
- Routine screening for BK viremia was performed at 3, 6, 12, and 24 months after transplant. BKV detection and quantitation was by real-time PCR.
- The management protocol for clinically significant BK viremia was monitoring of plasma BK viral load every 1-2 months, reduction of the MMF dose by half, followed by the addition of leflunomide and/or discontinuation of MMF in case of non-response to reduction of immunosuppression.

Results

- From 180 patients, 50 were maintained on a steroid-free regimen and were excluded from the study. The Tac group consisted of 78 patients and the Sir group of 47 patients.
- The incidence of any detectable BK viremia and clinically significant BK viremia were 35.9% (28/78) and 17.9% (14/78) in the Tac group (P=0.04), and 19.1% (9/47) and 4.3% (2/47) in the Sir group (P=0.02), respectively. On univariate analysis, variables impacting the risk of BK viremia were male gender.
- Kaplan–Meier analysis (Fig. 2) showed a higher BK free survival in the Sir group compared to the Tac group (P=0.044). The Kaplan–Meier test also demonstrated that, of patients BK free at the time of the switch, only 1 patient subsequently developed BK viremia on Sir. Patients on Tac continued to develop BK viremia at various time points including beyond the first year.
- The Sir group had significantly higher eGFR at 6, 12, and 24 months after transplant.
  The Tac group had a significantly higher proportion of early rejections (Table 2).

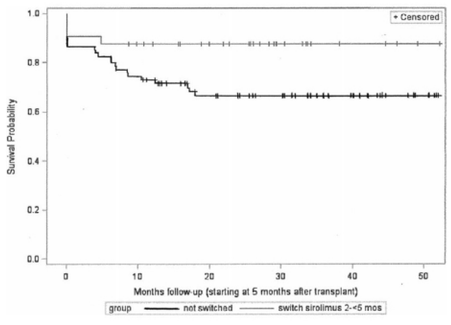

Figure 2: Kaplan Meier survival curves for the tacrolimus (black,n=74) and sirolimus (gray, n=32) groups, Time 0 corresponds to 5 months post transplant. Initial drop in both curves at time 0 corresponds to 25 months post transplant. The difference between the 2 survival cvurves is statically signicant (P=0.04 using the log-rank test).

Table 2

Variable	Tracrolimus	Sirolimus	P-value
Number of patients	78	47	
GFR (mL/min)			
6months	53.4 (36 - 70)	64.5 (46 - 83)	**0.001**
12months	55.0 (35 - 75)	63.6 (42 - 85)	**0.032**
24months	51.3 (29 - 74)	63.6 (39 - 88)	**0.016**
Rejection			
Early (before 6 months)	11 (14.1%)	0 (0.0%)	**0.007**
Late (after 6 months)	4 (5.1%)	3 (6.4%)	0.0764
Graft failure	7 (9.0%)	2 (4.3%)	0.322
Death	3 (3.8%)	1 (2.1%)	0.596

P-values < 0.05 in bold are significant.
GFR, glomerular filtration rate.

Conclusion

- In this study the switch from Tac to Sir is associated with lower incidence of BK viremia in the Sir group
- A Sir based regimen might also have. Importantly, no increase in graft losses or rejection episodes occurred in the Sir group, and patients on Sir had a higher eGFR at each examined time point, compared with the Tac group (6).

References

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