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Commentry

Negative Impact of CMV and BKV Infections on Kidney-Allograft Function at 1-Year Post-Transplantation: Can it Be Changed by Modifying Immunosuppression?

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Kidney transplantation is a well-established therapy for end-stage kidney disease and provides very good long-term kidney-allograft survival provided there is adequate immunosuppression. However, every attempt to minimize immunosuppression substantially has been disastrous and has resulted in acute rejection episodes and/or the de novo occurrence of donor-specific alloantibodies, causing antibody-mediated rejection [1].

Conventional immunosuppression includes a first phase where patients receive an induction therapy (lymphocyte-depleting agents or basiliximab therapy) in addition to, in most cases, high doses of a calcineurin inhibitor (CNI: cyclosporine A or tacrolimus), plus an antimetabolite (mycophenolic acid [MPA] or azathioprine), and high doses of steroids. At three to six months post-transplantation, lower doses of CNI are needed (plus an antimetabolite), with or without very low doses of steroids.

Chronic immunosuppression has many drawbacks such as opportunistic infections over the short term, mostly viral infections (i.e., cytomegalovirus [CMV], BK virus [BKV] infections), and de novo cancers in the longer term, which are mostly driven by viruses such as Epstein-Barr virus (EBV), human papilloma virus (HPV), and human herpes 8 (HHV8).

Until two decades ago, the major concern was CMV-associated infection or disease that caused direct and indirect effects such as decreased patient and graft survival, post-transplant de novo diabetes, cardiovascular morbidity, etc. [2]. However, when efficacious anti-CMV agents became available, i.e., ganciclovir and valganciclovir, the burden of CMV infection was decreased significantly. Nonetheless, the cost of anti-CMV agents is very high, and in countries where it is not reimbursed (e.g., Brazil), the incidence of CMV infection/disease within the first year post-transplantation can be as high as 37.6% in kidney-transplant patients that have had no CMV prophylaxis and where immunosuppression has relied on tacrolimus + MPA + steroids [3].

Because CMV infection became of lesser concern, we have witnessed an increase in BKV infection (e.g., BKV viruria and BKV viremia), which can develop in up to 31% of patients within the year post-transplantation [4]. This BKV replication has a major negative impact on the kidney allograft, i.e., it induces BKV-associated nephropathy (BKVAN) in up to 8% of patients [4], and this may ultimately lead to allograft loss [5]. As yet, it is not clear whether a post-transplantation BKV infection is derived from the donor or the recipient.

Abend et al. have shown that donor-neutralizing BKV serostatus correlates significantly with the incidence of post-transplant BKV viremia, i.e., donor–recipient pairs with a D+/R- neutralizing serostatus had the greatest risk of BKV viremia (odds ratio, 4.9; 95% confidence interval [CI], 1.7–14.6; $P = 0.004$) [6]. Recently, Solis et al. have shown that kidney recipients with high BKV genotype-specific neutralizing antibody titers against the replicating strain had a lower risk of developing BKV viremia (hazard ratio [HR], 0.44; 95%CI, 0.26–0.73; $P = 0.002$). Thus, each log-10 increase in neutralizing antibody titer decreased the risk of developing viremia by 56%. In addition, replicating strains were consistent with donor transmission in 95% of cases of early BKV replication [4]. At present, the prevention of BKV infection relies on detecting BKV replication at post-transplantation: when it occurs, we decrease immunosuppression, but it is not clear whether converting the patient from MPA to everolimus, combined with low doses of CNI (instead of full doses of CNI) is effective at decreasing BKV replication [5].

Most adult kidney-transplant candidates are EBV seropositive. However, the risk of primary EBV infection is very high in EBV-seronegative kidney-transplant recipients with an EBV-seropositive donor (D+/R-) and may cause a life-threatening post-transplant lymphoproliferative disorder (PTLD) [7]. If that combination occurs (D+/R-), we need to i) adopt a weaker immunosuppressive regimen and avoid lymphocyte-depleting agents at transplantation, ii) use an immunosuppressive protocol that contains mTOR-inhibitors (sirolimus, everolimus) as a maintenance therapy, and iii) closely monitor for EBV viremia for at least two years post-transplantation.

In this issue of *EBioMedicine*, Blazquez-Navarro et al. report on a sub-study within the randomized, multi-center, investigator-initiated Harmony trial (NCT 7900724022). The trial included 541 kidney-transplant recipients that were prospectively monitored within the first year post-transplantation for blood viral loads of CMV, BKV, and EBV during eight predetermined hospital visits. The results were correlated with clinical outcome parameters. Viral monitoring was

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non-interventional and centrally performed. In total, 3716 serum samples were analyzed for viral load using qPCR [8].

What were the striking findings? Firstly, BKV had the highest prevalence, i.e., BKV viremia was detected at least once to be above the threshold in 48.1% of patients, and 10.9% of patients had at least one elevated viral load, i.e., >10,000 copies/mL. In addition, 20.1% of patients had prolonged BKV viremia (i.e., more than one positive measurement) and the rate of BKV clearance by 1-year post-transplantation was only 80.5%. Secondly, CMV viremia was detected at least once in 17% of patients, but only 7.21% of patients had elevated CMV viremia, i.e., >2000 copies/mL. In addition, 6.47% of patients had prolonged CMV viremia and the rate of CMV clearance by 1-year post-transplantation was 95.3%. CMV viremia was significantly and positively associated with prolonged cold ischemia time, acute rejection, and with high tacrolimus trough levels. Thirdly, EBV viremia was detected at least once in 20.1% of patients, but only 6.83% of patients had elevated EBV viremia, i.e., >2000 copies/mL. In addition, 6.65% of patients had prolonged EBV viremia and EBV clearance was 85.7% by 1-year post-transplantation. Only two patients presented with PTLD; however, only one of these had detectable EBV replication. Fourthly, both these patients with high BKV viremia (vs. no viremia) and high CMV viremia (vs. no viremia) had a significant decrease in estimated glomerular filtration rate (eGFR) by 1-year post-transplantation (median reduction of 8.9 and 13.9 8.9 mL/min/1.73m^2, respectively). Fifthly, patients that had combined BKV and CMV reactivations, even at low viral-load levels (>1000 and 4000 copies/mL, respectively), had a significantly reduced eGFR at 1-year post-transplantation (11.7 mL/min/1.73m^2) compared to non-reactivating patients ($P = 0.02$). Moreover, these patients with combined BKV/CMV reactivations had a lower eGFR (although not statistically significant) compared to patients that had a mono-virus reactivation at 1-year post-transplantation (median difference in eGFR of 3.33 mL/min/1.73 m^2). Sixthly, EBV replication was not associated with the decline in eGFR at 1-year post-transplantation.

What lessons can be drawn from this study? Firstly, within the first year post-transplantation, it is useless to monitor EBV viremia; conversely, it is of utmost importance to prospectively monitor for BKV viremia and CMV viremia (when no CMV prophylaxis is given). Secondly, when cold ischemia time is long or when a patient has an acute rejection it is advisable to provide prophylaxis against CMV (with valganciclovir). Thirdly, BKV replication is the most frequently observed viral infection. Fourthly, both CMV and BKV replication within the first year post-transplantation result in a decline of 1-year eGFR (as compared to patients that did not have BKV or CMV replication). Fifthly, when BKV is combined with CMV replication, even at low replication levels, it also has a detrimental effect on eGFR at 1-year post-transplantation as compared to patients having had none of the virus replicate.

It has been nicely shown that 1-year kidney allograft function estimated by GFR is one of the major predictive factors for long-term kidney allograft survival [9]. Therefore, every factor that might concur to its decline within the first-year post-transplantation should be modified where possible.

In the setting of BKV replication even if it is at a low level, what can we do apart from keeping on monitoring it? It is known that commercially available immunoglobulins (IVIgs) contain virus-neutralizing antibodies against all major genotypes of BKV; however, as of now, there is no evidence that giving IVIgs as soon as BKV viremia is detected can prevent the subsequent BKV-related deleterious effects [5]. There is no strong evidence to support the beneficial effect of mTOR-inhibitors to prevent BKV infection [5].

Recently, the 1-year results from the largest randomized controlled trial on 2037 de novo kidney-transplant recipients were published [10]. Patients received, in combination with induction therapy and corticosteroids, everolimus plus reduced exposure to CNIs (everolimus arm) or MPA with standard exposure to CNI (MPA arm). The primary end-point was a treated biopsy-proven acute rejection or an eGFR <50 mL/min per 1.73 m^2 at post-transplantation month 12. The primary end-point incidences were 48.2% with everolimus and 45.1% with MPA (difference 3.2%; 95%CI, −1.3% to 7.6%). A treated biopsy-proven acute rejection, graft loss, or death at post-transplantation month 12 occurred in 14.9% and 12.5% of patients treated with everolimus and MPA, respectively (difference 2.3%; 95%CI, −1.7% to 6.4%). The incidence of de novo donor-specific antibodies at 12 months and antibody-mediated rejection rate did not differ between the two arms. Finally, as could have been expected, CMV (3.6% vs. 13.3%) and BKV infections (4.3% vs. 8.0%) were statistically less frequent in the everolimus arm than in the MPA arm [10]. Taken together, with the results from Tedesco-Silva et al.'s study [3], these strongly suggest the need to give low immunological-risk patients an immunosuppressive therapy that combines low CNI exposure with low everolimus dose soon after kidney transplantation, instead of full CNI exposure plus MPA. This should then result in good renal function, a low percentage of de novo DSAs, and fewer incidences of CMV and BKV infections. In other words, this approach is safe and efficacious, and indeed could minimize the most frequent viral infections (CMV, BKV) that we have to deal with within the first year after kidney transplantation.

Disclosure

The authors have no conflicts of interest to declare.

References

Malvezzi, P., Rostaing, L., 2017. Renal transplantation in 2016: novel approaches to improve recipient and allograft outcomes. Nat Rev Nephrol 13 (2):73–74. https://doi.org/10.1038/nrneph.2016.190.

Eid, A.J., Razonable, R.R., 2010. New developments in the management of cytomegalovirus infection after solid organ transplantation. Drugs 70 (8):965–981. https://doi.org/10.2165/10898540-000000000-00000.

Tedesco-Silva, H., Felipe, C., Ferreira, A., et al., 2015. Tedesco-Silva H, Felipe C, Ferreira a, et al. Reduced incidence of cytomegalovirus infection in kidney transplant recipients receiving Everolimus and reduced tacrolimus doses. Am J Transplant 15 (10): 2655–2664. https://doi.org/10.1111/ajt.13327.

Solis, M., Velay, A., Porcher, R., et al., 2018. Neutralizing antibody-mediated response and risk of BK virus-associated nephropathy. J Am Soc Nephrol 29 (1):326–334. https://doi.org/10.1681/ASN.2017050532 [Epub 2017 Oct 17].

Jouve, T., Rostaing, L., Malvezzi, P., 2016. Place of mTOR inhibitors in management of BKV infection after kidney transplantation. J Nephropathol 5 (1):1–7. https://doi.org/10.15171/jnp.2016.01.

Abend, J.R., Changala, M., Sathe, A., et al., 2017. Correlation of BK virus neutralizing Serostatus with the incidence of BK viremia in kidney transplant recipients. Transplantation 101 (6):1495–1505. https://doi.org/10.1097/TP.0000000000001261.

Le, J., Durand, C.M., Agha, I., Brennan, D.C., 2017. Epstein-Barr virus and renal transplantation. Transplant Rev (Orlando) 31 (1):55–60. https://doi.org/10.1016/j.trre.2016.12.001.

Blazquez-Navarro, A., Dang-Heine, C., Wittenbrick, N., et al., 2018. BKV, CMV, and EBV interactions and their effect on graft function one year post-renal transplantation: results from a large multi-Centre study. EBioMedicine [in press].

Hariharan, S., McBride, M.A., Cherikh, W.S., et al., 2002. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 62 (1), 311–318.

Pascual, J., Berger, S.P., Witzke, O., et al., 2018. Everolimus with reduced Calcineurin inhibitor exposure in renal transplantation. J Am Soc Nephrol 29 (7):1979–1991. https://doi.org/10.1681/ASN.2018010009.