EDITORIAL

Urinary biomarkers: on the long road to personalized renal transplant medicine

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In 1954, the first long-term successful open renal transplant procedure between monozygotic twins was performed by the future Nobel laureate Joseph Murray. Since then, the complexity of renal transplant medicine has increased enormously. A more profound understanding of immunologic barriers, the introduction of potent immunosuppressive medications, and expanded surgical options including robotic-assisted kidney transplantation resulted in a significant improvement of short-term outcomes, although long-term allograft failure rates remain unacceptably high.[1]

In 2019, kidney transplantation is still considered the best available therapeutic option for patients with end-stage renal disease.

While the body of knowledge about transplant immunology steadily grows, the current standard of care in transplant recipients according to guidelines remains often an empirical approach with center-based immunosuppression protocols and clinical decision algorithms that frequently lack precision.[2] This results in a certain amount of risk for both over- and under-immunosuppression with the sequelae of drug toxicity, infection, and allograft rejection. Currently, only an archaic set of diagnostic techniques is validated to assess graft dysfunction. The standard noninvasive toolbox includes serial measurements of serum creatinine, estimated glomerular filtration rate, and proteinuria as well as monitoring drug-levels, viral loads, and donor-specific antibodies.[3] Unfortunately, the diagnostic gold standard, that is invasive renal transplant biopsy followed by histologic assessments according to the updated Banff 2013 classification, often detects allograft rejection or polyomavirus associated nephropathy (PVAN) after irreversible graft damage has already occurred.

Thus, noninvasive identification of patients at increased risk of graft dysfunction at a time point before histologic injury has occurred would be the ultimate goal. Theoretically, such an approach should permit an earlier, often preemptive, treatment of allograft rejection or PVAN, thereby reducing the need for kidney transplant biopsies.[4]

In view of this drawback, researchers used challenging strategies and sophisticated techniques, including omics technologies, in order to discover marker molecules in biological materials that could serve as such noninvasive predictors of allograft dysfunction. Biomarker studies in kidney transplant recipients often analyze nucleic acids or proteins from urine, a medium which might provide direct insight into the status of the transplanted organ.[5]

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Gniewkiewicz et al[6] focused on 2 promising urinary biomarker candidates in kidney transplantation: the chemokine (C-C motif) ligand 2 (CCL2) and the interferon-γ-induced protein of 10 kDa (CXCL10). The authors assessed the predictive value of both biomarker concentrations related to creatinine levels in urine for occurrence of histological features in simultaneously obtained protocol biopsies 12 months after transplantation. Renal biopsies of 40 patients with histological diagnoses of interstitial fibrosis and tubular atrophy (IF / TA), PVAN, and mild rejection were included. Univariate and multivariate logistic regression models identified urinary CCL2 to creatinine ratio (CCL2:Cr) as a significant independent predictor of PVAN, whereas urinary CXCL10 to creatinine ratio (CXCL10:Cr) reached only borderline significance. The authors suggest further evaluation of both biomarkers for the diagnosis of BK virus (BKV) infection.

At this point, some important questions arise: Is this finding in line with previous study results for urinary CCL2 and CXCL10 in kidney transplant recipients? Can urinary biomarkers facilitate the diagnosis of PVAN? And finally, how can these study results be integrated in the complex area of biomarker research?

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Urinary CCL2:Cr measured 6 months after transplantation shows a clear correlation with long-term allograft outcomes.[7] It can predict 24-month IF/TA as well as IF/TA plus inflammation, a surrogate marker for death-censored graft loss.[8] Urinary CXCL10 is elevated in both acute rejection and BKV infection; however, it does not allow differentiating between them.[9] In a recent study by Ho et al,[10] the 6-month urinary CXCL10:Cr ratio reflected inflammation within the tubulointerstitial and microvascular compartments and was predominantly elevated in peritubular capillaritis, but not glomerulitis. Furthermore, urinary CXCL10 corresponded with BKV, but not cytomegalovirus viremia.[10] Taken together, 6-month urinary CCL2:Cr and CXCL10:Cr alone seem to have similar prognostic performance, but when both are elevated, this suggests a worse prognosis.[7] The finding by Gniewkiewicz et al[6] that 12-month urinary CCL2:Cr but not CXCL10:Cr may significantly predict PVAN is novel and, at first glance, it warrants further investigations.

PVAN is a serious complication in kidney transplant patients that often leads to graft loss, and the diagnosis as well as management of BKV reactivation are challenging. Although the cumulative degree of immunosuppression is recognized as an important contributor to BK virus replication, risk factors vary across studies.[11] In addition, no specific antiviral agent has yet been approved for treatment, and the preferred therapeutic option is modulation of the immunosuppressive drug regimen, which often increases the risk of rejection. Consequent prospective quantitative screening for BKV DNA in urine, plasma, or serum appears to be a useful monitoring tool as BKV reactivation and graft infection usually progress through detectable stages. A prominent urine BKV replication followed by significant BKV load in blood (usually a plasma DNA PCR load >10 000 copies/ml) defines presumptive BK virus nephropathy and definitive histologic evidence is then obtained by biopsy as gold standard.

According to the current knowledge, the feasibility of a single 12-month urinary CCL2:Cr ratio as a prognostic or predictive biomarker candidate for PVAN is questionable, particularly as currently no time-to-event assessment or correlation with BKV load in blood or urine is available. Whether future studies will adequately address these limitations remains unclear. Of note, before initiating these follow-up studies, a precise definition of the biomarker type—diagnostic, predictive or prognostic—is mandatory.[12]

Despite this criticism, we believe that the reader can definitely learn from the aforementioned study as it highlights important difficulties of single-center trials in biomarker research. This is, on the one hand, the impossibility to design prospective studies of sufficient length and power resulting in small-scale trials with small patient numbers. In addition, different phenotypes of study populations with respect to ethnicity are often leading to heterogenity and inconsistent results. Further specific challenges in the renal transplant biomarker field are, among many others: a) focus on single urinary molecules that are often unable to represent the complex molecular signature of the graft, b) emphasis on tools for diagnosing ongoing acute rejection while not detecting PVAN, c) selection of the time point for testing in the posttransplant period, and d) choice of a robust, fast, and comparably inexpensive technique to produce replicable results. Gniewkiewicz et al[6] used the enzyme-linked immunosorbent assay technique that can be performed by most clinical laboratories, making this approach readily adoptable in clinical care.

Today, individualization of therapy has already become reality in oncology, using large-scale, high-throughput data generation and novel computational approaches to analyze these data sets. Recently, an in-depth review on data generation, computational analysis, and big science initiatives, with a special focus on applications to nephrology was published.[13] Although transplant medicine is far away from such a personalized precision-based approach, the introduction of urinary biomarkers as a matter of routine could be the first step towards this direction and could help in early identification of recipients who are at high risk of graft loss, leading to more intensive posttransplant surveillance.

Of particular note, the way for biomarkers from bench to bedside is long and difficult. Candidate biomarkers identified in internal single-center studies have to be tested in external multicenter trials to establish validity before adoption into clinical care.[14] A large randomized international multicenter phase II/III trial for urinary CXCL10 monitoring in adult renal transplant patients has started recruitment, but results are not expected before 2023.[15] Hopefully, this study will be another little piece of the puzzle towards desired individualization of renal transplant medicine at some indefinite future date.

ARTICLE INFORMATION

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