Symposium 11 - The role of clinical laboratory in kidney transplantation

IMMUNOSUPPRESSIVE DRUG MANAGEMENT FOR A PERSONALIZED THERAPY

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A limited number of immunosuppressive drugs (ISD) have been used as maintenance therapy in organ transplant patients. Calcineurin inhibitors (cyclosporine, tacrolimus), mTOR inhibitors (sirolimus, everolimus) and antimetabolites (azathioprine, mycophenolic acid) have been in use for more than 25 years in different combinations, with or without corticosteroids, for the prevention (and for a few, the treatment) of acute and chronic organ transplant rejection.
Clinical laboratories of pharmacology worldwide have set up analytical techniques based on LC-MS/MS for ISD in blood for routine therapeutic drug monitoring (TDM). These laboratories and their research partners have also conducted translational research by combining in vitro, ex vivo, in vivo and clinical approaches. They have used LC-MS/MS to explore the systemic and local pharmacokinetics of ISD, as well as to decipher their metabolic pathways and related isozymes. They have explored the influence of gene polymorphisms in the main metabolizing and target proteins. They have developed innovative PK, population PK and PK/PD models to evaluate many potential sources of PK variability. As a result, and by means of clinical studies, they have demonstrated the usefulness of: (i) pharmacogenetic testing for azathioprine and tacrolimus; (ii) TDM for mycophenolate mofetil; (iii) individualized blood concentration targets for tacrolimus. They have even contributed significantly to the management of anti-infective agents in transplant recipients, the refinement of graft function measurements and the setting-up of predictive clinical scores of graft survival to evaluate the benefit-risk balance of treatment strategies. Finally, they have convened international consensus conferences and published recommendations regarding the individual dose adjustment of ISD in recipients of organ transplants, as well as in patients with autoimmune diseases or cancer receiving these drugs.
Despite the quasi-absence of any new maintenance ISD in the field over the past 25 years, all these actions have significantly improved transplant patient care and prolonged graft survival, eliciting the extension of organ transplantation to older and more comorbid donors and recipients.

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BIOMARKERS AND MULTIMODALITY TESTING IN KIDNEY TRANSPLANTATION

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The primary objective in kidney transplantation shares three objectives: one kidney for life; optimal immunosuppression to avoid rejection, malignancy, and infections; and no biopsy. In other words, the future of kidney transplantation will focus on non-invasive tools to monitor the state of immunosuppression, guide therapy, and prevent complications. The transplant community is in search of biomarkers to help achieve this objective. The science behind recent biomarker discovery spans across artificial intelligence and multiple molecular biologic disciplines, including transcriptomics, proteomics, and metabolomics using samples obtained from the kidney, blood, and urine.
In this review, we will discuss the clinical value of recent biomarkers developed in the field of kidney transplantation including donor specific antibodies, donor-derived cell-free DNA, gene panels from blood and urine sample collections, and the iBox. We will discuss the strengths and weaknesses of each biomarker and argue the value of multimodality testing.
The future of kidney transplantation will depend on precision medicine. Novel non-invasive biomarkers will play a significant role in this journey. Interventional clinical trials and rigorous regulatory oversight are needed before generalizing the use of single or multi-modality biomarkers.

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KIDNEY FUNCTIONS AFTER TRANSPLANTATION : MORE THAN CREATININE

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Creatinine based equation is the most commun method for Glomerular Filtration Rate (GFR) estimation. However, it has been shown that the performance of all creatinine- based equations is worse in renal transplanted patients than in nontransplanted patients. Physiological limitations of serum creatinine is enhanced after transplantaion since tubular secretion could be impaired and muscular mass could change during the first year of transplantation. Currently, the Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation remained recommended by the Nephrology guidelines. A new race-free version of the CKD-EPI equation has been proposed but does not improve the follow-up of European transplanted patients. By contrast, the European Kidney Function Consortium equation seems to outperform both versions of the CKD-EPI equation. In addition, this equation could be used from children to oldest transplant recipients and in non-European contries. The cystatin C based equations have been proposed since cystatine seems independent of race and muscle mass but its concentration is more affected by inflammation, adiposity, smoking, levels of thyroid and corticosteroids.

Panel of endogenous filtration markers is a promising approach. Numerous low-molecular weight proteins such as beta trace or beta 2 microglobulin or metabolic waste products such as C-glycosyltryptophan or pseudouridine have been identified as candidate filtration markers. Multimetabolite panel could be assessed using « omic » approaches and could be interpretated via artificial intelligence.

Dynamic approaches including baseline values (age at transplantation, sex, weight) and longitudinal changes (glomerular filtration rate, proteinuria, hematocrit) could be usefull to appreciate or predict evolution of transplant functions. In addition, damage biomarkers such as KIM-1, NGAL, IL-18 and [TIMP-2]*[IGFBP7]) have been proposed for assessment of delayed graft function or one year GFR.

Finally, exogenous filtration biomarkers are considered the most accurate options to measure GFR. However standardization using non-radioactive (iohexol and iothalamate) and radioactive (51Cr-EDTA, 99mTc-DTPA, 125I iothalamate) should be achieved before using routinely in clinical laboratories.