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Authors

Zambeli-Ljepović, Alan
Abbasi, Ali B
Altshuler, Peter J

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Predicting Over-immunosuppression in Kidney Transplant Recipients: Steps Toward Precision Medicine

Alan Zambeli-Ljepović, MD,[1] Ali B. Abbasi, MD,[1] and Peter J. Altshuler, MD[1]

The field of solid organ transplantation continues to progress toward more personalized approaches to immunosuppression (IS) to optimize graft function while minimizing infectious sequelae. In this issue of *Transplantation*, Désy et al at the University Health Center of Quebec approach this concept in their article "A Risk Score Using a Cell-based Assay Predicts Long-term Over-immunosuppression Events in Kidney Transplant Recipients".[1] Building on years of work developing a peripheral blood mononuclear cell (PBMC)-based assay measuring TNF-α+ production by CD14+16+ intermediate monocytes incubated with Epstein-Barr virus peptides to assess for over-immunosuppression (OIS),[2] this article describes how this assay can be incorporated with clinical data to stratify kidney transplant recipients' risk of OIS. In a single-center cohort of 118 kidney transplant recipients with a median posttransplant follow-up of 6.3 y, 34% experienced an OIS event, which the authors defined as the composite outcome of opportunistic infection, severe infection leading to death, de novo malignancy (excluding nonmelanoma skin cancer unless it required reconstructive surgery or radiotherapy), and recurring infections leading to reduction of IS. Their predictive model of OIS, based on patient age and percentage of CD14+16+TNF-α+ monocytes, performed with adequate discrimination (c-statistic 0.71), good calibration, and was stable under varying definitions of OIS. The authors concluded that this in vitro PBMC assay shows promise in stratifying the risk of OIS among kidney transplant recipients.

A chief strength of this study is the duration of follow-up: between the incident and prevalent kidney transplant recipients, the median follow-up time was 6.3 y posttransplant and the median time to OIS event was 3.6 y after enrollment. This ensures that most OIS events were captured and builds on existing literature, which rarely describes infectious complications occurring >12 months after transplantation.[3] Additionally, the predictive model performed well under varying definitions of OIS, spanning from a selective one, including only life-threatening events, to a sensitive one, including mild OIS events that may not result in IS reduction.

As the authors themselves acknowledge, their work does suffer from several barriers to its immediate clinical applicability. This study, and the authors' prior investigations on which it is based, have all been single-center studies. It will be critical to demonstrate that this assay, which requires specific technical expertise and laboratory equipment for cell culturing, can be feasibly performed in different hospital settings and that its results remain valid in a multi-institutional cohort. Additionally, the study population lacks the power to detect potential contributions to the risk profile from clinical factors that differed between cases and controls (eg, cardiovascular disease, rates of rejection). The authors therefore are appropriately restrained in drawing conclusions from the observed results prior to completion of their forthcoming multicenter study for external validation of the PBMC assay.

This article's findings chip away at a critical gap in the clinical armamentarium for personalizing IS regimens for kidney transplant recipients (Figure 1). Despite the complex and dynamic nuances of every individual's immune system, current management strategies are limited by relatively crude tools for personalizing immune surveillance and choice of pharmacotherapy.[4] We as clinicians only realize that an IS regimen is inadequate when a patient reaches an extreme end of their immune spectrum—under-immunosuppressed to the point of rejection or over-immunosuppressed to the point of opportunistic infection or malignancy. This study's advances toward predicting the latter have two potential implications for clinical practice. First, they add nuance to population-level data on the infectious and malignant complications of OIS, whose timing is poorly described, especially in the long term.[3,5] Among patients stratified as high-risk using the PBMC assay, OIS events occurred not only in higher proportion but also with greater frequency, identifying a subset of patients who require a more cautious approach to IS management. Second, if externally validated, this PBMC assay can serve as an additional objective parameter to guide IS management and posttransplant surveillance strategies by

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[1] *Division of Transplant Surgery, Department of Surgery, University of California, San Francisco, CA.*

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Correspondence: Peter J. Altshuler, MD, Division of Transplant Surgery, Department of Surgery, University of California, 505 Parnassus Ave, Ste M896, San Francisco, CA 94143. (peter.altshuler@ucsf.edu).

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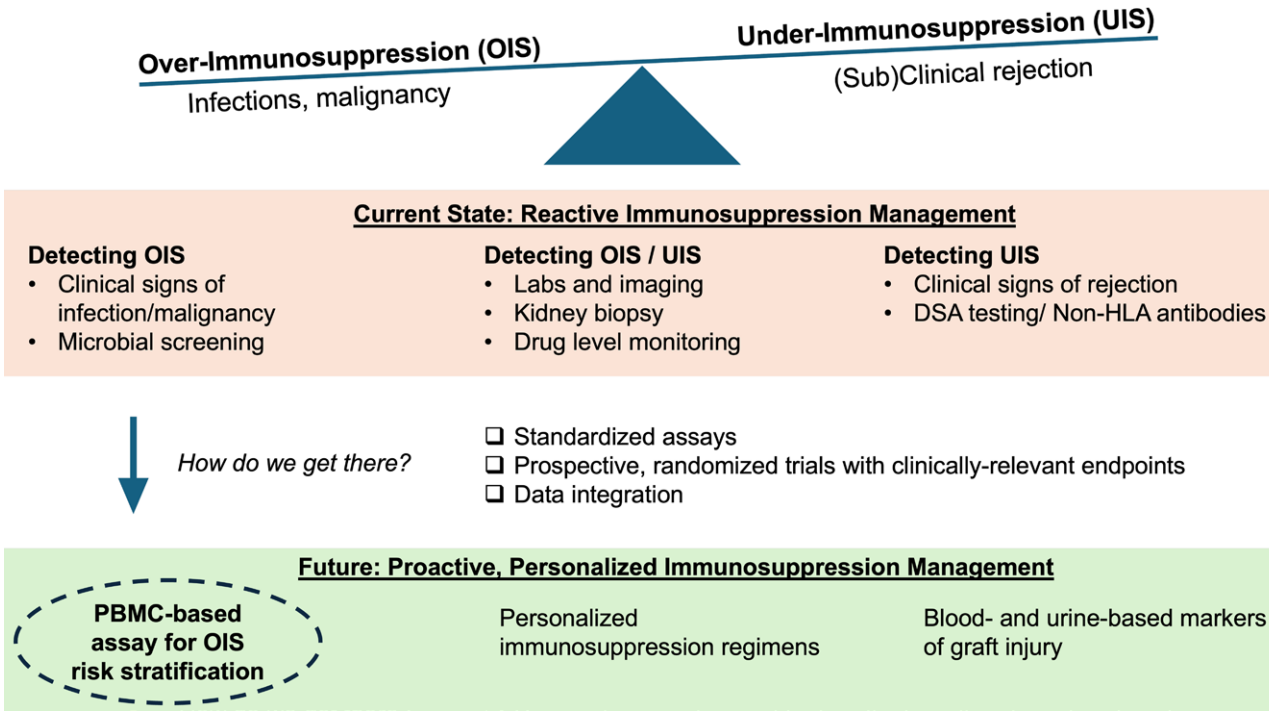

FIGURE 1. Schematic addressing balance between over- and under-immunosuppression.

preemptively identifying patients whose baseline IS regimen may need to be attenuated.

The Désy et al study, along with others like it, helps provide the framework for future directions in targeted IS management, balancing the risks of under- and over-immunosuppression. Determining a proactive strategy of adjusting IS regimens, rather than relying on reactive medication management, could help prevent both clinical and subclinical events related to the level of IS. The importance of detecting these subclinical changes has already been demonstrated—subclinical acute rejection occurs in up to 25% of kidney transplant recipients within 2 y posttransplantation and is associated with graft failure.[6] As with OIS risk assessment, current methods of assessing rejection risk (biochemical assessment of creatinine or proteinuria/hematuria, donor-specific antibody assays, and even biopsies) have limitations in accuracy, timing of detectability leading to treatment delays, cost, and safety (rate of major complications after kidney biopsy is 1%).[7] Novel, clinically validated methods to assess rejection risk, including donor-derived cell-free DNA assays[8] and urine biomarker-based assays,[9,10] are forthcoming. Ultimately, these tools to predict and/or mitigate risk, used individually or in combination, must be evaluated with prospective, multicenter randomized controlled trials to demonstrate their impact on the cardinal clinical outcomes: patient and graft survival.[7]

The future of kidney transplant surveillance includes a variety of strategies to better understand each transplant recipient's immune phenotype and reduce immunologic risk. Risk assessment tools like the PBMC assay can help clinicians proactively maintain the tenuous balance between over- and under-immunosuppression, while concurrent advancements in immune tolerance and pharmacologic advancements can limit unnecessary immune system depletion. Ultimately, thoughtful integration of these strategies will allow us to provide more precise and personalized long-term care for kidney transplant recipients.

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