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Study suggests reduced immunosuppression drug dose may be best for kidney transplant outcomes

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The kidney is the most commonly transplanted organ in the United States, with more than 17,000 transplants performed each year. Following kidney transplant, patients are routinely placed on a regimen of immunosuppressant medications to prevent organ rejection, which often includes calcineurin inhibitors (CNIs) as the backbone medication of this regimen. However, questions remain about the best use of these drugs to strike the balance between preventing rejection and avoiding drug-related complications. Researchers from the Perelman School of Medicine at the University of Pennsylvania, in partnership with ECRI Institute under the ECRI Institute-Penn Medicine Evidence-based Practice Center contract, investigated four immunosuppression strategies and found that many patients might benefit from a lower-than-standard dose of CNIs. Their findings are detailed in a study published this week in the *American Journal of Transplantation*, with additional research included online in an extended Agency for Healthcare Research and Quality (AHRQ) report.

One of the main hurdles in using immunosuppressant medications is finding the right balance between too little drug, which results in organ rejection, and too much drug, which can increase risk of infections, renal failure, cardiovascular disease and diabetes. As part of the larger AHRQ report, the team conducted an analysis of 105 studies from 1994 through 2015 to compare laboratory techniques for monitoring CNI drug levels, to examine the best times to collect CNI drug levels, and to

evaluate alternatives to using standard dose CNIs as part of the immunosuppressant regimen in kidney transplant recipients.

"A big question in the field is whether there is a benefit to prescribing an alternative CNI dose, or even an entirely different immunosuppressant regimen for kidney recipients," said Deirdre Sawinski, MD, an assistant professor in the division of Renal Electrolyte and Hypertension. "CNI dosing protocols have changed over time but the impact on clinical outcomes is unknown."

The AHRQ report and publication in the *American Journal of Transplantation* focused on determining whether the standard CNI recommendations provide the best results for patients and their kidneys. Researchers evaluated four CNI strategies to determine which had the best long-term clinical impact. These strategies included:

- Minimization: using a lower-than-standard CNI dosage
- Conversion: switching to a different class of immunosuppressants after starting a standard dosage CNI
- Withdrawal: tapering off of a CNI regimen without adding a new immunosuppressant
- Avoidance: the use of a immunosuppressant regimen that does not include CNIs from the start of therapy

"To answer this specific dosage question, we evaluated 88 randomized controlled trials that examined one or more of the four CNI strategies," said Craig A. Umscheid, MD, MSCE, an assistant professor of General Internal Medicine and Epidemiology and director of the Center for Evidence-based Practice. "Findings suggest that CNI minimization results in better clinical outcomes than standard dose CNI regimens. Evidence for the conversion and withdrawal strategies suggested trade-offs between improved renal function and higher risk of rejection, and the evidence for the avoidance strategy was insufficient to make

conclusions."

Researchers agree that there is more to be explored when it comes to CNI immunosuppression regimens and finding the best therapies for maintaining renal function over a longer period of time. The study notes that a majority of the research analyzed only evaluated low-risk patients and did not examine high-risk kidney recipients, such as those with second transplants, other organ transplants, or HIV. The available studies also tended to evaluate the older CNI cyclosporine, rather than the newer CNI tacrolimus, which is now more commonly used. In addition, there were limited data on patient outcomes after long-term use of CNI regimens, which is a critical evidence gap given that patients are living longer following transplants, and adverse events associated with CNIs can often take years to manifest.

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