



# Effective Health Care

## Calcineurin Inhibitor Minimization, Withdrawal, and Avoidance Strategies for Kidney Transplantation Nomination Summary Document

### Results of Topic Selection Process & Next Steps

- The topic, *Calcineurin Inhibitor Minimization, Withdrawal, and Avoidance Strategies for Kidney Transplantation*, will go forward for refinement as a systematic review. The scope of this topic, including populations, interventions, comparators, and outcomes, will be further developed in the refinement phase.
- When key questions have been drafted, they will be posted on the AHRQ Web site and open for public comment. To sign up for notification when this and other Effective Health Care (EHC) Program topics are posted for public comment, please go to <http://effectivehealthcare.ahrq.gov/index.cfm/join-the-email-list1/>.

### Topic Description

**Nominator(s):** Health care professional association

**Nomination Summary:** Nomination is for the comparative effectiveness of therapeutic monitoring of cyclosporin and tacrolimus immunosuppression for renal transplantation, and the comparative effectiveness of antithymocyte globulin (ATG) and other multidrug strategies in minimizing the dose of tacrolimus for immunosuppression for renal transplantation.

**Staff-Generated PICO**

**Population(s):** All renal transplant patients

**Intervention(s):** Therapeutic monitoring with mass spectrometry/HPLC; therapeutic monitoring of cyclosporine or tacrolimus at two hours after administration ( $C_2$ ); immunosuppression with ATG and low dose tacrolimus; and multidrug strategies with lower doses of tacrolimus

**Comparator(s):** Therapeutic monitoring with immunoassays; therapeutic monitoring of cyclosporine or tacrolimus at trough ( $C_0$ ) time; immunosuppression with standard dosage tacrolimus without ATG; immunosuppression strategies with standard dose tacrolimus

**Outcome(s):** better organ survival rate, fewer rejections, less nephrotoxicity, cost savings

**Key Questions from Nominator:** KQ1. Mass Spectrometry versus Immunoassay: In renal transplants, does mass spectrometric analysis and therapeutic monitoring of tacrolimus as compared with immunoassay analysis and therapeutic monitoring produce:  
a. better organ survival rate,

- b. fewer rejections,
- c. less nephrotoxicity,
- d. cost savings?

KQ2. Cyclosporine and tacrolimus\* monitoring timepoints:  $C_2$  versus  $C_0$ : In renal transplants, does two hour post administration cyclosporine or tacrolimus monitoring ( $C_2$ ) compared to trough monitoring ( $C_0$ ) produce:

- a. better organ survival rate,
- b. fewer rejections,
- c. less nephrotoxicity,
- d. cost savings?

KQ3. Multidrug with low tacrolimus versus standard dose tacrolimus: In renal transplants, have multidrug protocols to target lower tacrolimus levels [4-6 ng/dL  $C_0$ ] been effective [compared to 8-10 ng/dL] at producing

- a. better organ survival rate,
- b. fewer rejection episodes,
- c. less nephrotoxicity,
- d. cost savings?

KQ4. ATG with low tacrolimus versus other regimens: Have acute rejection rates decreased with the addition of thymoglobulin to a tacrolimus low target level anti-rejection regimen in renal transplants?

KQ5. Sensitivity of monitoring for low dose tacrolimus [not a comparative effectiveness question; should probably be a subquestion of KQ1]: Are analytical capabilities sufficient to measure tacrolimus in the lower ranges that multidrug protocols to target lower tacrolimus levels [4-6 ng/dL  $C_0$ ] allow?

\* Subsequently added after discussion with nominator

### ***Alternative Staff Generated Draft Key Questions***

In practice, tacrolimus and cyclosporine are considered interchangeably; they have the same mechanism, benefits and harms. Below are alternative key questions that are broader in scope concerning calcineurin inhibitor minimization, withdrawal, and avoidance strategies for kidney transplantation.

KQ1. Monitoring assays for calcineurin inhibitors (CNIs)

KQ1a. Mass Spectrometry versus Immunoassay: In renal transplants, for therapeutic monitoring of the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus, how does mass spectrometric analysis compare with immunoassay analysis for: 1) organ survival, 2) acute and long-term rejections, 3) nephrotoxicity, 4) costs?

KQ1b. Sensitivity of monitoring for low dose CNIs: Are analytical capabilities sufficient to measure CNIs in the lower ranges that multidrug protocols targeting lower CNI levels allow?

KQ2. CNI monitoring timepoints:  $C_2$  versus  $C_T$ : In renal transplants, how does two hour post administration CNI monitoring ( $C_2$ ) compare with trough monitoring ( $C_T$ ) for: 1) organ survival, 2) acute and long-term rejections, 3) nephrotoxicity, 4) costs?

KQ3. Multidrug with calcineurin inhibitor (CNI) minimization versus standard dose CNI: In renal transplants, how effective are multidrug protocols for CNI minimization (low dose, withdrawal, avoidance, replacement, conversion) compared with conventional CNI strategies for: 1) organ survival, 2) acute and long-term rejections, 3) nephrotoxicity, 4) costs?

KQ4. Induction agent plus CNI minimization regimen versus induction agent plus conventional CNI regimen: In renal transplants, have protocols with an induction agent (antithymocyte globulin, alemtuzumab, basiliximab, daclizumab) plus CNI minimization (low dose, withdrawal, avoidance, replacement, conversion) been effective compared with an induction agent plus a conventional CNI regimen for: 1) organ survival, 2) acute and long-term rejections, 3) nephrotoxicity, 4) costs?

KQ5. CNI minimization strategies compared with each other: In renal transplants, what is the effectiveness of any CNI minimization strategy (low dose, withdrawal, avoidance, replacement, conversion) compared with any other CNI minimization strategy for: 1) organ survival, 2) acute and long-term rejections, 3) nephrotoxicity, 4) costs?

## Considerations

- The topic meets all EHC Program selection criteria. (For more information, see <http://effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/how-are-research-topics-chosen/>.)
- There have been more than 17,000 kidney transplants performed in the United States in 2011 alone and while early outcomes after kidney transplantation have improved dramatically in the last 2 decades, late outcomes remain stagnant and relatively poor. The same family of agents responsible for the improvement in early outcomes, namely the calcineurin inhibitors (CNIs, specifically tacrolimus/FK506 and Cyclosporine), are nephrotoxic and therefore also the same agents responsible for long-term kidney graft loss. Cyclosporine, has a narrow therapeutic window between efficacy and toxicity, thereby requiring monitoring of drug levels. Even less is known regarding tacrolimus monitoring time points.
- In addition, tacrolimus dose minimization strategies have raised the question of whether standard immunoassays and mass spectrometry/high-performance liquid chromatography are sensitive enough to detect and quantitate the lower doses of tacrolimus now being used.
- There are recent efforts in kidney transplantation to reduce exposure to CNIs in the hopes of improving long-term kidney transplant outcomes. These new protocols, referred to mainly as CNI-minimization, CNI-avoidance, or CNI-withdrawal protocols, seek to reduce the amount of drug to which the patient is exposed, or seek to either eliminate CNI entirely as part of the maintenance immunosuppression regimen (either immediately in CNI-avoidance or early in the post-operative course in CNI-withdrawal).

- There is a significant volume of new evidence addressing this topic and long term outcomes have not improved in recent decades. A systematic review will outline the most effective choices among new drugs and monitoring strategies.