Early graft outcomes from de novo weight-based dosing compared to conservative dosing of tacrolimus in kidney transplant recipients: a multi-site perspective

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Background

Kidney transplantation is the preferred treatment for patients with end stage renal disease (ESRD) due to increased survival and better improvements in quality of life as compared to patients maintained on dialysis.

The preferred immunosuppressive regimen for patients receiving kidney transplantation includes prednisone, a mycophenolate product, and tacrolimus.

The package insert for tacrolimus recommends a weight-based dose of 0.1 mg/kg/day in two divided doses every 12 hours with goal trough concentrations ranging between 4-20 ng/mL.

Despite this recommendation, various transplant centers employ different dosing strategies, one being a more conservative dosing strategy that uses a low fixed dose regardless of weight.

The rational for conservative dosing is to prevent the risk of vasoconstriction of afferent arterioles in the glomerulus that can contribute to nephrotoxicity and subsequently delayed graft function (DGF).

Utilizing conservative dosing may delay discharge while waiting until tacrolimus levels become therapeutic.

DGF is a concern because it can lead to an increased risk for acute rejection, increased allograft immunogenicity, and decreased long-term patient and graft survival.

Objectives

Primary objective

• To determine if weight-based dosing of tacrolimus immediately post-transplant has an impact on delayed graft function compared to conservative dosing of tacrolimus

Secondary objectives

• The time to the first therapeutic tacrolimus level in the weight-based and conservative dosing groups (days)
• The number of tacrolimus levels drawn during hospital admission
• Dosing: time to a therapeutic level (days) defined as a level drawn 10 ± 2 hours following previous dose of tacrolimus. A therapeutic tacrolimus trough concentration level is 8-10 (±1) ng/mL.
• Number of tacrolimus dose changes (increase, decrease, hold, and/or discontinued) during hospital admission
• Infection: documented positive blood/urine/tissue cultures from recipient, CMV PCR results, EBV PCR results, HSV PCR results, elevated viral load indicating BK virus, or a positive PCR for Closstridum difficile through 90 days post-transplant
• Rejection: biopsy proven acute rejection (cellular or antibody mediated) as assessed by pathologist through 90 days post-transplant

Methods

Study design

• IRB approved, multicenter, retrospective, cohort study

Inclusion Criteria

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<th>Inclusion Criteria</th>
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<tr>
<td>Age ≥ 18 years of age</td>
<td>Utilization of medications that are strong CYP 3A4 inducers/inhibitors</td>
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<td>Living or deceased donor</td>
<td>Sublingual administration of tacrolimus</td>
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<td>Those with data needed for analysis</td>
<td>Subject death or transplant nephrectomy within 7 days of transplant</td>
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<td>Enrollment in investigational research studies</td>
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<td>Multi-organ transplant recipient</td>
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Endpoints

Primary endpoint

• DGF: the receipt of dialysis (intermittent hemodialysis or continuous renal replacement therapy) within 7 days of kidney transplantation

Secondary endpoints

• Dosing: time to a therapeutic level (days) defined as a level drawn 10 ± 2 hours following previous dose of tacrolimus. A therapeutic tacrolimus trough concentration level is 8-10 (±1) ng/mL.
• Number of tacrolimus dose changes (increase, decrease, hold, and/or discontinued) during hospital admission
• Infection: documented positive blood/urine/tissue cultures from recipient, CMV PCR results, EBV PCR results, HSV PCR results, elevated viral load indicating BK virus, or a positive PCR for Closstridum difficile through 90 days post-transplant
• Rejection: biopsy proven acute rejection (cellular or antibody mediated) as assessed by pathologist through 90 days post-transplant
• Adverse reactions
• Neurotoxicity: documented in the EMR in the setting of a supratherapeutic level (>12 ng/mL) during hospitalization with associated tremors or delirium
• Nephrotoxicity: defined as an increase in serum creatinine >30% from baseline, with a supratherapeutic tacrolimus level (>12 ng/mL), and no other cause for the increase has been documented by the care team
• Length of stay: the number of days that the transplant subject is hospitalized for the index admission
• Renal function: GFR as measured by MDRD at post-operative days 30, 60, and 90

Statistical Methods

• The primary outcome is the incidence of delayed graft function and will be analyzed using a chi-square test (nominal data) with descriptive statistics.
• The secondary outcomes that will be assessed are daily in-hospital tacrolimus dose requirements until discharge, estimated creatinine clearance measured by the MDRD study equation (continuous variable) and acute rejection episodes (categorical variable with values: 0, 1, >1) through day 30 and 90 of transplant, group differences in occurrence of nephrotoxicity (categorical variable: 0, 1, >1), occurrence of neurotoxicity (categorical variable: 0, 1, >1), between the two groups on day 30 and 90 post-transplantation.
• Descriptive statistics will be performed on the two groups. Mean with standard deviation or median, with inter-quartile range will be calculated for the continuous secondary endpoints, and frequency and proportion will be calculated for categorical secondary endpoints.
• Continuous secondary outcomes will be assessed through a two sample t-test or Wilcoxon, and categorical data will be assessed through a chi-square test (or Fisher’s exact where appropriate) for differences between the two groups.

References

• Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN / SRTR 2011 Annual Data Report. Rockville, MD. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2012.

Disclosures

The authors of this presentation have no disclosures to provide concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation.