A CME/CE-certified Grand Rounds Activity

Best Practices in Care to Improve Outcomes for Transplant Recipients

Jointly provided by

pcme and Rockpointe

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global UMA and Rockpointe

This activity has been supported through an educational grant from Novartis Pharmaceuticals Corporation.
Educational Objectives

- Describe strategies to leverage center-specific data and best practices from transplant quality-improvement initiatives to improve processes of care.
- Discuss the importance of regular monitoring strategies that can allow early identification of graft rejection and allow for appropriate changes in immunosuppressant regimen.
- Identify patient barriers to adherence to improve implementation of strategies to engage patients and maximize adherence after transplantation.
Polling Question
Activity Survey

Please rate your level of confidence in using regular monitoring strategies that can allow early identification of graft rejection:

A. Not confident
B. Slightly confident
C. Confident
D. Very confident
E. Expert
Polling Question

Activity Survey

Please rate the degree of risk your program is willing to take with regard to donor and recipient selection and patient outcomes:

A. No risk
B. Slight risk
C. Moderate risk
D. High risk
Case Presentation

- 66-year-old male with T2DM for 16 years, hypertension for 20 years
- ESRD on hemodialysis for 4 years
- BMI = 36
- Single vessel coronary disease with PCI and stent 2 years ago
- Mitral valve replacement, on warfarin
- CPRA 0%
- Medicaid insurance
- ½ PPD smoker currently
Case Presentation (2)

- Deceased donor offer becomes available
- 62-year-old, hypertension, died of a cerebrovascular accident
- Terminal creatinine 1.4 mg/dL
- KDPI = 93%
- HLA matching: 1B and 1DR match
Polling Question
Activity Survey

Based on the characteristics of your patient and the kidney donor offer available, what is the expected 1-year **graft survival** based on KDPI?

A. 95%
B. 89%
C. 82%
D. 75%
KDPI and Graft Survival

Estimated Graft Survival Rates by KDPI

Organ Procurement and Transplantation Network. Available at: https://optn.transplant.hrsa.gov/resources/guidance/kidney-donor-profile-index-kdpi-guide-for-clinicians.
Polling Question
Activity Survey

Which of the following risk factors is/are **not** accounted for in the SRTR 1-year graft survival models?

A. Coronary artery disease
B. Candidate tobacco use
C. Candidate BMI
D. Candidate HLA mismatches
E. A and B
F. All of the above
How Do We Assess Risk and Effects on Program Outcomes?
SRTR Program Specific Reports (PSRs)
Tools to Monitor and Improve Your Program

The PSR contains:

- Program summary
- Waiting-list information
  - Waiting-list activity
  - Candidate characteristics
  - Candidate outcomes
- Transplant information
  - Donor and recipient characteristics
  - Patient and graft survival
- Living donor follow-up summary (if applicable)
SRTR Timelines for Evaluation

- The SRTR examines 2.5 year cohorts for outcomes – and determines the number of observed events (graft or patient loss) vs the number of expected events.
- But reports lag behind real time up to a year to allow events to accrue – so it’s old news in some cases.

### Cohorts Evaluated in the Fall 2017 PSR Cycle

<table>
<thead>
<tr>
<th>Cohort Type</th>
<th>Event Type</th>
<th>Start Date</th>
<th>End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft survival (1-Year Cohort)</td>
<td>Undergone transplant</td>
<td>July 1, 2014</td>
<td>December 31, 2016</td>
</tr>
<tr>
<td>Graft survival (3-Year Cohort)</td>
<td>Undergone transplant</td>
<td>January 1, 2012</td>
<td>June 30, 2014</td>
</tr>
<tr>
<td>Patient survival (1-Year Cohort)</td>
<td>Undergone transplant</td>
<td>July 1, 2014</td>
<td>December 31, 2016</td>
</tr>
<tr>
<td>Patient survival (3-Year Cohort)</td>
<td>Undergone transplant</td>
<td>January 1, 2012</td>
<td>June 30, 2014</td>
</tr>
</tbody>
</table>

Scientific Registry of Transplant Recipients. Available at: https://www.srtr.org/reports-tools/psr-reporting-timeline.
### How Does SRTR Risk Adjust Outcomes?

#### 1 year Deceased Donor Graft Survival Risk Adjustment Factors

<table>
<thead>
<tr>
<th>Candidate (at listing)</th>
<th>Any Previous Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidate (at listing)</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>Candidate (at listing)</td>
<td>Symptomatic Peripheral Vascular Disease</td>
</tr>
<tr>
<td>Candidate (at listing)</td>
<td>Total Serum Albumin (g/dL)</td>
</tr>
</tbody>
</table>

**Recipient (at transplant)**
- Age at Transplant (years)
- BMI (kg/m², calculated from height and weight)
- HIV Serostatus
- Most Recent CPRA (%)
- Primary Diagnosis
- Primary Source of Payment
- Procedure Type
- Total Cold Ischemia Time (hours)
- Total ESRD Time at Transplant (days)
- HLA A Mismatches (calculated)
- HLA DR Mismatches (calculated)

*Noticeably absent – cardiovascular disease (other than PVD), socio-economic factors (other than insurance)*

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*Scientific Registry of Transplant Recipients. Available at: https://www.srtr.org/reports-tools/risk-adjustment-models-transplant-programs.*
## 1-Year Patient Survival Deceased Donor-Recipient Factors

Not the Same List as for Graft Survival

<table>
<thead>
<tr>
<th>Candidate (at listing)</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidate (at listing)</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>Candidate (at listing)</td>
<td>Highest Education Level</td>
</tr>
<tr>
<td>Candidate (at listing)</td>
<td>Race</td>
</tr>
<tr>
<td>Candidate (at listing)</td>
<td>Symptomatic Peripheral Vascular Disease</td>
</tr>
<tr>
<td>Candidate (at listing)</td>
<td>Total Serum Albumin (g/dL)</td>
</tr>
<tr>
<td>Recipient (at transplant)</td>
<td>Age at Transplant (years)</td>
</tr>
<tr>
<td>Recipient (at transplant)</td>
<td>HBV Core Antibody</td>
</tr>
<tr>
<td>Recipient (at transplant)</td>
<td>HCV Serostatus</td>
</tr>
<tr>
<td>Recipient (at transplant)</td>
<td>HIV Serostatus</td>
</tr>
<tr>
<td>Recipient (at transplant)</td>
<td>Most Recent CPRA (%)</td>
</tr>
<tr>
<td>Recipient (at transplant)</td>
<td>Previous Solid Organ Transplant</td>
</tr>
<tr>
<td>Recipient (at transplant)</td>
<td>Primary Diagnosis</td>
</tr>
<tr>
<td>Recipient (at transplant)</td>
<td>Primary Source of Payment</td>
</tr>
<tr>
<td>Recipient (at transplant)</td>
<td>Total Cold Ischemia Time (hours)</td>
</tr>
<tr>
<td>Recipient (at transplant)</td>
<td>Total ESRD Time at Transplant (days)</td>
</tr>
<tr>
<td>Recipient &amp; Donor</td>
<td>HLA A Mismatches (calculated)</td>
</tr>
</tbody>
</table>

## 1-Year Graft Survival and Patient Survival

### Donor Factors

<table>
<thead>
<tr>
<th>Donor Factor</th>
<th>GRAFT SURVIVAL</th>
<th>PATIENT SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO Blood Group</td>
<td></td>
<td>ABO Blood Group</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>Age (years)</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td></td>
<td>Anti-HCV</td>
</tr>
<tr>
<td>Arginine Vasopressin</td>
<td></td>
<td>Arginine Vasopressin</td>
</tr>
<tr>
<td>BMI (kg/m², calculated from height and weight)</td>
<td></td>
<td>BMI (kg/m², calculated from height and weight)</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td></td>
<td>BUN (mg/dL)</td>
</tr>
<tr>
<td>Cigarette Use (&gt;20 pack years) Ever</td>
<td></td>
<td>Cigarette Use (&gt;20 pack years) Ever</td>
</tr>
<tr>
<td>Clinical Infection of the Lung (Confirmed or Unconfirmed)</td>
<td></td>
<td>Clinical Infection of the Lung (Confirmed or Unconfirmed)</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td>Diuretics</td>
</tr>
<tr>
<td>Drug-Treated Systemic Hypertension</td>
<td></td>
<td>Drug-Treated Systemic Hypertension</td>
</tr>
<tr>
<td>eGFR (mL/min/1.72m², calculated from SCr, age, gender, race)</td>
<td></td>
<td>eGFR (mL/min/1.72m², calculated from SCr, age, gender, race)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td>Ethnicity</td>
</tr>
<tr>
<td>History of Cancer</td>
<td></td>
<td>History of Cancer</td>
</tr>
<tr>
<td>Kidney Donor Risk Index (KDRI, calculated*)</td>
<td></td>
<td>Kidney Donor Risk Index (KDRI, calculated*)</td>
</tr>
<tr>
<td>Local vs Regional/National Share</td>
<td></td>
<td>Local vs Regional/National Share</td>
</tr>
<tr>
<td>Serum Creatinine (g/dL)</td>
<td></td>
<td>Serum Creatinine (g/dL)</td>
</tr>
<tr>
<td>T4</td>
<td></td>
<td>T4</td>
</tr>
<tr>
<td>Was this donor recovered under DCD protocol?</td>
<td></td>
<td>Was this donor recovered under DCD protocol?</td>
</tr>
</tbody>
</table>

Scientific Registry of Transplant Recipients. Available at: https://www.srtr.org/reports-tools/risk-adjustment-models-transplant-programs.
## Criteria Used by MPSC to Identify Transplant Programs that Require Further Scrutiny

<table>
<thead>
<tr>
<th>Large Centers</th>
<th>Small Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>(≥10 transplants in 2.5-year period)</td>
<td>(≤9 transplants in 2.5-year period)</td>
</tr>
<tr>
<td>Higher than expected HR for mortality or graft failure with either of the following criteria:</td>
<td>≥1 events* in a 2.5-year period</td>
</tr>
<tr>
<td>• Probability &gt;75% that the HR is &gt;1.2</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>• Probability &gt;10% that the HR is &gt;2.5</td>
<td></td>
</tr>
</tbody>
</table>

* Events are defined as any death or graft loss within 1 year of transplant.

Bayesian Methods for Assessing Transplant Program Performance

Large Program – HR = 1.67 (death rate 67% higher than expected; O/E = 1 is as expected)
299 transplants in 2.5 year cohort
13 patient deaths in 1 year (6.97 expected based on risk adjustment)

Small Program – HR = 1.37 (death rate 37% higher than expected; O/E = 1 is as expected)
6 transplants in 2.5 year cohort
1 patient death in 1 year

CUSUM reports are better suited to ongoing quality improvement because they:

1. Show actual events in the time they occurred, rather than an average that can mask periods of high or low events

2. Cover a 3 year period up to 2 months prior to release date, so are more relevant to a program’s current practice and quality efforts

* Outcomes assessed: first-year posttransplant patient and all-cause graft survival. † At this time, SRTR produces CUSUM charts for all kidney, heart, lung, and liver programs.

Quality Improvement Methods and Strategies

What CMS Expects

- Quality Assessment and Performance Improvement
- An effective transplant quality assurance and performance improvement (QAPI) program is ongoing and comprehensive, dealing with the full range of services offered by the transplant program, including patient safety, clinical care, quality of life, and those services provided under contract or arrangement
- The hospital leadership and governing body must be clearly engaged in QAPI oversight
- The transplant program must have systems in place to monitor care and services in all phases and settings of transplant and living donation, drawing from multiple sources
- The transplant QAPI program uses a methodical approach to determine when in-depth analysis is needed to fully understand improvement opportunities, causes, and implications of change for care and services delivered
- The transplant QAPI program must define, implement, and evaluate performance improvement interventions with the objective of improving quality of care
Case Presentation

- Patient accepts the kidney, basiliximab induction, followed by tacrolimus-MMF-prednisone
- Delayed graft function, 10 days; serum creatinine declines to 1.8-2.1 mg/dL range; BP 138/84 on metoprolol, amlodipine
- Week 4: BK serum viral load 11,300, MMF discontinued, tacrolimus dose reduced to target level 6-8 ng/mL
- Week 8: BK viral load 2,800, new DSA to HLA B3 at 1,800 MFI
Case Presentation

- Week 12: BK viral load, 975; serum creatinine, 2.1; tacrolimus level, 3.3; patient admits to missing his nighttime dose

- Week 15: serum creatinine, 2.4; tacrolimus level, 5.1; BP 142/86; HLA B3 DSA now at 2,600 MFI; urine P/Cr, 0.3

- Week 16: serum creatinine, 2.5; tacrolimus level, 5.2; BP 140/88; remains on warfarin, metoprolol, amlodipine. Ultrasound of transplant kidney unremarkable except for elevated resistive indices (0.85)
The cause of this patient’s increasing serum creatinine is:

A. T cell-mediated rejection
B. Polyomavirus nephropathy
C. Antibody-mediated rejection
D. Acute tacrolimus nephrotoxicity
E. All of the above
F. I cannot tell based on available information
Subclinical Injury and Graft Loss

Our patient’s known risk factors are circled in red

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Polling Question
Activity Survey

In light of the serum creatinine increase, you next decide to:

A. Hold warfarin, admit for IV heparin infusion, biopsy once anticoagulation adequately reversed
B. Empirically treat with plasmapheresis and IVIG for presumed antibody-mediated rejection
C. Measure donor-derived cell-free DNA
D. Empirically treat with rATG for T-cell mediated rejection
E. Do nothing, continue to follow blood work
Graft Survival in DeKAF

Diagnosis of CNI Nephrotoxicity Does Not Predict Allograft Survival

- n=440 “troubled grafts”
- Baseline creatinine <2 mg/dL
- Creatinine increase >25%

Subclinical Acute Rejection

- Defined as histologic acute rejection (cellular or antibody-mediated) with stable renal allograft function (stable creatinine)
- Currently diagnosed on a “protocol” or surveillance biopsy
- Only about half of transplant programs perform surveillance biopsies
  - Logistics, cost, risk of biopsy the most frequently reported reasons why not
Currently Used Biomarkers in Kidney Transplantation

• Gold standard:
  - Serum creatinine, urine protein/creatinine, immunosuppressive drug levels
  - Indication kidney biopsy

• Commonly used adjuncts
  - Viral monitoring (BK, CMV, EBV)
  - Donor-specific HLA antibody testing
  - Protocol kidney biopsy (various time points)

• Developing biomarkers
  - Donor-derived cell-free DNA (dd-cfDNA, Allosure)
  - Blood gene expression profiles (Trugraf, kSORT)
  - Urine biomarkers (CXCL9, gene expression profiles)
Need for Improved Detection of Under- and Over-Immunosuppression and Differential Diagnosis

*Personalized Medicine*

- The ideal biomarker is non-invasive, inexpensive and provides a diagnosis with high accuracy and in a subclinical setting (before creatinine goes up)
- Ideal biomarkers do not exist in medicine, but development moves towards better biomarkers
- Serum creatinine is not sensitive or specific to renal allograft injury or the cause – a lagging indicator of injury
Biomarkers in Development
Donor-Derived Cell-Free DNA as a Biomarker in Transplantation

Cell-Free DNA (cfDNA)
- Fragments of DNA in the blood that originate from cells undergoing cell injury and death
- DNA degrades into nucleosomal units consisting of ~166 bases
- cfDNA is cleared from the blood by the liver and kidney, and has a short half-life of ~30 minutes

Key Results from Peer-Reviewed Publications
- dd-cfDNA is very low in stable transplant recipients
- dd-cfDNA is elevated at the time of rejection
- dd-cfDNA decreases following successful treatment
  - De Vlaminck, Sci Transl Med. 2014 (heart), Grskovic, J Mol Diagn. 2016 (heart)
dd-cfDNA is very sensitive but not specific for ABMR in patients with graft dysfunction.

Low dd-cfDNA (<1%) in Patients with Graft Dysfunction has a Very Low Probability to be ABMR

<table>
<thead>
<tr>
<th>Performance metric</th>
<th>AlloSure test performance at 1% threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROC/AUC</td>
<td>0.87 (95% CI 0.75-0.97)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>81%</td>
</tr>
<tr>
<td>Specificity</td>
<td>83%</td>
</tr>
<tr>
<td>NPV</td>
<td>96%</td>
</tr>
<tr>
<td>PPV</td>
<td>44%</td>
</tr>
</tbody>
</table>

Molecular Classifiers for Acute Kidney Transplant Rejection

*In Peripheral Blood by Whole Genome Gene Expression Profiling*

Differentiates normal (TX) from acute rejection (AR) from acute dysfunction without rejection (ADNR)

AUCs for the 200-classifier set obtained from the full study sample set of 148 samples. These results demonstrate that there is no over-fitting of the classifier.

A Peripheral Blood Diagnostic Test for Acute Rejection in Renal Transplantation – kSORT

Urinary-cell mRNA Profile and Acute Cellular Rejection: Kidney Allografts

A First Biopsy Sample Showing Acute Cellular Rejection
B Biopsy Sample Showing No Rejection
C Both Groups, 270 Days before Biopsy
D Both Groups, 40 Days before Biopsy

Multicenter Validation of Urinary CXCL9 as a Risk-Stratifying Biomarker for Kidney Transplant Injury

Case Presentation, continued

- Biopsy is performed – Banff 1A acute cellular rejection, no features of AMR (c4d negative, minimal capillaritis) and SV40 negative, treated with pulse methylprednisone
- Donor-derived cell-free DNA level is 0.21%
- Tacrolimus dose is increased to target a level of 6-8, MMF restarted at reduced dose
- Week 20: BK viral load undetectable, serum creatinine, 2.3; tacrolimus level, 8.9
- Week 24: BK viral load undetectable; DSA to HLA B3 at 2,800 MFI; serum creatinine, 2.3; tacrolimus level, 2.9. Patient admits to frequently forgetting to take his nighttime dose
Polling Question
Activity Survey

At this point, you recommend to the patient that he:

A. Use an alarm to remind him to take his medication
B. Increase the dose of tacrolimus to target a level of 8-10
C. Ask his neighbor to help him with his medications
D. Change to a once-daily tacrolimus formulation
E. Change from generic tacrolimus to Prograf because the innovator formulation has better bioavailability
Adjusted Rate of Allograft Failure in the US

- All-cause graft failure
- Return to dialysis or retransplant
- Death with function

United States Renal Data System. 2013 Annual Data Report.
Why Do Kidneys Fail? Mayo Experience

1996-2006: 330 of 1317 KTX with graft loss at mean 50-month follow-up
  138 (43.4%) due to death
  39 (11.8%) due to 1° non-function
  153 (46.3%) due to graft failure (biopsies mean 4.7 months prior to graft loss):

- Of “IF/TA”
- Of “glomerular disease”
- 1/4 history of acute rejection
- 40% “transplant glomerulopathy” (~HLA Ab?)
- Acute rejection (12%)
- Glomerular disease (37%)
- IF/TA (31%)
- Med/Surg (16%)

• ONLY 1 GRAFT LOSS ATTRIBUTED SOLELY TO CNI TOXICITY

Antibody-mediated Rejection and Non-adherence

Almost half of antibody-mediated rejection (ABMR) is due to nonadherence

ABMR = antibody-mediated rejection
Non-adherence Predicts DSA Development

- 315 consecutive recipients without donor-specific antibody (DSA)
  - Mean follow-up: 6 years
- 47 (15%) developed de novo DSA
- Adherent recipients
  - n=268
  - 8% de novo DSA
- Nonadherent
  - n=47
  - 49% de novo DSA

Health Care Non-adherence and Graft Survival

Retrospective, longitudinal cohort study, n=4,646, assessed non-adherence though use of Medication Possession Ratios (MPR) and no-shows for blood work and clinic appointments.

Adjusted for age, gender, race, marital status, co-morbidities, donor characteristics, immunologic risks and baseline immunosuppression, rejection and delayed graft function.

Late Graft Loss: A Changing Paradigm

- Chronic rejection is the most frequent cause of death-censored graft loss
- Chronic rejection is commonly due to insufficient immunosuppression
  - Inappropriate prescription (minimizing or avoidance strategies)
  - Patient non-adherence
Risk Factors for Non-adherence

- Insurance status
- Access to care
- Provider-patient communication
- Transition to adult transplant program (pediatric)

- Health system/health care provider factors
- Sociodemographic factors
- Condition-related factors
- Patient-related psychosocial factors
- Treatment-related factors
- More frequent doses
- Greater total number of medications
- Side effects
- Medication taste/size (pediatric)

- Adolescent/young adult
- Minority ethnicity
- Low socioeconomic status
- Family distress (pediatric)

- Longer time since transplant
- Transplant from living donor
- Better perceived health
- Physical limitations

- Past nonadherence
- Low health literacy/knowledge about illness
- Psychological distress
- Low self-efficacy
- Poor social supports
- Low perceived vulnerability to poor outcomes (pediatric)
- Forgetfulness/cognitive impairment
- Daily routine changes

Strategies to Improve Adherence

• Provider level
  – Avoid under-dosing (no margin for missed doses)
  – Simplified regimens
**Time in Therapeutic Range (TTR)**

- n=538 Tac-treated patients, target level 6-9 ng/ml (0-3 mos); 5-8 ng/mL (4-12 mos); MMF-90%, rATG 50%
- TTR<60% considered high-risk from data with warfarin

**TIME IN THERAPEUTIC RANGE (5-10 NG/ML) IN FIRST YEAR**

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dnDSA Development is Preceded by Drop in Tacrolimus Levels

- 492 patients; 96% 1st transplant, <10% CPRA>80, follow up 87 mos, mean of 97 tacrolimus levels/patient
- Tacro level CV: dnDSA (39.7) vs no dnDSA (33.8), P=0.001
SYMPHONY: “Low Dose” Tacrolimus 4-7 ng/mL

12-month randomized open-label multicenter trial (n=1645)
4 arms (IL2R induction in “low” arms, MMF/Prednisone for all)

<table>
<thead>
<tr>
<th>Mos post-transplant</th>
<th>Tacrolimus level</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mo</td>
<td>6.4</td>
</tr>
<tr>
<td>36 mo</td>
<td>6.5</td>
</tr>
</tbody>
</table>

12 months

<table>
<thead>
<tr>
<th>Regimen</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CyA “standard”</td>
<td>57.1</td>
</tr>
<tr>
<td>CyA “low”</td>
<td>59.4</td>
</tr>
<tr>
<td>Tacrolimus “low”</td>
<td>65.4*</td>
</tr>
<tr>
<td>Srl “low”</td>
<td>56.7</td>
</tr>
</tbody>
</table>

“Low-dose” Tacrolimus Results in More Rejection and DSA

- Phase IV 2-arm RCT, n=186 low-risk; basiliximab-tacro (level 8-12)-MPA-steroids withdrawn by 10 wks.
- At 4 mos:  Arm 1: 50% tacrolimus ER dose reduction (level >3 mcg/L);
  Arm 2: Tacrolimus ER, level 7-12 mcg/L

- dnDSA in 6/87 Arm 1 pts; 0 in Arm 2 pts
- No difference in eGFR at 12 months post-transplant

Target Tacrolimus Levels at 12-months Post-transplant

**RECENT RCTs**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Achieved 12-mos Tac levels (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMPHONY</td>
<td>6.4</td>
</tr>
<tr>
<td>OPTICEPT</td>
<td>6-7.5</td>
</tr>
<tr>
<td>HARMONY</td>
<td>6-7</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>6-8 (24 wk)</td>
</tr>
<tr>
<td>De Graav, 2017</td>
<td>6.8</td>
</tr>
<tr>
<td>Gatault, 2017</td>
<td>5.6* vs 7.4</td>
</tr>
</tbody>
</table>

No evidence that Tac levels <6 ng/mL during the first post-transplant year are safe or effective (with MMF) “Target” level ≠ “achieved” level

* "Low" dose arm: increased rejection
Once-daily Formulations of Tacrolimus

Normalized Pharmacokinetic Profile to Prograf
(Dose conversion: Envarsus - 30%, Advagraf + 8%)

<table>
<thead>
<tr>
<th>Tac-ER*</th>
<th>Tac-ER*</th>
<th>LCP-Tac*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_0$</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>Similar</td>
<td>Lower</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>Similar</td>
<td>Delayed</td>
</tr>
<tr>
<td>AUC</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Dose change</td>
<td>~8% higher</td>
<td>30% lower</td>
</tr>
</tbody>
</table>

*Compared to twice-daily IR-tacrolimus

Extended-Release Tacrolimus vs Twice-Daily Tacrolimus RCTs

- Basiliximab, MMF and corticosteroids in all subjects, both studies
- No difference compared to twice-daily tacrolimus

Graft survival

Treatment failure

P=n.s.

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Time to Event, days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>365</td>
</tr>
<tr>
<td></td>
<td>548</td>
</tr>
<tr>
<td></td>
<td>730</td>
</tr>
<tr>
<td></td>
<td>912</td>
</tr>
<tr>
<td></td>
<td>1,095</td>
</tr>
<tr>
<td></td>
<td>1,278</td>
</tr>
<tr>
<td></td>
<td>1,460</td>
</tr>
</tbody>
</table>

Persistence and Adherence in Kidney Recipients

Effect of Dosing Frequency

- 219 patients randomized to once-daily or twice-daily tacrolimus

<table>
<thead>
<tr>
<th></th>
<th>Once-daily (n=145)</th>
<th>Twice-daily (n=74)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistence, 6 mos</td>
<td>82%</td>
<td>72%</td>
<td>0.08</td>
</tr>
<tr>
<td>Adherence, 6 mos</td>
<td>88%</td>
<td>79%</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

- Doses were missed more frequently in the evening than in the morning (11.7% vs 14.2%; \( P=0.0035 \))

Terminology

- **Adherence**
  - Extent to which patients take medications as prescribed – timing, dosage, and frequency

- **Compliance**
  - Patient’s passive following of provider’s orders

- **Persistence**
  - Duration of time patient takes medication from initiation to discontinuation of therapy
What Can Centers Do?

- Multidisciplinary approach
- Electronic monitoring and notification
- Personalize education programs
  - Culturally and content appropriate
  - Reinforce but don’t confuse
  - More face-time
- Engage patients and their family
- Track pharmacy refills
Use of Electronic Monitoring to Predict Patterns of Early Medication Adherence in Renal Transplantation

MEMS (Medication Event Monitoring System): A microprocessor embedded in the cap of a medication bottle records every opening and closing of the cap.

- 195 patients
- 44 (22.6%) decreased adherence by 7% or more in month 2 post tx
- Acute rejection
- Early graft loss

Synergistic Effect of Epitope-Mismatch and Non-adherence on Graft Survival

- 195 patients monitored with MEMS
- Mean follow-up: 6 years

Eplet Mismatch Modulates Effect of Tacrolimus Trough Levels on the Development of dnDSA

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Use of Electronic Monitoring with Reminders and Physician Notification

- Wireless pill bottle opening RCT, de novo transplants
- Bottle-measured tacrolimus adherence during the last 90 days of 180 day trial

No difference in CV of tacrolimus levels between groups

Interventions for Medication Non-Adherence

- Relative few trials, mainly in adults
  - Limited effectiveness
  - Multi-component interventions are more efficacious but not feasible on large scale
  - Efficacy evaluated primarily during intervention period
  - Since no permanent cure, intervention should ideally be given for as long as medical therapy is needed

- Most practical intervention is modifying immunosuppression regimen from twice-a-day to daily dosing

Case Presentation, continued

- Patient switches to a once-daily tacrolimus formulation
- He immediately notes that it is much easier for him to adhere to this tacrolimus regimen
- Tacrolimus levels consistently remain between 6-8 for the remainder of the first post-transplant year, 5-7 thereafter
- Serum creatinine remains stable between 2.2-2.6 mg/dL, no significant proteinuria, BK viral load remains undetectable, low level class I DSA persists
Summary

• Transplant centers should have effective quality assurance and performance improvement programs in order to optimize patient outcomes and to help achieve acceptable program-specific reports.

• Adoption of one of the newer approaches to better risk stratify and mitigate chronic under-immunosuppression due to provider under-dosing and patient non-adherence may help improve allograft survival.

• Novel non-invasive biomarkers to evaluate alloimmune injury are emerging and may represent a valuable adjunctive tool in the management of kidney recipients.