Preventing DSA-Mediated Renal Allograft Injury:

*Practical Strategies to Maintain Adequate Immunosuppression in Individual Patients*

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Stanley C. Jordan, MD, FASN, has a financial interest/relationship or affiliation in the form of:

*Consultant* for Genentech, Inc.; Hansa Medical; Novartis Pharmaceuticals Corporation; and Vitaeris Inc.

*Grant/Research Support* from Genentech, Inc.; Hansa Medical; and Novartis Pharmaceuticals Corporation.

Stanley C. Jordan, MD, FASN, does intend to discuss either non-FDA-approved or investigational use with the following products/devices: therapeutic modalities to prevent/treat antibody-mediated rejection in kidney transplant recipients.

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*Grant/Research Support* from Alexion Pharmaceuticals Inc.; Astellas; Bristol-Myers Squibb; Novartis Pharmaceuticals Corporation; Oxford Immunotec, Inc.; and Quark Pharmaceuticals, Inc.

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This CME activity is jointly provided by Medical Learning Institute, Inc. and PVI, PeerView Institute for Medical Education. This activity is supported by an educational grant from Astellas.
A Closer Look at DSAs as Mediators of Allograft Injury

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David Geffen School of Medicine at UCLA
Director, Nephrology & Transplant Immunology
Medical Director, Kidney Transplant Program
Cedars-Sinai Medical Center
Los Angeles, California
Patients With De Novo DSA Have Early (0-6 Months) TCMR With More Intense PTC Inflammation

<table>
<thead>
<tr>
<th>TCMR PTC Score</th>
<th>de novo DSA</th>
<th>P &lt; .05</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>No DSA</td>
<td></td>
</tr>
</tbody>
</table>

De Novo DSA Generation

- APCs present alloantigens to $T_{FH}$ cells
- $T_{FH}$ cells activate Bn cells to become Bm and plasmablasts
- Plasmablasts evolve to plasma cells and generate DSAs

Source: Peter Nickerson

## Etiology of Allograft Failure: Changing the Way We Think

<table>
<thead>
<tr>
<th>Past</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primarily a T-cell–mediated process</td>
<td>• Insufficient control of the humoral arm of a recipient’s immune system by current immunosuppressive regimens</td>
</tr>
</tbody>
</table>

Progressively superseding the historical dogma that such allograft losses were caused by CNI toxicity and CAN

Understanding the Causes of Kidney Transplant Failure: The Dominant Role of AMR and Nonadherence


Distribution of Histologic Diagnosis and Adherence Status Expressed as Probability Plots Conditional on Time of Biopsy Post Transplant

- No major abnormalities
- Borderline
- T-cell–mediated rejection
- Polyoma virus nephropathy
- Antibody-mediated rejection
- Glomerular diseases
- Atrophy-fibrosis
- Mixed rejection
- Other

Days Post Transplantation

Probability

5 10 50 100 500 1,000 5,000 10,000
Evidence for Antibody-Mediated Injury as a Major Determinant of Late Kidney Allograft Failure

Kaplan-Meier Analysis of the Impact of Primary or Secondary Local Diagnosis of CNI Nephrotoxicity on Kidney Allograft Survival After For-Cause Biopsy

Log rank = 3.46
P = .0630

Death-Censored Graft Survival by Clinical Phenotype and dnDSA Status\textsuperscript{1}

\textbf{Post-Transplant Graft Survival}

\begin{itemize}
  \item Green line: No dnDSA no dysfunction (n = 388)
  \item Brown line: No dnDSA dysfunction (n = 56)
  \item Blue line: Subclinical dnDSA (n = 45)
  \item Red line: Clinical dnDSA (n = 19)
\end{itemize}

\textit{P} < .0001

dnDSA Development: Impact of Adherence

Graft Survival in Type 1 and Type 2 AMR Patients and By IF/TA Scores (N = 80)\(^1\)

Graft Survival in Type 1 and Type 2 AMR Patients and By DSA Scores (N = 80)

dnDSAs Portend Poor Graft Outcomes

Kidney Graft Survival Following cAMR Diagnosis

Current Therapies Show Some Beneficial Effects

Kidney Graft Survival After cAMR Based on Treatment

Survival Probability

Time, Months

- Steroid/IVIG + rituximab or thymoglobulin
- Steroid/IVIG alone or in combination
- No treatment

a $P < .001$

The impact of donor-specific anti-HLA antibodies on late kidney allograft failure

Alexandre Loupy, Gary S. Hill and Stanley C. Jordan

Abstract | Despite improvements in outcomes of renal transplantation, kidney allograft loss remains substantial, and is associated with increased morbidity, mortality and costs. Identifying the pathologic pathways responsible for allograft loss, and the attendant development of therapeutic interventions, will be one of the guiding future objectives of transplant medicine. One of the most important advances of the past decade has been the demonstration of the destructive power of anti-HLA alloantibodies and their association with antibody-mediated rejection (ABMR). Compelling evidence exists to show that donor-specific anti-HLA antibodies (DSAs) are largely responsible for the chronic deterioration of allografts, a condition previously attributed to calcineurin inhibitor toxicity and chronic allograft nephropathy. The emergence of sensitive techniques to detect DSAs, together with advances in the assessment of graft pathology, have expanded the spectrum of what constitutes ABMR. Today, subtler forms of rejection—such as indolent ABMR, C4d-negative ABMR, and transplant arteriopathy—are seen in which DSAs exert a marked pathological effect. In addition, arteriosclerosis, previously thought to be a bystander lesion related to the vicissitudes of aging, is accelerated in ABMR. Advances in our understanding of the pathological significance of DSAs and ABMR show
Mechanisms of Donor-Specific Antibody-Mediated Endothelial Injury in Renal Allografts

Model Linking TCMR, dnDSA, and AMR With Graft Loss

De Novo DSA Treatment Options


- ↑↑ tacrolimus/MMF ± prednisone
- IVIG ± pheresis (FDA ~SOC¹)
- Rituximab (anti-CD20)
- Bortezomib (proteosome inhibitor)

- Eculizumab (C5a inhibitor)/C1INH
- IdeS?
- IL-6/IL-6R inhibitors?
Therapeutic Options for AMR

Targeting cAMR and TG: Can It Be Treated?
IL-6 and Antibody-Mediated Rejection

- Chronic DSA+ AMR and TG limit the function and longevity of renal allografts, accounting for the majority of graft losses in the United States.
- This results in increased cost to the healthcare system, increased stresses on patients and their families, and reduced life expectancy on dialysis.
- Currently, there are no good therapies for cAMR and TG.
- Here, we explore the use of tocilizumab (anti-IL-6R) in patients with resistant cAMR TG.
Signaling Pathways for IL-6/IL-6R

IL-6 Drives B-Cell Activation and Differentiation to Antibody-Producing Plasma Cells

IL-6 Shapes T-Cell Immunity\(^1\)

- **Naïve T Cell**
  - TGF-β
  - IL-12, IL-6
  - IL-4, IL-6
  - IL-1, IL-6
  - IL-21, IL-6

- **T-Reg**
  - TGF-β, IL-10
  - Fox P3
  - IL-6

- **T H1**
  - Stat-1, T-bet
  - γ-IFN
  - IL-4
  - IL-5 & IL-13

- **T H2**
  - Stat-6
  - GATA-3
  - IL-4
  - Allergy; atopic disease

- **T H17**
  - Stat-3, RORC
  - IL-17A, IL-17F
  - IL-21, IL-22
  - Cytotoxic T cells; autoimmunity; allograft rejection

- **T FH**
  - Bcl6
  - IL-21
  - B cells → plasma cells

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Anti-IL-6/IL-6R Therapies Modify Inflammatory T-Cell Responses and Induce Regulatory T Cells

Anti–Interleukin 6 Receptor Antibodies Attenuate Antibody Recall Responses in a Mouse Model of Allosensitization

Irene Kim, Gordon Wu, Ning-ning Chai, Andrew S. Klein, and Stanley Jordan

Background. Interleukin (IL)-6 is a regulatory cytokine for T helper type 17 (Th17) and Treg cells and a potent stimulus for B/plasma cells. The current study evaluated the effect of IL-6 receptor (IL-6R) blockade with an anti–IL-6R monoclonal (mMR16-1) in alloantibody recall responses.

Methods. A mouse model of human leukocyte antigen (HLA) A2 sensitization was used for studies to evaluate the efficacy of anti–IL-6R on alloantibody recall responses and to examine the impact of IL-6R blockade on Th17, Treg, follicular T helper (Tfh) and plasma cells using multiparameter flow cytometry, flow antibody binding, and enzyme-linked immunospot (ELISpot) assay.

Results. Re-exposure of C57BL/6 mice to HLA-A2+ skin allografts resulted in a surge of donor-specific (anti–HLA-A2) immunoglobulin (Ig)G antibodies. Anti–IL-6R treatment significantly decreased but did not eliminate alloantibody responses (IgG mean fluorescence intensity, 486 ± 153 vs. control 792 ± 193, P = 0.0076). Flow cytometry analysis showed that anti–IL-6R treatment resulted in reduction of IL-21+CD4+ (Th17) cells (P = 0.006 vs. control) and CXCR5+CD4+ Tfh cells (P = 0.04), but increased foxp3+CD4+ (Treg) cells in the CD4+ population (P = 0.04 vs. control). The IgG ELISpot experiments showed a significant reduction of IgG spots in the bone marrow and the spleen cells from the anti–IL-6R–treated mice. In vitro treatment of mouse hybridoma (PA2.1) cultures with anti–IL-6R decreased IgG spot formation but had limited effect on cell proliferation.

Conclusion. The data indicate that anti–IL-6R therapy attenuates alloantibody recall responses by modulating a
Anti–IL-6R Inhibits Plasma Cell IgG Production and Anti–HLA-A2 Antibody

Anti–IL-6R Significantly Suppressed IgG+ Plasma Cells in the Bone Marrow and Spleens Demonstrated in an ELISpot Assay

Detection of Anti–HLA-A2 IgG Antibodies in Conditioned Media of BM Cell Cultures by Flow-Antibody Binding Assay

BM            Spleen
Anti–IL-6R
Control

Anti–IL-6R
+ mM16-1
-mM16-1

Spot Counts/Well

Spleen            BM

Anti–IL-6R
Control

Mean Fluorescence Intensity

Spot Counts/Well

Spleen            BM

Anti–IL-6R
Control

a $P < .01$. b $P < .05$.
A Phase I/II Trial of the Interleukin-6 Receptor Specific Humanized Monoclonal (Tocilizumab) + Intravenous Immunoglobulin in Difficult to Desensitize Patients

Ashley A. Vo, PharmD,1 Jua Choi, PharmD,1 Irene Kim, MD,1 Sabrina Louie, MPH,1 Kristen Cisneros, RN,1 Joseph Kahwaji, MD,1 Mieko Toyoda, PhD,2 Shili Ge, PhD,2 Mark Haas, MD,3 Dechu Puliyanda, MD,1 Nancy Reinsmoen, PhD,4 Alice Peng, MD,1 Rafael Villicana, MD,1 and Stanley C. Jordan, MD1

Background. Current desensitization (DES) methods are not always effective. Thus, novel, more effective approaches are desirable. Interleukin (IL)-6 is an attractive target as it promotes B-cell differentiation to plasma cells, is important for immunoglobulin production, and induces Th17 cells. Here, we undertook a phase I/II pilot study of DES using a novel drug (anti-IL-6 receptor (IL-6R), Tocilizumab [TCZ]) + intravenous Ig (IVlg) to assess safety and limited efficacy. Methods. From July 2012 to November 2013, 10 patients unresponsive to DES with IVlg + Rituximab were treated with IVlg + TCZ. Patients received IVlg on days 0 and 30 at 2 g/kg and TCZ 8 mg/kg on day 15 then monthly for 6 months. If transplanted, patients received IVlg once and TCZ monthly for 6 months. Results. No differences in baseline characteristics were seen in patients not transplanted versus transplanted. Two patients in each group developed serious adverse events: not transplanted- pulmonary congestion with epilepticus (likely not related) versus transplanted infective colitis with colonic perforation and Bell Palsy (both possibly related). Five of 10 patients were transplanted. Mean time to transplant from first DES was 25 ± 10.5 months but after TCZ was 8.1 ± 5.4 months. Six-month protocol biopsies showed no antibody-mediated rejection. Donor-specific antibody strength and number were reduced by TCZ treatment. Renal function at 12 months was 60 ± 25 ml/min. Conclusions. Tocilizumab and IVlg appear to
**Tocilizumab Protocol for Desensitization Pre and Post Transplant**

**Schema for Desensitization With IVIG + TCZ**

- Day -30: IVIG (2 g/kg)
- Day 0: Tocilizumab (8 mg/kg)
- Day 15:
  - IVIG (2 g/kg)
  - Tocilizumab (8 mg/kg)
- Day 30:
  - IVIG (2 g/kg)
  - Tocilizumab (8 mg/kg)
- Day 45: Tocilizumab (8 mg/kg)
- Day 75: Tocilizumab (8 mg/kg)
- Day 105: Tocilizumab (8 mg/kg)
- Day 119: Tocilizumab (8 mg/kg)
- Day 135: Tocilizumab (8 mg/kg)
- Day 149: Tocilizumab (8 mg/kg)
- Day 180+: Tocilizumab (8 mg/kg)

**Acceptable Crossmatch/DSA Reduction**

**Schema for Post Transplant**

- Day 0: Tocilizumab (8 mg/kg)
- Day 2:
  - IVIG (2 g/kg)
  - Tocilizumab (8 mg/kg)
- Day 30:
  - Tocilizumab (8 mg/kg)
- Day 60:
  - Tocilizumab (8 mg/kg)
- Day 90:
  - Tocilizumab (8 mg/kg)
- Day 120:
  - Tocilizumab (8 mg/kg)
- Day 150:
  - Tocilizumab (8 mg/kg)
- Day 180:
  - Tocilizumab (8 mg/kg)
- Day 300:
  - Tocilizumab (8 mg/kg)

**Pathway 1-H**

- DSA levels
  - Allo-CFC (IFNγ + NK cells)
  - CD4+/CD25+/Fox P3+ cell numbers
  - Th17+ cell numbers
  - CD19+/CD38+/CD27+
  - Quantitative immunoglobulins, CRP (at days -30 and 180)

**Induction:** alemtuzumab; maintenance: prograf/cellcept/pred

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DSA Patterns Before and After Transplantation

Course of Immunodominant DSAs

Mean Immunodominant DSA Scores for TCZ-Treated and Transplanted Patients

Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients


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2Pass Translational Research Center for Organ Transplantation, INSTITUT UZIL, Biostatistics Department, Paris, France
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Extending the functional integrity of renal allografts is the primary goal of transplant medicine. The development of donor-specific antibodies (DSAs) posttransplantation leads to chronic antibody-mediated rejection (cAMR) and transplant glomerulopathy (TG), resulting in the majority of graft losses that occur in the United States. This reduces the quality and length of life for patients and increases costs. There are no approved treatments for cAMR. Evidence suggests the preclinical efficacy of anti-IL-6 monoclonal treatment of cAMR. Extending the functional integrity of renal allografts is the primary goal of transplant medicine. The development of donor-specific antibodies (DSAs) posttransplantation leads to chronic antibody-mediated rejection (cAMR) and transplant glomerulopathy (TG), resulting in the majority of graft losses that occur in the United States. This reduces the quality and length of life for patients and increases costs. There are no approved treatments for cAMR. Evidence suggests the preclinical efficacy of anti-IL-6 monoclonal treatment of cAMR.

Abbreviations: AE, adverse event; AMR, antibody-mediated rejection; cAMR, chronic active AMR; DSAs, donor-specific antibodies; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; IDSA, immunodominant donor-specific antibody; IF/TA, interstitial fibrosis/tubular atrophy; IL-6R, Interleukin-6 receptor; IL-10; intercellular range; NSTEMI, non-ST-segment elevation myocardial infarction; PLEX, plasma exchange; SAE, severe adverse event; T/H, T helper cell; TG, transplant glomerulopathy; Th17, T helper 17 cell; Treg, T regulatory cell

Received 14 September 2016, revised 01 February 2017 and accepted for publication 08 February 2017

Introduction
Antibody-mediated rejection (AMR) is a unique, significant, and often severe form of allograft rejection. Significant advances have occurred in our ability to prevent patients who are at risk for AMR and to diagnose AMR (1, 2). The pathophysiology of AMR suggests a primary role for antibodies, B cells, and plasma cells. As a result, IVIG, rituximab, and/or plasma exchange (plasmapheresis, PLEX) has been leveraged for the treatment of acute AMR (3, 4). Despite the success of these therapies, posttransplantation AMR, chronic active AMR (cAMR), and transplant glomerulopathy (TG) remain significant problems that are often refractory to current therapies (4). Data from the Deterioration in Kidney Allograft Function study show that most graft losses in the current era of immunosuppression have evidence of AMR with positive C4d staining (28). It is estimated that 5000 allografts are lost each year in the United States, primarily from cAMR and TG (29). The current treatment paradigms rely on reduction of antibody levels to prevent AMR. This misses the importance of maintaining immunosuppression and investigating novel methods to prevent or treat AMR (AMR) that directly address the reduction of donor-specific antibodies (DSAs) and antibody-producing cells.

Tocilizumab Treatment of cAMR and TG: Treatment Protocol

75 patients with chronic active AMR ± transplant glomerulopathy (TG)

39 patients treated with IVIG + rituximab ± plasma exchange (SOC)

37 patients who failed IVIG + rituximab + plasma exchange
Treated with tocilizumab 8 mg/kg monthly for 6 to 18 months

Patients followed for up to 5 years post treatment with assessments
Kidney Allograft and Patient Survival After Treatment With Tocilizumab for cAMR

eGFRs in Adult and Pediatric Patients Treated With Tocilizumab for cAMR

Allograft Phenotype
Pre and Post Tocilizumab Treatment

Identification of Rejection Phenotypes According to the Characteristics of the Dominant Donor-Specific Anti-HLA Antibody

Death-Censored Kidney Allograft Survival According to IgG iDSA Subclass Status

Impact of Tocilizumab on Total IgG Anti-HLA Antibody Levels and IgG Subclass DSAs in cAMR Patients

<table>
<thead>
<tr>
<th></th>
<th>Pre Tocilizumab</th>
<th>Post Tocilizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total IgG, mg/mL</strong></td>
<td>13.0 ± 2.5</td>
<td>10.8 ± 3.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>IgG1, μg/mL</strong></td>
<td>9.5 ± 5.2</td>
<td>6.9 ± 4.6&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>IgG2, μg/mL</strong></td>
<td>4.0 ± 2.4</td>
<td>2.4 ± 1.0&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>IgG3, μg/mL</strong></td>
<td>1.3 ± 1.4</td>
<td>0.7 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>IgG4, μg/mL</strong></td>
<td>0.3 ± 0.2</td>
<td>0.2 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Anti-HLA-IgG (score)</strong></td>
<td>99 ± 79</td>
<td>71 ± 71&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>DSA (score)</strong></td>
<td>10.0 ± 8.7</td>
<td>4.8 ± 6.8&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>IgG3 (MFI, x1,000)</strong></td>
<td>9.5 ± 27.9</td>
<td>2.2 ± 4.4&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>IgG4 (MFI, x1,000)</strong></td>
<td>2.4 ± 7.2</td>
<td>0.5 ± 1.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < .05 and .05 < b P < .1 vs pre tocilizumab.

Tocilizumab Induces Regulatory T Cells Post Transplant in Primate Model of Lung Transplantation

Tocilizumab + ATG Induction Dramatically Improves Lung Allograft Survival in Incompatible Primates¹

Use of the Streptococcal IgG Endopeptidase (IdeS) to Eliminate Pathogenic Donor Specific Antibodies
Mechanism of Action of IdeS with Implications for CDC and ADCC

IgG → IdeS → sclIgG

Complement(+)/FcγR(+) → CDC(+)/ADCC(+)

Complement(-)/FcγR(+/-) → CDC(-)/ADCC(+/-)

Complement(-)/FcγR(-) → CDC(-)/ADCC(-)

Solutions to Remove Pathogenic IgG in Patients


Therapeutic plasma exchange/immunoadsorption
IdeS Protocols for Desensitization: United States and Sweden

**Sweden**
- CXM
- IdeS
- ATGAM
- DD or LD treatment

**United States**
- CXM
- IdeS
- Alemtuzumab, day 4 post treatment

> IVIG, 2 weeks post treatment

**DSA/safety**
- TAC + MMF + steroids

SDS-Page and Western Blot Analysis of Serum Pre and Post IdeS Treatment

Impact of IdeS on HLA Antibodies in Single Antigen Luminex and C1q Luminex Assay

Sum and Strongest DSAs Pre Transplant and 1 Month Post IdeS¹

Conclusions

B cells and antibodies have emerged as primary mediators of chronic allograft loss and the pre-eminent immunologic barrier to transplantation.

Therapies for prevention and treatment of AMR are advancing beyond traditional immunosuppressive drugs to immune modulation, primarily through induction of regulatory T cells and biologic alteration of T-effector cells and the complement system.
Striking the Right Balance: What Can We Do to Achieve and Maintain Adequate Immunosuppression After Kidney Transplantation?

Alexander Wiseman, MD, FAST
Professor of Medicine, Division of Renal Diseases and Hypertension
Medical Director, Kidney and Pancreas Transplant Programs
University of Colorado School of Medicine
Aurora, Colorado
The Role of Specific Immunosuppressive Agents in DSA Formation
OPTN/SRTR 2013 Annual Data Report: Immunosuppression in Adult Kidney Transplant Recipients

Production of dnDSA is a major risk factor for acute and chronic antibody-mediated rejection and graft loss after all solid organ transplantation.

What do we know about the risk of individual immunosuppressive agents and their ability to prevent dnDSA production?
## Induction Therapy: A Comparison of the Risk of dnDSA

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>F/U, y</th>
<th>Induction Regimen</th>
<th>Maintenance Regimen</th>
<th>Univariate or Multivariate Analysis (dnDSA)</th>
<th>P</th>
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<tr>
<td><strong>rATG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Brokho et al 2014:</td>
<td>114</td>
<td>3</td>
<td>rATG or BAS</td>
<td>TAC MMF Steroids</td>
<td>HR = 0.16 rATG vs BAS</td>
<td>.003</td>
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<tr>
<td>Retrospective, single-center study</td>
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<tr>
<td>Huang et al 2012:</td>
<td>145</td>
<td>1</td>
<td>rATG, BAS, or none</td>
<td>CsA or TAC MPA Steroids</td>
<td>7.4% rATG 40% BAS 7.1% none</td>
<td>.030</td>
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<tr>
<td><strong>Alemtuzumab</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Todeschini et al 2013:</td>
<td>48</td>
<td>2</td>
<td>ALEM or rATG/BAS</td>
<td>CsA or SRL MMF Steroids to day 7</td>
<td>57% ALEM 12.5% rATG/BAS</td>
<td>.01</td>
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<td>Retrospective, single-center matched control study</td>
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<td><strong>Rituximab</strong></td>
<td></td>
<td></td>
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<tr>
<td>Tydén et al 2012:</td>
<td>71</td>
<td>3</td>
<td>RITUX or placebo</td>
<td>TAC MMF Steroids</td>
<td>3% RITUX 16% placebo</td>
<td>.10</td>
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<td>Prospective, multi-center double-blind study</td>
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<td><strong>Bortezomib</strong></td>
<td></td>
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<tr>
<td>Ejaz et al 2013:</td>
<td>40</td>
<td>1</td>
<td>rATG or rATG/RITUX or rATG/BORT or rATG/RITUX/BORT</td>
<td>TAC MMF Steroids</td>
<td>30% rATG 30% rATG/RITUX 10% rATG/BORT 30% rATG/RITUX/BORT</td>
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<td>Prospective, two-center randomized study</td>
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</tbody>
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rATG Versus Basiliximab\textsuperscript{1}

- 114 consecutive, moderately sensitized (+DSA/-FXM) recipients of deceased donor kidney transplants from 2009 to 2011
- rATG: n = 85; basiliximab: n = 29
- 36-month follow-up

<table>
<thead>
<tr>
<th>Kidney Function at 12 Months</th>
<th>Basiliximab</th>
<th>ATG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR ± SD, mL/min</td>
<td>55 ± 17</td>
<td>56 ± 25</td>
<td>.9</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.4 ± 0.4</td>
<td>1.4 ± 0.5</td>
<td>.8</td>
</tr>
<tr>
<td>UPC, mg/mg</td>
<td>0.3 ± 0.4</td>
<td>0.4 ± 0.4</td>
<td>.4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>DSA at 12 Months</th>
<th></th>
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<tbody>
<tr>
<td>dnDSA (MFI ± SD)</td>
<td>3,652 ± 12,835</td>
<td>455 ± 1,828</td>
<td>.02</td>
</tr>
<tr>
<td>DSA (MFI ± SD)</td>
<td>4,060 ± 6,300</td>
<td>2,454 ± 4,265</td>
<td>.2</td>
</tr>
</tbody>
</table>

rATG Versus Basiliximab (Cont’d)¹

2.1: We recommend using a combination of immunosuppressive medications as maintenance therapy including a **CNI and an antiproliferative agent, with or without corticosteroids** (1B)

2.2: We suggest that **tacrolimus be the first-line CNI used** (2A)

2.3: We suggest that **mycophenolate be the first-line antiproliferative agent** (2B)

2.5: We recommend that **if mTORi are used, they should not be started until graft function is established and surgical wounds are healed** (1B)

Calcineurin Inhibitor Maintenance Therapy: A Comparison of the Risk of dnDSA¹

<table>
<thead>
<tr>
<th>Study</th>
<th>Organ Type</th>
<th>N</th>
<th>Follow-Up</th>
<th>Maintenance Regimen</th>
<th>Univariate or Multivariate Analysis</th>
<th>Use of Therapy According to Presence/Absence of dnDSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper et al 2011: Retrospective, single-center cohort study</td>
<td>Kidney or kidney-pancreas</td>
<td>244</td>
<td>2 y</td>
<td>Various</td>
<td>NA</td>
<td>TAC was used in 77% of patients with dnDSA and 90% of patients with no dnDSA (P = .009)</td>
</tr>
<tr>
<td>Huang et al 2012: Retrospective, single-center cohort study</td>
<td>Kidney</td>
<td>145</td>
<td>1 y</td>
<td>CsA or TAC MPA Steroids</td>
<td>22% CsA, 4% TAC</td>
<td>.02</td>
</tr>
<tr>
<td>Lachmann et al 2006: Prospective, single-center cohort study</td>
<td>Kidney</td>
<td>1,043</td>
<td>&gt;6 mo to 4 y</td>
<td>CsA or TAC ± MMF/AZA ± Steroids</td>
<td>35% CsA, 20% TAC</td>
<td>.05</td>
</tr>
<tr>
<td>Hourmant et al 2005: Prospective, single-center cohort study</td>
<td>Kidney</td>
<td>1,229</td>
<td>5 y</td>
<td>Various</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

CNI and DSA Formation

- 2007-2009: 244 consecutively transplanted kidney and kidney/pancreas recipients without pre transplant DSA screened for dnDSA at 1, 6, 12, and 24 months and when clinically indicated
- DSA detected in 27% of all patients by protocol or indication screening
  - DSA+ associated with rejection (9.5% vs 27%), lower GFR, and graft loss

### Table: DSA+ and DSA- by Induction and Immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>All patients, n (%)</th>
<th>DSA+, n (%)</th>
<th>DSA-, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>71 (29)</td>
<td>18 (28)</td>
<td>53 (30)</td>
<td>.73</td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>162 (66)</td>
<td>43 (66)</td>
<td>119 (66)</td>
<td></td>
</tr>
<tr>
<td>IL-2RA</td>
<td>11 (5)</td>
<td>4 (6)</td>
<td>7 (4)</td>
<td></td>
</tr>
<tr>
<td><strong>Immunosuppression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/M/P</td>
<td>212 (87)</td>
<td>50 (77)</td>
<td>162 (90)</td>
<td>.009</td>
</tr>
<tr>
<td>S/M/P</td>
<td>16 (6.5)</td>
<td>6 (9)</td>
<td>10 (6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16 (6.5)</td>
<td>9 (14)</td>
<td>7 (4)</td>
<td></td>
</tr>
</tbody>
</table>

Tacrolimus-based therapy was associated with lower incidence of DSA formation

### Examples of CNI-Sparing Clinical Trials: CNI Avoidance Protocols

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison Groups</th>
<th>Pts, n</th>
<th>F/U, mo</th>
<th>Incidence of AR</th>
<th>Graft Function</th>
<th>Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekberg et al (ELITE-Symphony)</td>
<td>CsA-MMF-pred vs DAC-MMF-pred with: low-dose TAC; low-dose CsA; low-dose SRL</td>
<td>1,645</td>
<td>12</td>
<td>↓ in low TAC-MMF-pred</td>
<td>↑ in low TAC-MMF-pred</td>
<td>↑ in low TAC-MMF-pred</td>
</tr>
<tr>
<td>Larson et al</td>
<td>TAC-MMF-pred vs SRL-MMF-pred</td>
<td>165</td>
<td>33</td>
<td>Similar</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Flechner et al (ORION)</td>
<td>SRL-TAC (elimination at 13 wk)-pred vs SRL-MMF-pred</td>
<td>443</td>
<td>24</td>
<td>↑ SRL-MMF-pred</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Vincenti et al (BENEFIT)</td>
<td>belatacept (more intensive)-MMF-pred vs belatacept (less intensive)-MMF-pred</td>
<td>666</td>
<td>12</td>
<td>↑ belatacept</td>
<td>↑ belatacept</td>
<td>Similar</td>
</tr>
<tr>
<td></td>
<td>vs CsA-MMF-pred</td>
<td></td>
<td></td>
<td>(more &amp; less intensive)MMF-pred</td>
<td>(more &amp; less intensive)-MMF-pred</td>
<td></td>
</tr>
<tr>
<td>Durrbach et al (BENEFIT-EXT)</td>
<td>belatacept (more intensive)-MMF-pred vs belatacept (less intensive)-MMF-pred</td>
<td>543</td>
<td>12</td>
<td>Similar</td>
<td>↑ belatacept</td>
<td>Similar</td>
</tr>
<tr>
<td></td>
<td>vs CsA-MMF-pred (ECD)</td>
<td></td>
<td></td>
<td>(more &amp; less intensive)-MMF-pred</td>
<td>(more &amp; less intensive)-MMF-pred</td>
<td></td>
</tr>
</tbody>
</table>

Examples of CNI-Sparing Clinical Trials: CNI Elimination Protocols—Conversion to SRL-Based Regimen

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison Groups</th>
<th>Pts, n</th>
<th>F/U, mo</th>
<th>Incidence of AR</th>
<th>Graft Function</th>
<th>Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebranchu et al (CONCEPT)</td>
<td>CsA-MMF-pred vs SRL-MMF-pred</td>
<td>193</td>
<td>13</td>
<td>Similar</td>
<td>↑ SRL-MMF-pred</td>
<td>Similar</td>
</tr>
<tr>
<td>Weir et al (Spare-the-Nephron)</td>
<td>CsA or TAC-MMF vs SRL-MMF</td>
<td>299</td>
<td>24</td>
<td>Similar</td>
<td>↑ SRL-MMF</td>
<td>Similar</td>
</tr>
<tr>
<td>Schena et al (CONVERT)</td>
<td>CsA or TAC-MMF or AZA-pred vs SRL-MMF-pred</td>
<td>275</td>
<td>24</td>
<td>Similar</td>
<td>↑ SRL-MMF-pred for GFR &gt;40 mL/ min/1.73 m²</td>
<td>Similar</td>
</tr>
</tbody>
</table>

Belatacept and CNI Avoidance\textsuperscript{1-3}

**BENEFIT and BENEFIT-EXT trials**
- Basiliximab/MMF/pred plus less intensive belatacept, more intensive belatacept, or CsA

**Acute Rejection Rates at 1 Year**

<table>
<thead>
<tr>
<th></th>
<th>BENEFIT</th>
<th>BENEFIT-EXT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection Rates</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>14.1</td>
<td>17.7</td>
</tr>
</tbody>
</table>

**BENEFIT GFR: 7-Year Follow-Up**

\[ P < .001 \text{ for overall treatment effect} \]

Belatacept: dnDSA Development\textsuperscript{1,2}

**BENEFIT: Proportion of Patients Who Developed dnDSAs by Month 84 (Year 7)\textsuperscript{1}**

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Belatacept MI (n = 219)</th>
<th>Belatacept LI (n = 226)</th>
<th>CsA (n = 215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>3</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Class I DSA, n</td>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Class II DSA, n</td>
<td>2</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Class I and II DSA, n</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

95% CI
- Belatacept MI: 0.28-3.95
- Belatacept LI: 0.84-5.36
- CsA: 7.34-15.91

**BENEFIT-EXT: Cumulative event rates of dnDSAs\textsuperscript{2}**

<table>
<thead>
<tr>
<th>Month</th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 36</td>
<td>2.3</td>
<td>1.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Month 60</td>
<td>6.2</td>
<td>2.4</td>
<td>17.1</td>
</tr>
<tr>
<td>Month 84</td>
<td>6.2</td>
<td>4.5</td>
<td>22.9</td>
</tr>
</tbody>
</table>

## mTOR Inhibitor Maintenance Therapy: A Comparison of the Risk of dnDSA

<table>
<thead>
<tr>
<th>Study</th>
<th>Organ Type</th>
<th>N</th>
<th>Time From Transplant to Switch</th>
<th>F/U</th>
<th>Maintenance Regimen</th>
<th>Univariate or Multivariate Analysis (dnDSA)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early switch (&lt;1 y) to mTOR inhibitor</strong></td>
<td>Liver</td>
<td>749</td>
<td>—</td>
<td>1 y</td>
<td>SRL (n = 119) or no SRL (n = 630) at 1 y ± MMF/AZA ± CsA/TAC ± Steroids</td>
<td>OR = 0.66</td>
<td>.36</td>
</tr>
<tr>
<td><strong>Early switch (&lt;1 y) to mTOR inhibitor</strong></td>
<td>Kidney</td>
<td>127</td>
<td>3 to 4 mo</td>
<td>Median 3.5 y</td>
<td>CsA or CsA converted to EVR (months 3-4.5) MPA Steroids</td>
<td>HR = 2.67</td>
<td>.04</td>
</tr>
<tr>
<td><strong>Late switch (&gt;1 y) to mTOR inhibitor</strong></td>
<td>Kidney</td>
<td>270</td>
<td>Mean, 1.3 y</td>
<td>Mean 3.8 y</td>
<td>TAC switched to SRL ± Steroids to month 3</td>
<td>HR = 2.4</td>
<td>.04</td>
</tr>
<tr>
<td><strong>Late switch (&gt;1 y) to mTOR inhibitor</strong></td>
<td>Kidney</td>
<td>35</td>
<td>Median 69 mo (range 3-375)</td>
<td>2 y</td>
<td>CNI switched to mTOR inhibitor ± MMF/AZA ± steroids</td>
<td>8.6% mTOR inhibitor; 0% controls (n = 10)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Late switch (&gt;1 y) to mTOR inhibitor</strong></td>
<td>Various</td>
<td>131</td>
<td>Mean 73 mo</td>
<td>1 y</td>
<td>CNI switched to EVR ± CNI or CNI ± MMF (controls)</td>
<td>6.7% EVR; 11.1% controls</td>
<td>.39</td>
</tr>
</tbody>
</table>

From two randomly controlled trials, at 3 to 4.5 months post transplant, 127 patients randomized to continue CsA or converted to EVR

- 7/65 (10.8%) on CsA developed DSA (median: 991 days)
- 14/61 (23.0%) on EVR developed DSA (median: 551 days; \( P = .048 \))

Antiproliferative Agent and dnDSA (Tacrolimus Maintenance): MPA Versus mTOR Inhibitor

- Retrospective case-control study
- 66 patients treated with TAC/mTOR inhibitor/prednisone (SRL = 30, EVR = 36) vs 132 patients treated with TAC/MPA/prednisone

No difference in rates of DSA formation or clinical outcomes

De Novo Donor-Specific Antibody Formation and Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>mTOR Inhibitor Group (N = 66)</th>
<th>Mycophenolate Group (N = 132)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DSA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 1 mo</td>
<td>11 (16.7%)</td>
<td>13 (9.8%)</td>
<td>.18</td>
</tr>
<tr>
<td>Within 6 mo</td>
<td>17 (25.8%)</td>
<td>20 (15.2%)</td>
<td>.07</td>
</tr>
<tr>
<td>Within 1 y</td>
<td>19 (28.8%)</td>
<td>29 (22.0%)</td>
<td>.27</td>
</tr>
<tr>
<td>Overall</td>
<td>20 (30.3%)</td>
<td>37 (28.0%)</td>
<td>.73</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 1 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>7 (36.8%)</td>
<td>8 (27.6%)</td>
<td>.66</td>
</tr>
<tr>
<td>1,000 to &lt;3,000</td>
<td>8 (42.1%)</td>
<td>13 (44.8%)</td>
<td></td>
</tr>
<tr>
<td>3,000 to &lt;5,000</td>
<td>1 (5.3%)</td>
<td>5 (17.2%)</td>
<td></td>
</tr>
<tr>
<td>≥5,000</td>
<td>3 (15.8%)</td>
<td>3 (10.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Outcomes at 1 y (N = 198)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAC trough mean (SD)</td>
<td>5.4 (2.5%)</td>
<td>6.5 (2.8%)</td>
<td>.020</td>
</tr>
<tr>
<td>Mean GFR(SD)</td>
<td>56.8 (17.9%)</td>
<td>55.5 (16.9%)</td>
<td>.62</td>
</tr>
<tr>
<td>Mean imputed GFR(SD)</td>
<td>55.9 (19.1%)</td>
<td>51.9 (21.3%)</td>
<td>.20</td>
</tr>
<tr>
<td>Proteinuria median(IQR)</td>
<td>0.1 (0.1%-0.3%)</td>
<td>0.1 (0%-0.2%)</td>
<td>.20</td>
</tr>
<tr>
<td>Acute rejection, no. (%)</td>
<td>6 (9.1%)</td>
<td>15 (11.4%)</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>(1 AMR, 2 cellular, 3 mixed)</td>
<td>(1 AMR, 5 cellular, 5 clinical, 2 mixed, 2 NA)</td>
<td></td>
</tr>
</tbody>
</table>

## Antimetabolite or Purine Synthesis Inhibitor Maintenance Therapy: Comparison of the Risk of dnDSA

<table>
<thead>
<tr>
<th>Study</th>
<th>Organ Type</th>
<th>N</th>
<th>Follow-Up</th>
<th>Maintenance Regimen</th>
<th>Univariate or Multivariate Analysis</th>
<th>Use of Therapy According to Presence/Absence of dnDSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del Bollo et al 2014: Retrospective, single-center cohort study</td>
<td>Liver</td>
<td>232</td>
<td>Median 36.5 mo</td>
<td>Various</td>
<td>NA</td>
<td>MMF was used in 90% of pts with dnDSA vs 71% of pts with no dnDSA (P = .04)</td>
</tr>
<tr>
<td>Kaneku et al 2013: Retrospective, single-center cohort study</td>
<td>Liver</td>
<td>749</td>
<td>1 y</td>
<td>MMF or none/AZA ± CsA/TAC ± Sirolimus ± Steroids</td>
<td>OR = 1.00 MMF vs no MMF</td>
<td>.99</td>
</tr>
<tr>
<td>Lachmann et al 2006: Prospective, single-center cohort study</td>
<td>Kidney</td>
<td>1,043</td>
<td>&gt;6 mo to 4 y</td>
<td>MMF or AZA or no antimetabolite CsA or TAC ± Steroids</td>
<td>39% AZA 26% MMF 19% none</td>
<td>.37</td>
</tr>
<tr>
<td>Piazza et al 2006: Retrospective, single-center cohort study</td>
<td>Kidney</td>
<td>449</td>
<td>Not stated</td>
<td>MMF or AZA CsA Steroids</td>
<td>8% MMF 23% AZA</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hourmant et al 2005: Prospective, single-center cohort study</td>
<td>Kidney</td>
<td>1,229</td>
<td>5 y</td>
<td>Various</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

## Steroid Maintenance Therapy: A Comparison of the Risk of dnDSA

<table>
<thead>
<tr>
<th>Study</th>
<th>Organ Type</th>
<th>N</th>
<th>Follow-Up</th>
<th>Maintenance Regimen</th>
<th>Univariate or Multivariate Analysis</th>
<th>Use of Therapy According to Presence/Absence of dnDSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del Bollo et al 2014: Retrospective, single-center cohort study</td>
<td>Liver</td>
<td>232</td>
<td>Median 36.5 mo</td>
<td>Various</td>
<td>NA</td>
<td>Steroids used in 19% of pts with dnDSA and 44% of pts with no dnDSA ($P = .02$)</td>
</tr>
<tr>
<td>Kaneku et al 2013: Retrospective, single-center cohort study</td>
<td>Liver</td>
<td>749</td>
<td>1 y</td>
<td>Steroids or no steroids ± CsA/TAC ± MMF/AZA ± Sirolimus</td>
<td>OR = 0.67 steroids vs no steroids</td>
<td>.23</td>
</tr>
<tr>
<td>Hoshino et al 2012: Prospective, single-center cohort study</td>
<td>Kidney</td>
<td>72</td>
<td>1 y</td>
<td>Clonal depletion Steroids ± CNI, MMF, or sirolimus</td>
<td>ARR = 0.92 per 2.5 mg/day ↑ in steroid dose</td>
<td>.03</td>
</tr>
<tr>
<td>Delgado et al 2009: Prospective, single-center, double-blind randomized study</td>
<td>Kidney</td>
<td>37</td>
<td>≤5 y</td>
<td>TAC MMF Steroid withdrawal at day 7 (n = 21) or standard steroids (n = 16)</td>
<td>0% steroid withdrawal; 6.3% standard steroids</td>
<td>.43</td>
</tr>
<tr>
<td>Lachmann et al 2006: Prospective, single-center cohort study</td>
<td>Kidney</td>
<td>1,043</td>
<td>&gt;6 mo to 4 y</td>
<td>Steroids or no steroids CsA or TAC ± MMF/AZA</td>
<td>27% steroids; 33% no steroids</td>
<td>.44</td>
</tr>
<tr>
<td>Hourmant et al 2005: Prospective, single-center cohort study</td>
<td>Kidney</td>
<td>1,229</td>
<td>5 y</td>
<td>Various</td>
<td>NA</td>
<td>Steroids used in 22%, 40% &amp; 43% of pts with no antibodies, dnDSA or non-DSA (NS)</td>
</tr>
</tbody>
</table>

Dosing Considerations: What Are the Limitations?
The Symphony Trial: Defining Today’s “Gold Standard”

- 12-month randomized, open-label multicenter trial (N = 1,645)
- Four arms (all receive basiliximab induction, MMF/prednisone)
  - CsA 150 ng/mL to 300 ng/mL x 3 months, then 100 ng/mL to 200 ng/mL
  - CsA 50 ng/mL to 100 ng/mL
  - TAC 3 ng/mL to 7 ng/mL
  - SRL 4 ng/mL to 8 ng/mL

At 12 months:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Acute Rejection, %</th>
<th>GFR, mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA “standard”</td>
<td>25.8</td>
<td>57.1</td>
</tr>
<tr>
<td>CSA “low”</td>
<td>24.0</td>
<td>59.4</td>
</tr>
<tr>
<td>TAC “low”</td>
<td>12.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SRL “low”</td>
<td>37.2</td>
<td>56.7</td>
</tr>
</tbody>
</table>

<sup>a</sup> P<0.05 vs SRL “low” and vs CSA “standard”

Symphony and CNI Minimization

<table>
<thead>
<tr>
<th>Drug Trough</th>
<th>Tacrolimus (4-7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>6.4</td>
</tr>
<tr>
<td>36 months</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Lower Mean Tacrolimus Troughs Increase Risk of dnDSAs in the First Year of Kidney Transplant

Scott Davis, MD, Jane Gralla, PhD, Suhong Tong, MS, Patrick Klem, PharmD, Alexander Wiseman, MD, James Cooper, MD
Patient Flowchart

Included
N = 884

Excluded
n = 341

Pretransplant DSA (n = 268)
Liver-Kidney (n = 14)
DSA/TAC Data (n = 59)

Patients
n = 543

Total TAC levels: 11,859
Mean number TAC level: 21.8

dnDSA-
n = 425
(78.3%)
dnDSA+
n = 118
(21.7%)

Survival to DSA by Mean TAC Troughs (ng/mL)\textsuperscript{1}

Odds Ratios for Mean TAC Trough Ranges (ng/mL) Compared With >8 ng/mL By 12 Months

Adjusted for HLA mismatches, age, sex, ethnicity, donor type, induction, and DGF

Time to dnDSA by Mean TAC 1 Week to 12 Months

Tacrolimus Intrapatient Variability and the Evolution of Acute and Chronic Histologic Lesions

- TAC intrapatient variability (IPV) analyzed from months 6 to 12 after transplantation in a cohort of 220 renal recipients for whom paired protocol biopsies at 3 months and 2 years were available.

**CV (%) = (SD/mean TAC concentration) x 100**

Example: TAC troughs from five measures are 4.9, 7.0, 9.3, 4.1, and 8.1
- Mean = 6.68
- Standard deviation = 2.17
- CV (%) = 2.17/6.68 x 100 = 32.4%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of available TAC concentrations (mean ± SD)</td>
<td>5.3 ± 1.9</td>
</tr>
<tr>
<td>Mean TAC concentration ± SD (ng/mL)</td>
<td>9.6 ± 1.6</td>
</tr>
<tr>
<td>TAC CV (%)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>19.7 ± 10.1</td>
</tr>
<tr>
<td>Median</td>
<td>18.4</td>
</tr>
<tr>
<td>Range (min to max)</td>
<td>1.2 to 54.9</td>
</tr>
</tbody>
</table>

## Predictors of Chronic Histologic Scores in Multivariate Regression


<table>
<thead>
<tr>
<th>Histologic Parameter at 2 y</th>
<th>Predictor(s)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ci ≥2</td>
<td>• ci ≥2 at month 3</td>
<td>4.73</td>
<td>1.74-12.90</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>• Borderline/subclinical acute rejection at month 3</td>
<td>2.45</td>
<td>1.01-5.96</td>
<td>.048</td>
</tr>
<tr>
<td></td>
<td>• Donor age, years</td>
<td>1.03</td>
<td>1.00-1.05</td>
<td>.030</td>
</tr>
<tr>
<td></td>
<td>• CV tertile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– High</td>
<td>2.80</td>
<td>1.25-6.32</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>– Middle</td>
<td>1.70</td>
<td>0.73-3.91</td>
<td>.217</td>
</tr>
<tr>
<td></td>
<td>– Low</td>
<td>Ref.</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ct ≥2</td>
<td>• ct ≥2 at month 3</td>
<td>11.52</td>
<td>2.03-65.41</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>• Borderline or subclinical acute rejection at month 3</td>
<td>2.42</td>
<td>0.97-6.06</td>
<td>.059</td>
</tr>
<tr>
<td></td>
<td>• Donor age, years</td>
<td>1.03</td>
<td>1.00-1.05</td>
<td>.056</td>
</tr>
<tr>
<td></td>
<td>• CV tertile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– High</td>
<td>2.67</td>
<td>1.12-6.35</td>
<td>.027</td>
</tr>
<tr>
<td></td>
<td>– Middle</td>
<td>1.42</td>
<td>0.57-3.53</td>
<td>.453</td>
</tr>
<tr>
<td></td>
<td>– Low</td>
<td>Ref</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Predictors of Chronic Histologic Scores in Multivariate Regression (Cont’d)¹

<table>
<thead>
<tr>
<th>Histologic Parameter at 2 y</th>
<th>Predictor(s)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>cv ≥2</td>
<td>Donor age, years</td>
<td>1.02</td>
<td>0.99-1.05</td>
<td>.089</td>
</tr>
<tr>
<td>cg ≥2</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ah ≥2</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>De novo ah</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Donor age, years</td>
<td>1.03</td>
<td>1.00-1.05</td>
<td>.047</td>
</tr>
<tr>
<td></td>
<td>• CV tertile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– High</td>
<td>4.30</td>
<td>1.67-11.12</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>– Middle</td>
<td>2.76</td>
<td>1.04-7.31</td>
<td>.041</td>
</tr>
<tr>
<td></td>
<td>– Low</td>
<td>Ref.</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>• Mean TAC trough, ng/mL</td>
<td>1.28</td>
<td>1.04-1.57</td>
<td>.022</td>
</tr>
</tbody>
</table>

High IPV is related to accelerated progression of chronic histologic lesions before any evidence of renal dysfunction.

**Conclusion**

**Cutoff:**
- <14.4%
- <22.1%
- >22.1%

**Mean CV:**
- Low: 9.8%
- Middle: 18.3%
- High: 31.1%

**TAC trough:**
- Low: 9.5
- Middle: 9.6
- High: 9.7

Use of Drug-Level Monitoring (IPV) to Assess Under-Immunosuppression/Adherence

- 356 patients measured TAC variability while on stable dose; median follow-up: 3.72 years
- Composite endpoint: late allograft rejection, TG, or graft loss (including death)

Does Time-Varying Exposure to TAC Increase Risk of Long-Term Adverse Outcomes in Adult KTRs?¹

<table>
<thead>
<tr>
<th>TacSD Threshold</th>
<th>HR (95% CI) for Primary Composite Endpoint</th>
<th>( P )</th>
<th>HR (95% CI) for Secondary Composite Endpoint</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.5 vs ≤1.5</td>
<td>1.33 (0.75, 2.37)</td>
<td>.33</td>
<td>1.23 (0.60, 2.51)</td>
<td>.58</td>
</tr>
<tr>
<td>&gt;2 vs ≤2</td>
<td>1.50 (0.89, 2.54)</td>
<td>.13</td>
<td>1.44 (0.73, 2.86)</td>
<td>.29</td>
</tr>
<tr>
<td>&gt;2.5 vs ≤2.5</td>
<td>1.84 (1.04, 3.25)</td>
<td>.04</td>
<td>1.99 (0.96, 4.12)</td>
<td>.06</td>
</tr>
<tr>
<td>&gt;3 vs ≤3</td>
<td>2.56 (1.42, 4.62)</td>
<td>&lt;.001</td>
<td>2.77 (1.30, 5.89)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Conclusion

Increased time-dependent TacSD may be an independent risk factor for adverse kidney transplant outcomes; TacSD may serve as a monitoring tool to identify high-risk patients.

Impact of Within-Patient Variability in TAC Blood Levels on Kidney Graft Loss

- Analysis of 310 deceased-donor adult renal transplants performed from 1998 to 2013

### Multivariate Cox Regression Analysis for DCGL

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV &gt;30%</td>
<td>2.613</td>
<td>1.361-5.016</td>
<td>.004</td>
</tr>
<tr>
<td>GFR, per 1 mL/min per 1.73 m²</td>
<td>0.955</td>
<td>0.931-0.979</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Proteinuria, per 1 g</td>
<td>1.240</td>
<td>1.123-1.369</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

# Risk Factors for dnDSA Development

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>dnDSA− (n = 271)</th>
<th>dnDSA+ (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient's age</td>
<td>51 ± 13</td>
<td>48 ± 12</td>
<td>.110</td>
</tr>
<tr>
<td>Recipient's sex (male)</td>
<td>71.2%</td>
<td>64.1%</td>
<td>.363</td>
</tr>
<tr>
<td>Cold ischemia time, h</td>
<td>18.3 ± 7.3</td>
<td>19.4 ± 6.5</td>
<td>.409</td>
</tr>
<tr>
<td>Transplant number</td>
<td>1.3 ± 0.6</td>
<td>1.5 ± 0.9</td>
<td>.057</td>
</tr>
<tr>
<td>Transplant number &gt;1</td>
<td>20.3%</td>
<td>38.5%</td>
<td>.011</td>
</tr>
<tr>
<td>Peak PRA</td>
<td>4.8 ± 14.2</td>
<td>10.8 ± 21.7</td>
<td>.115</td>
</tr>
<tr>
<td>Mismatches</td>
<td>3.8 ± 1.2</td>
<td>3.9 ± 0.9</td>
<td>.647</td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>2.6%</td>
<td>7.7%</td>
<td>.091</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>25.1%</td>
<td>23.1%</td>
<td>.785</td>
</tr>
<tr>
<td>Steroid withdrawal</td>
<td>55.0%</td>
<td>46.2%</td>
<td>.299</td>
</tr>
<tr>
<td>DGF</td>
<td>23.3%</td>
<td>25.0%</td>
<td>.817</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>20.4%</td>
<td>35.9%</td>
<td>.031</td>
</tr>
<tr>
<td>1-year GFR, mL/min per 1.73 m²</td>
<td>50 ± 17</td>
<td>51 ± 16</td>
<td>.624</td>
</tr>
<tr>
<td>1-year 24-h proteinuria, g</td>
<td>0.8 ± 1.5</td>
<td>0.9 ± 2.1</td>
<td>.629</td>
</tr>
<tr>
<td>CV &gt;30%</td>
<td>35.4%</td>
<td>51.3%</td>
<td>.056</td>
</tr>
</tbody>
</table>

dnDSA Development: Impact on Graft Survival

Death-Censored Graft Survival Curve

Cumulative Survival

Developed dnDSA
Did not develop dnDSA

Log rank $P < .001$

Years After Transplantation

Tacrolimus level variability is a strong risk factor for dnDSA development and DCGL; variability should be added to the current monitoring of kidney transplant recipients because of its relationship with adherence and to graft outcome.

Persistent BK Viremia Does Not Increase Intermediate-Term Graft Loss But Is Associated With dnDSA

- 785 kidney or kidney–pancreas transplant recipients; median: 3 years follow-up
- 132 (17%) recipients developed BK viremia (IS dose reduction)
- Median duration of BK viremia: 140 days (IQR 40 to 393 days)
- Neither the presence nor the duration of BK viremia had a deleterious effect on patient or graft survival
- Persistent BK viremia was associated with an increased risk of developing dnDSA, particularly class II DSA (HR 2.55 [95% CI, 1.30-4.98])

TAC and CsA both require careful management to ensure sufficient dosing for therapeutic effectiveness, while avoiding toxicity.

Routine monitoring of drug levels can be employed to balance efficacy while limiting side effects.
Optimizing Immunosuppression in Clinical Practice
Minimizing Variability in CNI Exposure: Impact of Once-Daily Dosing

Tacrolimus Blood Concentration–Time Profile of Representative Subject From Each Dosing Regimen

67% Group Tacrolimus Pharmacokinetics

85% Group Tacrolimus Pharmacokinetics

100% Group Tacrolimus Pharmacokinetics

Correlation Between Tacrolimus Concentration and AUC

Twice-Daily Dosing

Concentration and AUC

Once-Daily Dosing

Conclusion

Tacrolimus given once daily in the morning, at 85% of the twice-daily dose, provides safe and equivalent drug exposure to twice-daily dosing; this convenient dosing schedule may help to increase compliance and lower costs.

Comparison of the Main Characteristics of the Two Clinically Available Once-Daily Formulations of TAC¹

<table>
<thead>
<tr>
<th>Abbreviation (Trade Name)</th>
<th>Formulation</th>
<th>Strengths</th>
<th>Conversion Ratio From IR-TAC</th>
<th>Recommended Starting Dose a</th>
<th>Cmin–AUC₀-2₄ Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-TAC (Astagraf XL)</td>
<td>Once daily</td>
<td>Capsules in 0.5, 1, 3, and 5 mg</td>
<td>1 to 1</td>
<td>0.10-0.20 mg/kg/day</td>
<td>r² ≥ 0.57</td>
</tr>
</tbody>
</table>
| LCP-TAC (Envarsus XR)     | Once daily, MeltDose | Tablets in 0.75, 1, and 4 mg  
(0.85 for blacks)      | 1 to 0.7                                    | 0.17 mg/kg/day               | r² ≥ 0.85                  |

a According to Summary of Medical Product Characteristics of both drugs.
Evaluating the Pharmacokinetics of Once-Daily TAC

From January 2009 to January 2010, switch from IR-TAC to ER-TAC in 130 stable RTRs

Conclusion
Conversion from IR-TAC to once-daily ER-TAC appears to be safe and convenient up to 2 years after conversion in some recipients

Evaluating the Pharmacokinetics of Once-Daily TAC (Cont’d)¹

- Comparison of PK and pathology for IR-TAC and ER-TAC in living kidney transplantation: prospective trial (N = 102 consecutive adult patients)

**Conclusion**

Clinical efficacy, safety, and PK profile of ER-TAC are same as those of IR-TAC

Conversion From IR-TAC to LCP-TAC: Phase 2 Trial

- Adult stable kidney transplant patients on IR-TAC capsules were converted to once-daily TAC tablets (LCP-TAC); patients continued on once-daily LCP-TAC for days 8 to 21; trough levels were to be maintained between 5 ng/mL and 15 ng/mL; 24-hour pharmacokinetic assessments were done on days 7 (baseline pre-switch), 14, and 21.

Conclusions

- Stable kidney transplant patients can be safely converted from IR-TAC to LCP-TAC
- The greater bioavailability of LCP-TAC allows for once-daily dosing and similar (AUC) exposure at a dose ~30% less than the total daily dose of IR-TAC
- LCP-TAC displays flatter kinetics characterized by significantly lower peak-trough fluctuations

Long-Term Outcomes With ER-TAC, IR-TAC, and Twice-Daily CsA

- 638 subjects receiving de novo kidney transplants were randomized to one of three treatment arms: once-daily ER-TAC, twice-daily IR-TAC, or twice-daily CsA
  - All subjects received basiliximab induction, MMF, and CsA

No differences in patient or graft survival between groups at 3 years

LCP-TAC Versus IR-TAC in De Novo Kidney Transplants: Phase 3 Double-Blind RCT\textsuperscript{1}

- 543 kidney transplant recipients randomized to LCP-TAC versus twice-daily IR-TAC
- eGFR equivalent between groups throughout 2 years

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A Steady-State Head-to-Head Pharmacokinetic Comparison of All FK-506 (TAC) Formulations (ASTCOFF): Study Design

- An open-label, prospective, randomized, two-arm, three-period crossover study

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ASTCOFF: Mean Whole Blood Concentrations of Tacrolimus

---

**Observed Mean Whole Blood Time-Concentration Curves**

TDD Conversion Rate 1:1:0.8 IR-TAC:ER-TAC:LCP-TAC

**Normalized to IR-TAC Mean Whole Blood Time-Concentration Curves**

TDD Conversion Rate 1:1.08:0.7 IR-TAC:ER-TAC:LCP-TAC

---

Pharmacokinetic Parameters in ASTCOFF: Observed Results\textsuperscript{1,a}

<table>
<thead>
<tr>
<th>Observed PK Parameter</th>
<th>LCP-TAC</th>
<th>ER-TAC</th>
<th>IR-TAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDD, md/day</td>
<td>4.9 ± 2.3</td>
<td>6.1 ± 2.9</td>
<td>6.1 ± 2.9</td>
</tr>
<tr>
<td>Median, IQR</td>
<td>4.8 (3.3-6.3)</td>
<td>6.0 (4.0-8.0)</td>
<td>6.0 (4.0-8.0)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24}$, h*ng/mL</td>
<td>213.4 ± 83.1</td>
<td>165.0 ± 50.0</td>
<td>176.5 ± 50.8</td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>13.9 ± 5.3</td>
<td>13.2 ± 4.4</td>
<td>14.5 ± 5.5</td>
</tr>
<tr>
<td>$C_{\text{min}}$, ng/mL</td>
<td>6.8 ± 2.9</td>
<td>5.1 ± 1.8</td>
<td>6.1 ± 1.7</td>
</tr>
<tr>
<td>$T_{\text{max}}$, h</td>
<td>5.9 (1.5, 14.0)</td>
<td>1.9 (0.9, 5.9)</td>
<td>1.5 (0.9, 20.0)</td>
</tr>
<tr>
<td>Fluctuation, %</td>
<td>83.6 ± (51.7)</td>
<td>118.9 ± (48.4)</td>
<td>112.6 ± (53.1)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Parameter $\text{AUC}_{0-24}$, $C_{\text{max}}$, $C_{\text{min}}$: Presented arithmetic mean ± SD; Parameter TDD: Presented arithmetic mean ± SD; $T_{\text{max}}$: Presented median (min, max).

## Pharmacokinetic Parameters in ASTCOFF: Comparisons¹,a

<table>
<thead>
<tr>
<th>Observed PK Parameter</th>
<th>LCP-TAC vs IR-TAC (%)</th>
<th>ER-TAC vs IR-TAC (%)</th>
<th>LCP-TAC vs ER-TAC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDD, md/day</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Median, IQR</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-24&lt;/sub&gt;, h*ng/mL</strong></td>
<td>117.0 (107.9, 127.0)</td>
<td>93.1 (85.8, 101.0)</td>
<td>125.7 (114.1, 138.5)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .002</td>
<td><em>P</em> = .149</td>
<td><em>P</em> &lt; .001</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</strong></td>
<td>94.7 (85.8, 104.4)</td>
<td>91.8 (83.2, 101.3)</td>
<td>103.1 (92.4, 115.0)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .354</td>
<td><em>P</em> = .150</td>
<td><em>P</em> = .638</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;min&lt;/sub&gt;, ng/mL</strong></td>
<td>107.0 (97.6, 117.2)</td>
<td>83.0 (75.7, 90.9)</td>
<td>128.9 (117.4, 141.6)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .223</td>
<td><em>P</em> = .001</td>
<td><em>P</em> &lt; .001</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt;, h</strong></td>
<td>3.0 (1.6, 4.4)</td>
<td>0.1 (-0.4, 0.5)</td>
<td>3.0 (1.9, 4.0)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> &lt; .001</td>
<td><em>P</em> = .670</td>
<td><em>P</em> &lt; .001</td>
</tr>
<tr>
<td><strong>Fluctuation, %</strong></td>
<td>-29.0 (-48.4, -9.6)</td>
<td>6.4 (-13.1, 25.7)</td>
<td>-35.3 (-53.4, -17.3)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .004</td>
<td><em>P</em> = .518</td>
<td><em>P</em> &lt; .001</td>
</tr>
</tbody>
</table>

¹ Parameter AUC<sub>0-24</sub>, C<sub>max</sub>, C<sub>min</sub>: Presented RGM in percent (90% CI) derived from ANCOVA models that included fixed effects of treatment, sequence, period (LCP-TAC vs ER-TAC analyses), and random effect of subjects (sequence). *P* was from two-sample *t*-test.

ASTCOFF: Group Mean Daily Tacrolimus Trough Levels\(^1\)

**Conclusions**

Results from this comparative PK study of all three innovator TAC formulations, conducted in stable renal transplant recipients, demonstrate that there are significant PK differences between LCP-TAC and both IR-TAC and ER-TAC and that formulations are not interchangeable with LCP-TAC.

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Astagraf XL® to Understand the Impact of Immunosuppression on De Novo DSA Development and Chronic Immune Activation in Kidney Transplantation (ASTOUND)<sup>1</sup>

- Primary outcome: combined incidence of DSA or immune activation (peripheral blood molecular profiling) at 1 and 2 years post transplant

**Diagram:**
- HLA-mismatched first kidney transplant, PRA ≤50%, no DSA
- Induction,<sup>a</sup> MMF/pred maintenance (N = 550)
- Astagraf XL
  - TAC C<sub>0</sub> ≥6 ng/mL
- TAC (Prograf and generics)
  - TAC C<sub>0</sub> ≥6 ng/mL

<sup>a</sup> Per center protocol.
Both the type and the degree of immunosuppression contribute to the risk of DSA formation.

The current standard of care (TAC-based immunosuppression) is susceptible to intrapatient variability that is clinically meaningful.

Novel monitoring tools, TAC CV, and newer formulations (once-daily preparations) may mitigate these risks.

A hypothesis to be proven: Incorporation of “higher-level monitoring” and long-acting CNI preparations may reduce DSA/immune activation and improve long-term graft survival.
Please remember to complete and submit your Post-Test and Evaluation for CME credit.

Missed anything?

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Thank you and good afternoon.