Corticosteroid-Sparing in Adult Renal Transplantation: Gambling with Allografts, or Strong Data?

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Learning Objectives

1. Discuss evolution of immunosuppression and its effects on corticosteroid use in renal transplants
2. Evaluate benefits and risks of corticosteroid use in renal transplant recipients
3. Identify consequences and their associated risk factors with corticosteroid-sparing regimens
4. Devise an evidence-based corticosteroid-sparing protocol for renal transplantation
I. Renal Transplantation

A. Treatment of choice for end-stage renal disease (ESRD) vs. dialysis\(^1\)
   1. Prolongs the life of a person with ESRD
   2. Improves the health and quality of life of a person with ESRD
   3. Decreases long-term healthcare costs compared to dialysis

B. First successful renal transplants in the United States (US) \(^2-4\)
   1. 1954: first living donor transplant performed on identical twins
   2. 1964: first deceased donor transplant performed on an unrelated recipient

C. Improvements over the last 50 years
   1. Surgical techniques
   2. Organ preservation techniques
   3. Pharmacologic\(^5-8\)
      a. 1950s: Originally used corticosteroids (CCS), 6-mercaptopurine (6-MP), and total body irradiation (TBI)
      b. 1960s
         i. Azathioprine (AZA) + CCS led to first successful outcomes in unrelated renal transplants
         ii. Anti-lymphocyte globulin (ALG) first agent used for induction or rejection
      c. 1980s
         i. Cyclosporine (CyA) became available in the US, drastically reducing rejection rates
         ii. Muromonab (OKT3) first approved biologic that reversed steroid-resistant rejection
      d. 1990s
         i. Tacrolimus (Tac) became available, eventually replacing CyA at most centers
         ii. Mycophenolate (MMF/MPS) replaced AZA at most centers due to decreased rejection
         iii. Sirolimus (SRL), first mTOR inhibitor, introduced as alternative to AZA or MMF/MPS
         iv. Rabbit anti-thymocyte globulin (rATG) improved efficacy/safety of treating rejection
      e. 2000s
         i. Everolimus (ERL) approved as second mTOR inhibitor for organ transplant
         ii. Belatacept (BELA) approved in renal transplant with CCS + MMF/MPS as first biologic for maintenance therapy

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**Figure 1**: Advancements in immunosuppression and correlations to 1 year allograft survival and rejection

- 6-MP
- TBI
- CCS
- AZA
- ALG
- CyA
- OKT3
- Tac
- MMF/MPS
- rATG
- SRL
- ERL
- BELA

Adapted from Zand et al.\(^9\)
D. Current long-term patient and allograft survival\textsuperscript{10}

![Graph showing patient and allograft survival over years.]

From OPTN/SRTR Annual Report Adjusted Patient Survival by Year of Transplant

**Figure 2.** Current 1, 5, and 10 year patient and allograft survival

1. Reasons for allograft loss
   a. Death with a functioning allograft reported as most common cause, occurring in up to 40% of cases\textsuperscript{11}
      i. Defined as recipient death with intact allograft function (free from dialysis)
      ii. Long-term causes of death after renal transplant are primarily cardiovascular related\textsuperscript{12-15}

![Pie chart showing long-term causes of death in renal transplants.]

**Figure 3.** Long-term causes of death in renal transplants

b. Chronic allograft nephropathy, interstitial fibrosis/tubular atrophy (CAN/IFTA)\textsuperscript{3}
   i. Defined as progressive deterioration of kidney function
   ii. Associated non-immunologic factors
      (1) Chronic disease states: hyperlipidemia or hypertension
      (2) Infection: cytomegalovirus or BK polyoma virus
      (3) Delayed allograft function (DGF)
      (4) Ischemia-reperfusion injury
      (5) Calcineurin inhibitor toxicity
      (6) Glomerular hyperfiltration
      (7) Donor risk factors: expanded criteria and donation after cardiac death (DCD)
iii. Associated immunologic factors
(1) Acute or subclinical rejection
(2) Human leukocyte antigen (HLA) mismatches
(3) Elevated panel reactive antibodies (PRA)
(4) Inadequate immunosuppression
(5) Repeat transplant
(6) Medication non-adherence

II. Immunosuppression in Renal Transplant

A. Purpose
1. Induce immunologic acceptance
2. Prevent immune-mediated damage of transplanted organ, allowing time for tissue repair
3. Improve long-term allograft and patient survival

B. Induction immunosuppression
1. Purpose: incite acute immune system suppression perioperatively by reducing the number of T and/or B cells capable of responding to antigen
2. Common agents
   a. Lymphocyte depleting (duration 9 to > 24 months)
      i. Rabbit anti-thymocyte globulin (rATG) (Thymoglobulin®)
      ii. Alemtuzumab (Campath®)
   b. Non-lymphocyte depleting: IL-2 receptor antagonists (IL-2RAs) (duration 40 to 120 days)
      i. Basiliximab (Simulect®)
      ii. Daclizumab (Zenapax®) – no longer on the market

C. Maintenance immunosuppression
1. Purpose: maintain allograft function by preventing rejection
2. Rationale for combination therapy
   i. Minimize risk of rejection and decrease drug toxicities by combining immunosuppressive agents at lower doses with various mechanisms of action

Figure 4. Specific sites of action for common immunosuppressive agents
3. Prevalence of maintenance regimens\(^\text{10}\)
   a. Triple therapy with Tac, MMF/MPS, and CCS is the most common regimen with 56% of all renal transplant recipients being discharged with the combination.

![Figure 5. Maintenance immunosuppression regimen at discharge in US (2009)"

4. Adverse effect profiles\(^\text{5}\)

   **Table 1.** Adverse effects of common immunosuppressive agents

<table>
<thead>
<tr>
<th></th>
<th>CCS</th>
<th>CyA</th>
<th>Tac</th>
<th>MMF/MPS</th>
<th>AZA</th>
<th>SRL</th>
<th>ERL</th>
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<td>Insomnia</td>
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<td>Psychosis</td>
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<td>Delayed wound healing</td>
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<td>GI toxicity</td>
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<td>++</td>
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<td>+</td>
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<tr>
<td>Aphthous ulcers</td>
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</tr>
</tbody>
</table>

D. Consequences of over-immunosuppression
1. Infection\(^\text{20}\)
   a. Risk depends on immunosuppression level and epidemiologic exposure
   b. Type of infection risk changes over time
      i. ≤ 1 month after transplant: nosocomial
      ii. 2 – 6 months after transplant: opportunistic infections
      iii. > 6 months after transplant: community-acquired and persistent infections
2. Malignancy\(^\text{21-22}\)
   a. T-lymphocytes, natural killer cells, and cytokines protect host from tumors
   b. Skin cancer most common with > 95% being non-melanoma skin cancer (NMSC)

E. Consequences of under-immunosuppression
1. Rejection\(^\text{23}\)
   a. Risk factors: HLA mismatches, PRA > 30%, presence of donor specific antibody, DGF, younger recipient, older donor, African Americans, cold ischemic time > 24 hours,
III. Immunosuppression-Sparing Protocols

A. Rationale\textsuperscript{24}
   1. Necessity of triple therapy has been challenged with improvements in immunosuppression
   2. Decreased risk for overall adverse effects, malignancy, and infection

B. Agents investigated
   1. Calcineurin inhibitors\textsuperscript{25}
      a. Aim to reduce nephrotoxicity as well as diabetogenic and hypertensive effects
      b. Sparing protocols showed significantly increased acute rejection rates and allograft loss
   2. CCS

IV. Focus on Corticosteroids

A. Common agents\textsuperscript{26}
   1. Methylprednisolone (Solu-MEDROL\textsuperscript{®})
   2. Prednisone (Deltasone\textsuperscript{®})
   3. Prednisolone (Prelone\textsuperscript{®})

B. Mechanism of action\textsuperscript{3,5, 27-28}
   1. Pharmacology
      a. Binds to glucocorticoid receptors in cytoplasm and translocates into nucleus where it alters transcription of cytokine genes
      b. Inhibits translocation of activating protein-1 (AP – 1) and nuclear factor kappa B (NF – κB) into nucleus, preventing induction of gene encoding for cytokines
   2. Clinical implications
      a. Inhibits cytokine production, specifically IL-1, IL-2, IL-3, IL-4, IL-6, TNF-α, and interferon-γ
      b. Decreases activation and proliferation of lymphocytes, macrophages
      c. Prevents macrophage antigen presentation and phagocytic activity
      d. Inhibits dendritic cells
      e. Suppresses production of inflammatory leukotrienes and prostaglandins
      f. Alters cell trafficking by decreasing ability of leukocytes to adhere to vascular endothelium

![Figure 6. Cells, chemokines, and cytokines affected by CCS MOA](image-url)
C. Doses are standardized or weight-based with high initial doses that are tapered over time

D. Pharmacokinetics
   1. Linear\textsuperscript{29}
      a. Peak level 2-3 hours after oral administration
      b. No measurable level 24 hours after administration
   2. Prednisone is hepatically metabolized to active prednisolone (80% bioavailability)
   3. Variation in pharmacokinetics\textsuperscript{28-29}
      a. Liver disease impairs conversion of active prednisone to prednisolone
      b. Obesity is associated with decreased clearance of methylprednisolone
      c. Chronic renal failure is associated with increased free fraction of prednisolone

E. Therapeutic drug monitoring
   1. No clinically validated methods available
   2. Could theoretically be assessed by total lymphocyte count, eosinophil count, or fasting pre-dose cortisol levels but monitoring is not practiced clinically\textsuperscript{29-30}

F. Drug interactions
   1. Phenobarbital and phenytoin accelerate metabolism of prednisone\textsuperscript{31}
   2. Oral contraceptives decrease methylprednisolone exposure\textsuperscript{32}
   3. Diltiazem increases prednisolone exposure by up to 20\%\textsuperscript{33}

G. Adverse effects\textsuperscript{34}
   1. Non-adherence due to adverse effects\textsuperscript{35-36}
      a. Undesirable CCS adverse effects have been linked to non-adherence in adolescents
         i. Acne
         ii. Striae
         iii. Cushingoid face
         iv. Truncal obesity
         v. Purpura
         vi. Weight gain
         vii. Mood disorders

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Condition} & \textbf{Proposed Underlying Mechanism} & \textbf{CCS-Related Incidence Post-Transplant} \\
\hline
Hypertension & Secondary to fluid retention & 15\% \\
\hline
Diabetogenesis & Increased insulin resistance, Altered carbohydrate metabolism & 10\% \\
\hline
Dyslipidemia & Altered lipoprotein metabolism: Stimulation of VLDL synthesis, Down-regulation of LDL receptors & \textit{Not assessed} \\
\hline
Cataracts/glaucoma & Unknown but theories include water accumulation, free radical damage, oxidation, and metabolic disturbances & 22\% \\
\hline
Osteoporosis & Increased bone resorption, Reduced bone formation & 2\% annually\textsuperscript{b} \\
\hline
\end{tabular}
\caption{Impact of common metabolic adverse effects of CCS on a renal transplant population}
\end{table}

\textsuperscript{a} Cost of disease and its complications
\textsuperscript{b} Rate of peripheral fractures
H. CCS-sparing protocols
   1. Rationale
      a. In contrast to other immunosuppressants with specific mechanisms of action, CCS have multiple sites of action and effects, many of which are redundant in combination therapy
      b. Minimization of metabolic adverse effects while maintaining similar rates of acute rejection
   2. Defining CCS protocols
      a. Sparing
         i. Avoidance (CSA): no CCS used
         ii. Early withdrawal (CSWD early): removal of CCS ≤ 14 days post-transplant
         iii. Late withdrawal (CSWD late): removal of CCS > 14 days post-transplant
      b. Standard (SC): chronic CCS with dose tapered to “physiologic levels” (5-10mg/day)

OVERVIEW

Objective

To compare patient and allograft survival in patients with “good” renal allograft function receiving either low-dose CCS or placebo beginning at 3 mo post-transplant

Design

Prospective, randomized, double-blind, placebo-controlled, multi-center study in 14 Canadian centers

Inclusion/Exclusion Criteria

- **Inclusion**: SCr ≤ 2.5 mg/dL (220 umol/L) at 90 days post-renal transplant
- **Exclusion**: acute rejection episodes in last 2 weeks, history of generalized malignant disease or localized malignant tumor removed in the past year

Induction

None

Maintenance Immunosuppression

- CyA PO bid + CCS PO every other day
- CyA PO with a goal trough of 75-200 ng/mL
- CCS (prednisone) PO 1 mg/kg every other day, tapered by 5 mg per dose until 0.3 mg/kg

Interventions

- **CSWD late**: POD 90 CCS changed to placebo every other day
- **SC**: POD 90 CCS changed to prednisone PO 0.25 mg/kg every other day and then decreased to 0.2 mg/kg every other day on POD 180

Follow-up

5 years

Outcomes

- **Primary**: patient and allograft survival at 5 years
- **Other**: SCr and CrCl at 1260 days (3.5 years), CCS-induced diabetes, cardiovascular events, infection, malignant neoplasia

Statistics

- ITT study population with post-hoc subgroup analyses
- Sample size of 500 recipients (250 per arm) needed to detect an upper proportion of success of 0.8 for a power of 80% and an alpha error of 5%
- Mantel-Cox test for statistical analysis of survival
- Weibull parametric modeling to identify risk factors and semiparametric Cox regression to estimate significance of assigned treatment and risk factors as confounding variables
- Two-tailed tests of significance for allograft and patient survival

RESULTS

Total Patients

- 1202 renal transplants between 1982 and 1985, 523 randomized
  - 239 not randomized due to allograft loss < 90 days (20% allograft loss)
- 260 randomized to CSWD late, 263 randomized to SC
- 266 of 523 ceased study drug for various reasons and returned to known prednisone therapy
- 58 patients (33 in CSWD late and 25 in SC) were found at time of analysis to have continued receiving known prednisone instead of test drug or placebo and were still included in ITT

Demographics (reported; not analyzed)

<table>
<thead>
<tr>
<th></th>
<th>SC (n=263)</th>
<th>CSWD late (n=260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior transplants (%)</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Highest mean PRA (%)</td>
<td>17 ± 1.7</td>
<td>17 ± 1.7</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>28 ± 0.8</td>
<td>27 ± 0.7</td>
</tr>
<tr>
<td>Cold ischemic time (hrs)</td>
<td>12 ± 0.5</td>
<td>13 ± 0.6</td>
</tr>
<tr>
<td>Living donor (%)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Donor death due to CVA (%)</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Race not reported</td>
<td></td>
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</tr>
</tbody>
</table>

Immunosuppression

CyA: mean levels at 1, 2, and 3 years were 110, 107, and 102 ng/mL
Outcomes

- Allograft survival at 5 years: 85% in SC vs. 73% in CSWD late (p = 0.03)
  - 60% of lost allografts in CSWD late had returned to known prednisone
  - Allograft survival in deceased donor retransplant recipients: 95% SC vs. 63% CSWD late (post-hoc analysis)
  - HLA-B mismatching (p=0.007), donor death from CVA (p=0.01), increased donor age (p=0.02), and male recipients (p=0.05) identified risk factors for allograft loss
- Patient survival at 5 years: no difference between groups; 94% SC vs. 92% CSWD late (p= NS)

### Patient/allograft survival including ITT population

<table>
<thead>
<tr>
<th>Other Outcomes</th>
<th>SC (n=263)</th>
<th>CSWD late (n=260)</th>
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<tbody>
<tr>
<td>SCr (mg/dL)</td>
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<td>2</td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td>55</td>
<td>53</td>
</tr>
<tr>
<td>CCS-induced DM (%)</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular events (%)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hypertensive episode (%)</td>
<td>82</td>
<td>78</td>
</tr>
<tr>
<td>Bacterial Infection (%)</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Fungal Infection (%)</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>Viral Infection (%)</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Malignant neoplasia (%)</td>
<td>5</td>
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</table>

### CONCLUSIONS

**Authors’ Conclusions**

- Allograft survival was worse in CSWD late
- Continued CCS use appears to be an advantage for deceased donor transplant recipients, especially those with previously failed transplants

**Strengths**

- First prospective, randomized, double-blind, placebo-controlled, multi-center trial to evaluate CCS withdrawal
- Longest blinded follow-up at time of publication (5 years)
- Evaluated adverse effects from CCS

**Limitations**

- CyA monotherapy is considered under-immunosuppression by modern standards
- High return rate to known CCS and many patients in CSWD late actually received CCS
- Primary and secondary outcomes not well described in study design
- Baseline characteristics did not include race or statistical analysis
- Industry-sponsored study

**Opinion**

- Low risk renal transplant recipients on CyA monotherapy and no induction
- High drop-out rate confounds variables creating questionable internal validity
- Identified late allograft loss (beyond 3 years) as a concern with CSWD late
- Identified deceased donor and repeat transplants as high-risk for CSWD late

<table>
<thead>
<tr>
<th>OVERVIEW</th>
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<tbody>
<tr>
<td>Objectives</td>
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<tr>
<td>Design</td>
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</tbody>
</table>
| Inclusion/Exclusion Criteria | • Inclusion: age 18-75 and non HLA-identical live or deceased donors  
• Exclusion: donor > 60 years, DCD, retransplant, multi-organ, PRA >20%, cold ischemia time > 24 hours |
| Induction | Basiliximab (per PI) |
| Maintenance Immunosuppression | CyA microemulsion (CyA-ME) + MPS +/- CCS  
• CyA-ME 5 mg/kg PO bid to achieve C₂ target of 1700 ng/mL for 1st mo then tapered to 900 ng/mL at 6 mo  
• MPS: 720 mg PO bid |
| Interventions | • CSA: received no IV or PO CCS  
• CSWD early: methylprednisolone IV 500 mg POD0 → 250 mg POD1 → 125 mg POD2 → Prednisolone PO 60 mg POD3 → 40 mg POD4 → 30 mg POD5 → 20 mg POD6 → then ceased  
• SC: above regimen + 10-30 mg/d ay mo 1, 10-20 mg/d ay mo 2, then 5-10 mg/d ay thereafter |
| Follow-up | 1 year |
| Outcomes | Primary:  
• GFR at 12 mos (calculated via Nankivell formula)  
• Change in BMD of lumbar spine  
Secondary:  
• Composite endpoint: death, allograft loss or biopsy-proven acute rejection (BPAR) at 3 & 12 mos  
• BPAR at 3 & 12 mos  
• Patient and allograft survival at 12 mos  
• Recipients free from CCS at 12 mos  
• Incidence of adverse events: blood pressure, lipid levels, blood glucose, change in hip BMD |
| Statistics | • ITT study population  
• Sample size of 89 recipients per arm needed for 80% power with a significance level of 0.05 to detect non-inferiority of CSA or CSWD early vs. SC  
  o Difference of ≤ 7 mL/min/1.73 m² considered non-inferior  
• Sample size of 58 recipients per arm needed for 80% power to detect a 3% difference by 2-sided t test of BMD of lumbar spine with a significance level of 0.05 based on SD of 5.745%  
• Wilcoxon rank-sum test for GFR  
• Kaplan-Meier graph for patient and allograft survival and log-rank for comparison data  
• Hochberg procedure for multiplicity of testing with BPAR |

<table>
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<tr>
<th>RESULTS</th>
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| Total Patients | 337 renal recipients were randomized and 335 were included in analysis  
• 111 in CSA, 115 in CSWD early, and 109 in SC were analyzed  
• By 12 mos: 59% of CSA and 71% of CSWD early remained CCS-free  
• 12% of SC had CCS withdrawn |
**Opinion**

- **Limitations**
  - Open-label design introduces bias for clinical treatment decisions
  - 41% of CSA initiated and 29% of CSWD early restarted CCS, and 12% of SC stopped CCS
  - Not representative of most US centers’ current immunosuppression
  - Reasons for patient death or allograft loss were not reported
  - 1 year follow-up limits the ability to observe long-term outcomes
  - Industry-sponsored study

- **Strengths**
  - Prospective, randomized, multi-center, international trial including centers in US
  - Standardized monitoring of CCS adverse events at pre-established time points minimized physician bias in an open label study
  - Used C2 as CyA monitoring, most accurately correlated with AUC
  - Compared both CSA and CSWD early to SC
  - Assessed renal function as primary outcome at 1 year

- **Authors’ Conclusions**
  - In low risk recipients receiving basiliximab, CyA-ME and MPS, CSWD early offers favorable risk/benefit with comparable renal function vs. SC
  - Preferable to CSA since high proportion required CCS introduction

**Conclusions**

- **Immunosuppression**
  - 98% received basiliximab
  - CyA-ME mean C2 (ng/mL): 790 ± 268 CSA, 805 ± 291 CSWD early, 808 ± 300 SC (p = NS)
  - MPS median dose (mg/day): 1437 CSA, 1438 CSWD early, 1440 SC (p = NS)

- **Primary Outcome**
  - Median GFR (mL/min/1.73m²): CSA 59 (44 – 73), CSWD early 59 (41 – 69), SC 61 (49 – 71)
    - 95% CI from SC: CSA (-7.8 to 2.7), CSWD early (-8.8 to 1.6) (non-inferiority not demonstrated)
    - Post-hoc observed case analysis (excluded patients who died or lost allograft)
      - 95% CI for median difference from SC: CSA (-3.8 to 6.4), CSWD early (-6.5 to 4.9)
  - BMD spine Δ (%): CSA(n=38) -1.8 ± 6.7, CSWD early(n=39) -1.8 ± 6, SC(n=36) -1.5 ± 9.9 (p = NS)

- **Secondary Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CSA (n=111)</th>
<th>CSWD (n=115)</th>
<th>SC (n=109)</th>
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<tr>
<td>Composite endpoint (%)</td>
<td>36**</td>
<td>30**</td>
<td>19*</td>
<td>0.007*</td>
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<tr>
<td>Patient survival (%)</td>
<td>95</td>
<td>98</td>
<td>98</td>
<td>NS</td>
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<tr>
<td>Allograft survival (%)</td>
<td>96</td>
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<tr>
<td>BPAR (%)</td>
<td>32&quot;</td>
<td>26&quot;</td>
<td>15&quot;°</td>
<td>0.004&quot;, 0.046°</td>
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<tr>
<td>Time to BPAR (days)</td>
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<td>5&quot;&quot;</td>
<td>104&quot;&quot;°</td>
<td>0.003&quot;, 0.022°</td>
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<tr>
<td>De novo diabetes meds (%)</td>
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<td>12</td>
<td>15'</td>
<td>0.01</td>
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<td>Lipid-lowering meds (%)</td>
<td>53&lt;</td>
<td>37&lt;</td>
<td>52&lt;</td>
<td>0.018&lt;</td>
</tr>
<tr>
<td>Median triglycerides (mg/dL)</td>
<td>142</td>
<td>142&quot;&lt;</td>
<td>168&quot;&lt;</td>
<td>0.03&quot;</td>
</tr>
<tr>
<td>Change in BMI (kg/m²)</td>
<td>1.03</td>
<td>0.88&quot;</td>
<td>1.88&quot;</td>
<td>0.008&quot;</td>
</tr>
</tbody>
</table>

- Mean number of biopsies per patient higher in CSA and CSWD early
- Patients who experienced BPAR in the CSA group had significantly lower CyA C2 levels
- No difference shown for change in hip bone mineral density, infections or malignancies

- **Authors’ Conclusions**
  - In low risk recipients receiving basiliximab, CyA-ME and MPS, CSWD early offers favorable risk/benefit with comparable renal function vs. SC
  - Preferable to CSA since high proportion required CCS introduction

- **Strengths**
  - Prospective, randomized, multi-center, international trial including centers in US
  - Standardized monitoring of CCS adverse events at pre-established time points minimized physician bias in an open label study
  - Used C2 as CyA monitoring, most accurately correlated with AUC
  - Compared both CSA and CSWD early to SC
  - Assessed renal function as primary outcome at 1 year

- **Limitations**
  - Open-label design introduces bias for clinical treatment decisions
  - 41% of CSA initiated and 29% of CSWD early restarted CCS, and 12% of SC stopped CCS
  - Not representative of most US centers’ current immunosuppression
  - Reasons for patient death or allograft loss were not reported
  - 1 year follow-up limits the ability to observe long-term outcomes
  - Industry-sponsored study

- **Opinion**
  - Low risk renal transplant recipients on CyA immunosuppression and basiliximab induction
  - Design intended to assess ability to maintain allograft function while reducing CCS effects
  - Non-inferiority of renal function not proven between ITT groups
  - Significantly increased BPAR did not show differences in allograft function
A. CCS-sparing with Tac-based immunosuppression\textsuperscript{42-50}  
1. Variety of marginally designed studies evaluating CSWD and CSA vs. SC (see Appendix I) 
   a. Rejection: variable results showing no difference or increased rates vs. SC  
      i. Majority treated with CCS  
   b. Allograft survival: no difference up to 2 years  
   c. Patient survival: no difference up to 2 years  
   d. Allograft function: variable results showing no difference or decreased CrCl vs. SC  
   e. Metabolic adverse effects of CCS  
      i. Diabetes: variable results showing fewer diabetes medications, lower incidence of new-onset diabetes after transplant (NODAT) and HgA1c in CSWD and CSA vs. SC  
      ii. Cholesterol: variable results showing fewer hyperlipidemia medications, lower total serum cholesterol, HDL, and LDL in CSWD and CSA vs. SC  
      iii. BMD: variable results; recent studies showed improved bone mineral density and reduced fracture risk in CSWD

OVERVIEW

<table>
<thead>
<tr>
<th>Objectives</th>
<th>To compare outcomes of early CSWD vs. SC in recipients receiving Tac/MMF-based immunosuppression with antibody induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective, randomized, double-blind, multi-center, placebo-controlled study in 26 U.S. centers</td>
</tr>
</tbody>
</table>
| Inclusion/Exclusion Criteria | • **Inclusion:** primary deceased and live donor renal transplant recipients aged 18-70 years, 30% reduction in SCr within 7 days post-transplant without dialysis, repeat transplants with prior allograft loss from technical reasons/recurrent disease (except FSGS) and PRA ≤ 25%, females of child bearing potential with negative pregnancy test and on birth control  
  • **Exclusion:** peak PRA ≥ 50%, current PRA ≥ 25%, multi-organ transplant, cold ischemic time ≥ 36 hrs, pediatric or ≥ 65 year-old donors, DCD, HLA identical live donor, recipients where CCS could not be discontinued, HIV+, dual renal transplant, acute rejection before POD 7 |
| Induction | Per center preference: rATG (1.5mg/kg IV X 4 doses) or IL-2RA (per PI) |
| Maintenance Immunosuppression | Tac PO daily + MMF PO bid + CCS  
  • Tac 0.15-0.2 mg/kg/day with target trough 10-20 ng/mL by POD 7 to 90, 5-15 ng/mL > POD 90  
  • MMF 2g IV or 3g PO per day POD 0-2 → 3g PO per day POD 3-14 → 2g PO per day > POD 15 |
| Interventions | • CSWD early: CCS POD 0-7 then discontinued  
  • SC: prednisone PO 0.4 mg/kg POD 8-14→0.3 mg/kg POD 15-29→0.2 mg/kg POD 30-89→0.15 mg/kg POD 90-119→0.1 mg/kg POD 120-180→5mg/day > POD 180 |
| Follow-up | 5 years |
| Outcomes | • **Primary**  
  o Composite endpoint (death, allograft loss, and moderate/severe acute rejection or acute rejection requiring antilymphocyte antibody therapy) at 5 years  
  • **Secondary**  
  o Patient and allograft survival  
  o Study drug discontinuation  
  o Framingham coronary heart disease risk estimates  
  o Frequency, severity, and treatment of acute rejection, NODAT, and hypertension  
  o Hyperlipidemia and use of lipid-lowering therapy  
  o Weight, infection, malignancy, leukopenia  
  o Calculated CrCl (Cockroft-Gault)  
  o Serious adverse events |
| Randomization | Randomized 1:1 stratified by race (African-American or not) and donor type (living vs. deceased) |
| Statistics | • ITT study population  
  • Assuming a rate of 10% in primary endpoint in the SC group, a sample size of 312 recipients was determined to detect 10% increase in the primary endpoint for a power of 80% and a one-tailed alpha error of 5%  
  • Kaplan-Meier and X² for primary outcome and individual components  
  • Wilcoxon rank sum test for continuous variable medians and t test for means  
  • Pearson’s X² test or Fisher exact test for categorical frequencies, as appropriate  
  • Kaplan-Meier product limit estimates and log-rank test for time to event data  
  • Logistic regression or Cox proportional hazards modeling for multivariate analyses  
  • SAS (two-tailed) for statistical analyses |
RESULTS

Total Patients
- 397 renal transplants randomized between November 1999 to November 2002
- 191 received CSWD early and 195 received SC
- 35% CSWD early and 37% of SC discontinued study drug

Demographics
- Similar baseline characteristics between groups

<table>
<thead>
<tr>
<th></th>
<th>CSWD early (n=191)</th>
<th>SC (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American (%)</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Living donor (%)</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Cold ischemic time (hr)</td>
<td>18 ± 6</td>
<td>17 ± 7</td>
</tr>
<tr>
<td>HLA mismatch (mean)</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Current PRA (%)</td>
<td>2 ± 5</td>
<td>2 ± 6</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>35</td>
<td>33</td>
</tr>
</tbody>
</table>

Immunosuppression
- Induction: (CSWD early vs. SC) rATG: 65% vs. 70%, IL-2RA: 35% vs. 30%
- Maintenance: Tac trough levels similar between groups; MMF dose reductions for leukopenia: 52% CSWD early vs. 27% SC (p < 0.001)

Primary Outcome
- Composite endpoint: 15.7% CSWD early vs. 14.4% SC (p=0.691)

Secondary Outcomes
- BPAR (%)
  - CSWD early: 18, SC: 11
  - p-value: 0.058*
- Patient survival (%)
  - CSWD early: 94, SC: 93
  - p-value: NS
- Allograft survival (%)
  - CSWD early: 94, SC: 96
  - p-value: NS
- CrCl (mL/min)
  - CSWD early: 59 ± 20, SC: 60 ± 21
  - p-value: NS
- Infections (%)
  - CSWD early: 39, SC: 44
  - p-value: NS
- Malignancies (%)
  - CSWD early: 11, SC: 11
  - p-value: NS

  *BPAR via Kaplan-Meier curve showed higher rates in CSWD early (p=0.042)

  Sub-group analysis
  - BPAR in CSWD early: rATG 14% vs. IL-2RAs 24% (p=0.09)
  - Allograft loss risk factors
    - African American: RR 4.3 (CI 1.5 – 12.7), p=0.08
    - Deceased donor: RR 4.1 (CI 1.2 – 13.7), p=0.021
    - Acute rejection: RR 5.1 (CI 1.7 – 15.1), p=0.03
    - CAN/IFTA: RR 41.1 (CI 12.5 – 135.9), p=0.001

- Metabolic adverse effects throughout 5 years that showed statistical significance

<table>
<thead>
<tr>
<th></th>
<th>CSWD early (n=191)</th>
<th>SC (n=195)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in triglycerides</td>
<td>Favored CSWD at all times except 60 mo</td>
<td>0.001-0.049</td>
<td></td>
</tr>
<tr>
<td>Anti-lipid therapy initiation (%)</td>
<td>51</td>
<td>67</td>
<td>0.038</td>
</tr>
<tr>
<td>NODAT requiring insulin (%)</td>
<td>4</td>
<td>12</td>
<td>0.049</td>
</tr>
<tr>
<td>Improvement in HgA1c (NODAT)</td>
<td>Favored CSWD at all times except 48 mo</td>
<td>0.001-0.048</td>
<td></td>
</tr>
<tr>
<td>Bone fracture/avascular necrosis (%)</td>
<td>5</td>
<td>11</td>
<td>0.041</td>
</tr>
</tbody>
</table>

- Post-hoc analysis
  - CAN/IFTA at 5 years greater in CSWD early group 10% vs. 4% (p=0.028)
  - “For cause” biopsies CSWD early 46% vs SC 33%, p=0.009
  - Over half of patients with CAN/IFTA diagnosed with 1st biopsy
## CONCLUSIONS

<table>
<thead>
<tr>
<th>Authors’ Conclusions</th>
<th>Early CSWD vs. SC with induction + Tac + MMF shows modest increase in BPAR but similar long-term allograft survival and function, as well as cardiovascular risk and bone disease benefits</th>
</tr>
</thead>
</table>
| **Strengths**        | • Prospective, randomized, double-blind, placebo-controlled, multi-center trial  
• Representative of most U.S. centers’ current immunosuppression  
• Included African-Americans  
• Randomization was stratified by donor type and race  
• Consistency in treatment of acute rejection and infection prophylaxis regimens  
• 5 year blinded follow-up |
| **Limitations**      | • CSWD early had significantly more dose reductions in MMF  
• No zero-hour biopsies to exclude donor renal disease  
• Industry-sponsored study |
| **Opinion**          | • No difference in composite endpoint or CrCl  
• CSWD early had significantly increased BPAR by Kaplan-Meier analysis  
• Significantly higher incidence of 5 year CAN/IFTA in CWSD early warrants longer follow-up  
• Lymphocyte-depleting induction preferred with CSWD early in low-moderate risk recipients |
VI. Summary

A. As 1 year incidence of acute rejection and allograft survival continue to improve, 5 and 10 year allograft survival have yet to show equivalent improvement
B. Death with a functioning allograft most common reason for allograft loss
   1. Primary causes are cardiovascular, infectious, and malignant complications
C. CCS linked to numerous cardiovascular complications and can indirectly contribute to infection and malignancy via over-immunosuppression
D. Original clinical evidence showed increased allograft loss in CyA-based CCS sparing protocols
E. Current clinical evidence
   1. Increased rejection rates in CCS sparing protocols
   2. Rejection rates do not correlate with increased patient and allograft loss or allograft function
   3. Mixed results in reducing CCS adverse effects
      a. Consistent underreporting of adverse effects
      b. Lack of routine assessment
      c. Multiple confounding factors (tacrolimus dose, pre-existing conditions, etc.)

VII. Recommendations

A. CCS sparing strategies should be considered for certain adult renal transplant populations
B. Populations most likely to benefit from CCS sparing strategies
   1. Recipients receiving induction
      a. Lymphocyte-depleting agent preferred for patients with known risk factors
   2. PRA <30%
   3. Living donors
   4. On adequate Tac + MMF/MPS immunosuppression
C. Populations CCS sparing strategies should be used with caution/avoided
   1. Highly sensitized patients
      a. Retransplants
      b. PRA > 30%
   2. Donor characteristics
      a. Donor age ≥ 65 years old
      b. DCD
   3. Delayed graft function
   4. Multi-organ transplant
   5. Cold ischemic time > 24 hrs
D. Need further well designed studies
   1. Powered for CAN/IFTA
   2. Showing 10 year follow-up
VIII. References

9. Zand MS. Figure 1. One-year first cadaveric renal allograft survival and rejection episodes over time. Adapted from “Immunosuppression and immune monitoring after renal transplantation”. Semin Dial 2005; 18: 511-9.
<table>
<thead>
<tr>
<th>Trial and Year</th>
<th>Design</th>
<th>Immunosuppression</th>
<th>Groups (# of pts)</th>
<th>Follow-up</th>
<th>Results CSA or CSWD vs. SC (p-value)</th>
</tr>
</thead>
</table>
| Vanreenterghem et al. 2005 | Prospective, randomized, multi-center, double-blind parallel group | **Induction:** None  
**Maintenance:** Tac + MMF | CSA at 3 mos (n = 279)  
SC (n = 277) | 6 mos | - Rejection: SS 6% vs. 1% (0.004)  
- Patient survival: 99% vs 98% (NS)  
- Allograft survival: 93% vs. 94% (NS)  
- Allograft function: SCr 1.57 vs. 1.49 (NS)  
- **Metabolic effects:** SS improved cholesterol, LDL, and HDL |
| Laftavi et al. 2005 | Prospective, randomized, single-center, open-label | **Induction:** rATG (CSWD only)  
**Maintenance:** Tac + MMF | CSA at day 7 (n = 32)  
SC (n = 27) | 1 yr | - Rejection (clinical): 13% vs. 11% (NS)  
- Rejection (subclinical): 1 pt vs. 1 pt (NS)  
- Borderline changes: 6 pts vs. 6 pts (NS)  
- Tac toxicity: 11% vs. 4% (NS)  
- Other: cholesterol significantly less in CSWD (0.03)  
- Fibrosis rates, BP similar between groups |
| Borrows et al. 2004 | Retrospective, single-center, case series | **Induction:** Basiliximab or Daclizumab (25% of pts)  
**Maintenance:** Tac + MMF | CSA at dy 7 (n = 101) | ≥ 1.5 yrs | - Rejection: 19% at 1 yr  
- Patient survival: 99% at 18 mos  
- Allograft survival: 97% at 18 mos  
- Allograft function: CrCl 52 mL/min at 18mos  
- **Metabolic effects:** 3.5% NODAT, NS changes from baseline in BP, HgA1c, and serum cholesterol |
| Sola et al. 2002 | Prospective, randomized, single-center, open-label | **Induction:** None  
**Maintenance:** Tac + MMF | CSA at 3 mos (n = 46)  
SC (n = 46) | 2 yrs | - Rejection: 6% vs. 3% (NS)  
- Patient survival: 100% vs. 100% (NS)  
- Allograft survival: 97% vs. 97% (NS)  
- Allograft function: CrCl 67 mL/min vs. 63 mL/min (NS)  
- **Metabolic effects:** No significant differences |
| Luan et al. 2009 | Retrospective, observational database review | **Induction:** CSWD- rATG 42%, anti IL-2 14%, Alemtuzumab 17%  
SC- rATG: 24%, anti-IL2: 33%, Alemtuzumab 2%  
**Maintenance:** Tac + 2nd agent (MMF most common) | CSA (n = 16491)  
SC (n = 79264) | 1 yr  
4 yr | - Patient survival: 98% vs. 98% 1 yr (p <0.0001)  
93% vs. 91% 4 yr (p <0.0001)  
- Allograft survival: 96% vs. 95% 1 yr (p <0.0001)  
85% vs. 82% 4 yr (p <0.0001) |
| Rostaing et al. 2005 | Prospective, multi-center, open-label, parallel group | **Induction:** Daclizumab  
**Maintenance:** Tac +MMF | CSA (n = 260)  
SC (n = 278) | 6 mos | - Rejection: 17% vs. 17% (NS)  
- Patient survival: 99% vs. 98% (NS)  
- Allograft survival: 92% vs. 96% (NS)  
- Allograft function: SCr 1.4 vs. 1.5 (NS)  
- **Metabolic effects:** NODAT 0.4% vs. 5% (<0.001), mean change in total cholesterol improved in CSA (0.006), significant change in t- and z-score (0.03) |
| Vitko et al. 2005 | Prospective, randomized, multi-center, open-label, parallel-group | **Induction:** Basiliximab (Tac only)  
**Maintenance:** Tac + MMF OR Tac | CSA (n=151)  
SC (n=141) | 6 mos | *reported as Tac + MMF vs. Tac mono vs. SC*  
- Rejection: 26% vs. 31% vs. 8% (<0.001)  
- Patient survival: 99% vs. 99% vs. 100% (NS)  
- Allograft survival: 97% vs. 95% vs. 96% (NS)  
- Allograft function: SCr 1.5 vs. 1.5 vs. 1.4 (NS)  
CrCl (mL/min) 59 vs. 55 vs. 65 (0.007)  
- **Metabolic effects:** NODAT and lipid profile similar |