Immunosuppression in liver transplant

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Baylor University Medical Center
Dallas, Texas
Overview

- drugs, common regimens and rejection
- everolimus
- sirolimus and hepatocellular carcinoma
- belatecept
- antibody mediated rejection
Liver transplant immunosuppression

- **CNI**
  - cyclosporine and tacrolimus
- **anti-metabolites**
  - mycophenolate mofetil/mycophenolic acid/azathioprine
- **mTOR**
  - sirolimus*/everolimus
- **biologics**
  - thymoglobin, IL-2 receptor antagonists
- **corticosteroids**

*black box warning against use in liver transplant
Immunosuppression at transplant

CNI side effects
renal toxicity
hypertension
hyperlipidemia
diabetes
Immunosuppression - biologics

advantages
potent, predictable
no renal toxicity

problems
cost
IV administration

Kim, Am J Transpl, 2018
Immunosuppression - mTOR

Sirolimus - black box warning for HAT, graft loss and death

Everolimus - FDA approved for renal sparing benefit

advantages
renal sparing effect
?cancer mitigation

disadvantages
hyperlipidemia
proteinuria
“fear of drug class”
use only ≥ 4 wks post-op

Kim, Am J Transpl, 2018
Immunosuppression - steroids

corticosteroids
10% liver-kidney transplant
10% recent rejection
20% autoimmune etiology
Rejection therapy

76% reduced

Kim, Am J Transpl 2018
Most common immunosuppression regimen

- TAC + mycophenolate + pred (weaned)
- 30% induction with biologic
- 10% mTOR
- 10–15% rejection
Everolimus vs. sirolimus

Everolimus
FDA approved

Sirolimus
FDA black box warning
1) STANDARD (TAC +/− MPA)

TAC
+/- MPA

Everolimus With Reduced Tacrolimus Improves Renal Function in De Novo Liver Transplant Recipients: A Randomized Controlled Trial

P. De Simone*, †, F. Nevens, L. De Carlis,
Everolimus With Reduced Tacrolimus Improves Renal Function in *De Novo* Liver Transplant Recipients: A Randomized Controlled Trial

P. De Simone, F. Nevens, L. De Carlis

- Everolimus is FDA-approved in liver transplantation.
- Compared to TAC Controls, there is an 8.50 mL/min/1.73m² higher eGFR with EVR+rTAC.
- The difference is statistically significant with *p* < 0.001.
Approval of mTOR - everolimus

- first new FDA drug approval in 16 yrs
- renal sparing benefit (TAC avoidance)
- potential HCC benefit
# mTOR inhibitors and cancer

<table>
<thead>
<tr>
<th>Tumor</th>
<th>agent</th>
<th>Reference</th>
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<tbody>
<tr>
<td>subependymal giant-cell astrocytomas</td>
<td>EVR</td>
<td>Krueger, NEJM, 2010</td>
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<tr>
<td>renal cell carcinoma</td>
<td>TEM</td>
<td>Hudes, NEJM, 2007</td>
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<tr>
<td>non-melanoma skin cancer</td>
<td>SIR</td>
<td>Malgo, Am J Transpl, 2010</td>
</tr>
<tr>
<td>insulinoma</td>
<td>EVR</td>
<td>Kulke, NEJM, 2009</td>
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<tr>
<td>mantle-cell lymphoma</td>
<td>TEM</td>
<td>Ansell, Cancer, 2008</td>
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<tr>
<td>angiomyolipoma</td>
<td>SIR</td>
<td>Bissler, NEJM, 2008</td>
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<tr>
<td>Kaposi’s sarcoma</td>
<td>SIR</td>
<td>Stallone, NEJM, 2005</td>
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</tbody>
</table>
Immunosuppression vs. side-effects
Immunosuppression vs. side-effects

rapamycin (sirolimus) breaks the rules
Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomized, Multicenter, Open-Label Phase 3 Trial
Edward K. Geissler, PhD,1 Andreas A. Schnitzbauer, MD,1,2 Carl Zülke, MD,1 Philipp E. Lamby, MD,1

![Flowchart diagram]

Geissler, Transplantation 2016
HCC and mTOR

- up to year 2, 79% pts on SIR > 50% of the time
- yr 2 – 7, ≥ 66% of pts remained on SIR
- median SIR level 5.7 – 7.0 ng/ml

Geissler, Transplantation 2015
HCC and mTOR

No difference in recurrence-free or overall survival with mTOR.

Geissler, Transplantation 2015
HCC and mTOR

Low-risk (Milan) HCC May have benefit.

Geissler, Transplantation 2015
HCC and sirolimus

No improvement in survival or HCC recurrence

?benefit in low-risk patients

SIR warning for death and graft loss in OLT.
Belatacept-Based Immunosuppression in De Novo Liver Transplant Recipients: 1-Year Experience From a Phase II Randomized Study

- intravenous costimulatory blocker
- approved in renal transplant
- no nephrotoxicity
- IV administration
Belatacept-Based Immunosuppression in *De Novo* Liver Transplant Recipients: 1-Year Experience From a Phase II Randomized Study
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Belatacept-Based Immunosuppression in *De Novo* Liver Transplant Recipients: 1-Year Experience From a Phase II Randomized Study

<table>
<thead>
<tr>
<th>Composite end point</th>
<th>Basiliximab + belatacept</th>
<th>Belatacept</th>
<th>Belatacept</th>
<th>Tac + MMF</th>
<th>Tac</th>
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</thead>
<tbody>
<tr>
<td>HD + MMF (n = 50)</td>
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<tr>
<td>6 months (primary end point), n (%)</td>
<td>24 (48.0)</td>
<td>20 (41.7)</td>
<td>23 (46.9)</td>
<td>8 (15.1)</td>
<td>19 (38.0)</td>
</tr>
<tr>
<td>Difference from Tac + MMF, % (95% CI)</td>
<td>32.9 (16.1–49.8)</td>
<td>26.6 (9.6–43.5)</td>
<td>31.9 (14.3–48.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Difference from Tac, % (95% CI)</td>
<td>10.0 (–8.7–29.6)</td>
<td>3.7 (–15.3–23.2)</td>
<td>8.9 (–9.8–28.4)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AR, n</td>
<td>20</td>
<td>15</td>
<td>15</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Death, n</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Graft loss, n</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Survival with a functioning graft, n (%)</td>
<td>45 (90.0)</td>
<td>43 (89.6)</td>
<td>38 (77.8)</td>
<td>49 (92.5)</td>
<td>45 (90.0)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(81.7–98.3)</td>
<td>(80.9–98.2)</td>
<td>(65.9–89.2)</td>
<td>(85.3–99.6)</td>
<td>(81.7–98.3)</td>
</tr>
</tbody>
</table>
Belatacept offered the hope of

new drug class,
no renal toxicity,
intermittent infusion.

Belatacept failed to demonstrate efficacy in liver transplant.
Antibody-mediated rejection

- liver rejection mediated by T-cells
- treatment directed at T-cells
  - OKT3, thymoglobulin
  - CNI’s
- liver rejection mediated by B-cells
  - donor-specific antibody
  - against HLA epitopes
Antibody-mediated rejection

- hyperacute
  - immediate, devastating, very rare
- acute
  - days, rare
- chronic
  - months/years, indolent
Antibody-mediated rejection

- liver initially considered protected from AMR
  - Kupffer cells
  - porous endothelium
  - dual blood supply
  - hepatic regeneration
Antibody-mediated rejection

- presence of DSA in serum
- positive hepatic C4d staining
- hepatic vascular endothelial injury
- absence of other type of injury
multivariable model

de novo DSA

HR = 1.99, p = 0.005

independent risk factor for death
Interventions vs. DSA

- no proven therapy for AMR

- removal of antibody
  - plasmapheresis

- suppression of antibody production
  - indirect immunosuppression
  - direct agents (rituximab, bortezomib)
Preformed Antibodies Detected by Cytotoxic Assay or Multibead Array Decrease Liver Allograft Survival: Role of Human Leukocyte Antigen Compatibility

survival in the Luminex-positive vs. Luminex-negative groups significant at year 1, but not at year 3 or year 5.

Prevalence, Course and Impact of HLA Donor-Specific Antibodies in Liver Transplantation in the First Year

preformed HLA DSA is common in liver at baseline, and even in rare instances where high levels persist with complement activation in the liver, they are well tolerated 1 yr post OLT
Antibody-mediated rejection

• important biologic phenomenon
• unclear clinical significance
• diagnosis is difficult
• treatment is stringent
  – plasmapheresis
  – increased immunosuppression
  – plasma cell toxins (side effects)
Antibody-mediated rejection

- very rare acute rejection
- combined with T-cell rejection

Otherwise AMR is trivial in day-to-day practice of transplant hepatology.

We do not routinely screen for AMR or do special stains on liver biopsy seeking the diagnosis.
Antibody-mediated rejection

• < 10% of patients

• presence of DSA ≠ graft injury

• identification/diagnosis is difficult

• no known therapy
AMR - diagnosis

- presence of donor specific antibody
- liver histology findings
  - C4d staining
  - endothelial damage
- absence of other cause of graft damage
AMR at Baylor Medical Center

• aware of its existence

• recognize is biologic significance

• don’t otherwise screen for DSA

• minimal clinical significance in day-day practice
Immunosuppression - mTOR

Kim, Am J Transpl, 2018
Antibody-mediated rejection

- recognized for decades
- liver “protected”
  - porous endothelium
  - Kupffer cells
  - regeneration
  - dual blood supply
- recent “rediscovery”
Preformed Class II Donor-Specific Antibodies Are Associated With an Increased Risk of Early Rejection After Liver Transplantation

Jacqueline G. O’Leary, Hugo Kaneku, Linda W. Jennings, Nubia Bañuelos, Brian M. Susskind, Paul I. Terasaki, and Göran B. Klintmalm

1. Annette C. and Harold C. Simmons Transplant Institute, Baylor University Medical Center, Dallas, TX; 2. University of California Los Angeles, Los Angeles, CA; and 3. Terasaki Foundation Laboratory, Los Angeles,

A) Preformed Class I

- No Antibody
- Class I DSA: MFI > 5000

B) Preformed Class II

- No Antibody
- Class II DSA: MFI > 5000

Multivariate Model

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preformed Class I or II: MFI ≥ 5000 vs. no MFI ≥ 1000</td>
<td>1.51</td>
<td>0.02</td>
</tr>
<tr>
<td>African American recipient</td>
<td>2.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatitis C viremia*</td>
<td>2.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Antibody-mediated rejection

• definition and diagnosis?
• confirming evidence of graft injury?
• treatment efficacy?
  – directed against antibody (expensive, risky)
  – plasmapheresis
  – Rituxan
  – bortezomib
Sirolimus (mTOR) is both an efficacious immunosuppressant and anti-malignancy drug.
• known
  – antibody-mediated rejection occurs in liver transplant recipients

• unknown
  – do some/all DSA’s lead to graft injury?
  – identification of patients with DSA to benefit from treatment?
Liver transplant immunosuppression

- TAC + mycophenolate + pred (weaned)
- 10 – 15 % ACR
- increasing patient/graft survival rates
- 30 % induction
- 10 % mTOR
Liver transplant immunosuppression

- everolimus FDA approved for renal-sparing effect

- sirolimus in HCC
  - no survival benefit
  - low-risk Milan HCC may benefit
  - warning in OLT for graft loss and death

- belatecept
  - improved renal function
  - higher rejection and death
  - warning in OLT against use
Prospective, randomized trial comparing RFS in mTOR-containing regimens vs. non-mTOR regimens

45 centers
2006 – 2009 enrollment
follow-up March 2014
HCC and SIR

Toso, Hepatology, 2010
Prospective Multicenter Clinical Trial of Immunosuppressive Drug Withdrawal in Stable Adult Liver Transplant Recipients

Carlos Benítez, María-Carlota Londoño, Rosa Miquel, Tommaso-Maria Manzia, Juan G. Abraldes

Profile of patient entered into withdrawal protocol

61 yo WM

TAC - 3.9 ng/ml

Cr – 1.3 mg/dl

11 years out from transplant

Normal LFT’s

Risk vs. benefit in weaning stable, long-term recipient
Prospective Multicenter Clinical Trial of Immunosuppressive Drug Withdrawal in Stable Adult Liver Transplant Recipients

Carlos Benítez, María-Carlosa Londoño, Rosa Miquel, Tommaso-Maria Manzia, Juan G. Abraldes.
Steroids – 1 yr post-transplant
Liver transplant immunosuppression

- excellent result (low ACR, high graft survival)
- no new agents in 20 years
- serum markers for ACR
- antibody mediated rejection
Percent liver-kidney transplants as of 7/31/18

Kim, Am J Transpl, 2018
An Ectopically Expressed Serum miRNA Signature Is Prognostic, Diagnostic, and Biologically Related to Liver Allograft Rejection

Abraham Shaked,1 Bao-Li Chang,1 Michael R. Barnes,2 Peter Sayre,3 Yun R. Li,1 Smita Asare,4 Michele DesMarais,3,4

231 patients

48 (21%) immunosuppression weaning

protocol serum samples

acute cellular rejection

miRNA signature
Everolimus With Reduced Tacrolimus Improves Renal Function in De Novo Liver Transplant Recipients: A Randomized Controlled Trial

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<th>Class</th>
<th>Drug</th>
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<tr>
<td>Calcineurin-inhibitor</td>
<td>Cyclosporine (Neoral)</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus (Prograf)</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>M. mofetil (Cellcept)</td>
</tr>
<tr>
<td></td>
<td>Mycophenolic acid (Myfortic)</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>Sirolimus (Rapamune)</td>
</tr>
<tr>
<td></td>
<td>Everolimus (Zortress)</td>
</tr>
</tbody>
</table>
HCC and mTOR

- SIR target range 4 – 10 ng/ml
- DUS before SIR started
- “low-risk” Milan patients
- “high-risk” over Milan patients