Future Directions:
Medications and Long Term Complications, Expanding our Options

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Immunosuppressive Regimens in Pediatric Liver Transplantation

SPLIT survey 27 centers responded

- No induction therapy
  - Tacrolimus and steroids 16 centers
  - Cyclosporin and steroids 1 center
    (steroids weaned off between 3 months and >1 year)

- Anti-IL2R induction
  - Tacrolimus and steroids 9 centers
    (steroids weaned off between 3 months and >1 year)

- ATG induction
  - Tacrolimus 1 center

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Long Term Complication

- Rejection
  - Late acute rejection
  - Chronic rejection
- PTLD and other cancers
- Growth failure
- Metabolic bone disease
- Renal dysfunction
- Hypertension
- Hyperlipidemia
- Increase cardiovascular risks
Immunosuppressive failure

Too little
OR
Too much
Approaches to immunosuppressive drug management

Traditional approach
- Monitor drug levels
- Protocol reductions in drug doses/levels over time
- Monitor liver function, renal function, viral loads, etc and respond
- Protocol biopsies
- Drug combinations to limit non-immune side-effects
Alternative Approaches

- Induction therapy
- Steroid withdrawal or avoidance
- Calcineurin inhibitor minimization
- Immune function monitoring
- New Immunosuppressive drugs
- Tolerance
Induction Immunotherapy
Induction agents

• Cytolytic agents
  – OKT3
  – ATG
  – Campath 1H

• Interleukin 2 receptor antagonists
  – Basiliximab
  – Daclizumab
Anti-IL-2R

- IgG1 monoclonal
- High affinity for IL-2R α-chain (CD25)
- Inhibit clonal expansion of activated T-lymphocytes
- Low antigenicity
- Minimal cytokine release
Pediatric Studies using IL-2R agents – Renal transplantation

• NAPRTCS – pooled kidney data
  – Daclizumab (n=284)
  – Basiliximab (n= 166)
  – No induction (n=711)

  – Incidence of AR 23-26% v 34% at 1 yr
  – Graft survival 95-97% v 93%

• Many single center reports
Pediatric Studies using IL-2R agents - liver

Single center data only

– Acute rejection

• 11.5% v 61%  (Ganschow et al)
• 30% v 63%    (Asensio et al)
• 39% v 75%    (Heffron et al)
Toxicity

• IL-2R antagonists very well tolerated
• Minimal cytokine release
• No hematological toxicities (no –penias)
• Concern regarding viral infection
  – EBV & CMV
  – Hepatitis C
Figure 1: K-M Analysis of Time to Death By Induction Therapy

None (n=2159)  p=0.03
IL-2 (n=283)  
ALG or OKT3 (n=260)  p=0.53

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Figure 2: K-M Analysis of Time to Graft Failure By Induction Therapy

By Induction Therapy

- None
- IL-2: p=0.0005
- ALG or OKT3: p=0.31
Figure 3: K-M Analysis of Time to First Rejection By Induction Therapy

- None
- IL-2: RR 0.646, p<0.0001
- ALG or OKT3

PERCENT REJECTION

MONTHS

0 6 12 18 24 30 36 42 48 54 60

0 20 40 60 80 100
Induction Agents - Conclusion

• Induction with IL-2R antagonist improves graft and patient survival and reduces incidence of early acute rejection

• Agents well tolerated and not associated with significant increase in complications

• Freedom from early rejection should enable more aggressive weaning of other immunosuppressive agents thus limiting short and long-term toxicities
Steroid Withdrawal or Avoidance
Steroid Withdrawal

• Benefits
  – Decrease steroid-related complications
    • Infections
    • Diabetes
    • Hypertension / Cardiovascular disease
  – Improve growth
  – Better adherence
  – Tolerance?
Steroid Usage By Follow-Up Time

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Steroid-free immunosuppression in Pediatric Liver Transplantation

- Induction therapy universal
- Tacrolimus based
- Adjunctive MMF or rapamycin common
- Reperfusion methylprednisolone bolus common
- Acute rejection treated with steroids
Calcineurin inhibitor minimization

• More a concern in renal transplantation because of renal injury from this class of drugs
• Substituted with MMF &/or Sirolimus
• Exchange one side–effect profile for another
• Increased rejection and graft loss seen
Immune function monitoring

• EBV viral load
• Cytokines – IL10, sCD30,
• HLA antibodies
• Lymphocyte markers – CTLA4
• Assay of donor specific alloreactivity
  – ELISPOT
• Assay of immune cell responses
  – Cyclex Immuknow – ATP concentrations in CD4+ T-cells
New immunosuppressive drugs

• Small molecules
  – Fingolimod (FTY720) – sphingosine 1-phosphate receptor modulator
  – FK778 – pyrimidine synthesis inhibitor
  – CP-690550 – JAK3 inhibitor
  – AEB-071 – protein kinase C inhibitor

• Biologics
  – Belatacept (LEA29Y) – anti-CD40
  – CTLA4Ig – blocks CD80/86 and CD28 co-stimulation pathways
  – Efalizumab – humanized anti-LFA1 antibody
Transplant Tolerance

Stable graft function without need for immunosuppressive drugs
Tolerance

“true” tolerance – a well functioning graft lacking histological signs of rejection, in the absence of any immunosuppressive drugs, in an immunocompetent host capable of accepting a second graft from the same donor origin while being able to reject a third-party graft.
Tolerance

• True tolerance
  – Identical twins
  – Bone marrow transplantation

• Operational tolerance
  – Emergent
  – Non-compliant
  – Elective

• Prope tolerance (IS minimization)
Clinically Tolerant Liver Transplant Recipients

<table>
<thead>
<tr>
<th>Method of Drug Withdrawal</th>
<th>Protocol</th>
<th>Emergent</th>
<th>Non-Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>28</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Age at TX (years)</td>
<td>11.8 +/- 15.5</td>
<td>3.5 +/- 4.5</td>
<td>19.8 +/- 22.6</td>
</tr>
<tr>
<td>Time from TX to wean (years)</td>
<td>5.7</td>
<td>3.13</td>
<td>7.3</td>
</tr>
<tr>
<td>Time from wean to drug withdrawal (years)</td>
<td>2.2 +/- 2.7</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Current time off IS (years) - mean</td>
<td>10.8 (2.1 – 15.1)</td>
<td>11.7 (4.6 – 15.7)</td>
<td>17.1 (6.9 – 24.7)</td>
</tr>
</tbody>
</table>

# Protocol Withdrawal

<table>
<thead>
<tr>
<th>Center</th>
<th>% patients off</th>
<th>% mild ACR</th>
<th>% Mod ACR</th>
<th>CR</th>
<th>Graft loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitt</td>
<td>19 (18/95)</td>
<td>23 (22/95)</td>
<td>3 (3/95)</td>
<td>3 duct injury</td>
<td>NR</td>
</tr>
<tr>
<td>Miami</td>
<td>19 (20/104)</td>
<td>52 (54/104)</td>
<td>5.7 (6/54)</td>
<td>2/104</td>
<td>1 Re-Tx</td>
</tr>
<tr>
<td>Kyoto</td>
<td>42 (49/115)</td>
<td>17.9 (20/115)</td>
<td>1 severe ACR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Mazariegos – presented at SPLIT annual meeting, Nashville, Oct 2007
Identifying and Monitoring Tolerance

- Significant viral infection
- Absence of rejection
- Staged immunosuppression reduction
- Assay of alloreactivity (Sindhi)
Tolerance Induction

• Central Tolerance
• Peripheral Tolerance
Central Tolerance

Results from intrathymic deletion of T-cells with high avidity for thymically expressed antigens

- Bone marrow transplantation
- Chimerism
  - Macrochimerism – Sykes et al
  - Microchimerism – Starzl et al
Peripheral Tolerance

Anergy induction, deletion or active regulation of effector T-cells

- Depleting protocols
- C0-stimulatory blockade
Barriers to Tolerance

Why are these approaches successful in rodents and not in humans?

• Drug toxicities
• Redundant co-stimulatory pathways
• Memory T-cells
Conclusion

• Long-term complications of transplantation are primarily a function of the need for immunosuppression
• Alternate approaches to immunosuppression may lessen the impact
• Only true tolerance will eliminate risks
• Operational tolerance exists and may be inducible