I have no financial disclosures
Presentation goals

- Rationale for Induction
- Historical perspective
- Types of Induction therapies
- Comparative studies
- Take home message
Aggressive alloimmune response
Ischemia reperfusion injury-endothelial damage

Ferrar C et al. Cold Spring Harb Perspect Med v.3(10); 2013 PMC3784815
Steps in T-Cell–Mediated Rejection

- Host and donor antigen-presenting cells move to lymphoid organs
- Naive and central memory T cells recirculate between secondary lymphoid organs
- Host–graft adaptation (stabilized by immunosuppressive drugs)
- Antigen-presenting cells meet T cells in secondary lymphoid organs
- Traffic controlled by S-1-P receptors and chemokine receptors
- Endothelial arteritis
- Interstitial infiltrate with tubulitis
- Kidney
- Lymph node
What is induction therapy?

- Use of intensive immunosuppressive therapy at initiation of treatment
- Starts before reperfusion of an organ during transplantation
- High dose corticosteroids, lymphocyte non-depleting or depleting agents are used for induction
- High dose calcineurin inhibitors if no induction therapy is used
Why do you need induction therapy?

- Suppress the initial massive immune response
- Prevent acute rejection of mis-matched organs
- Prolong allograft survival
- Corticosteroid minimization
- Decrease toxicity of maintenance immune suppression
Historical evolution of post transplant Immune suppression

- Targeted at T cells
- High dose steroids
- Induction agents used:
  - Minnesota anti-lymphocyte globulin
  - Total body irradiation
  - Muromonab-CD3
Induction Immunosuppression Improves Long-Term Graft and Patient Outcome in Organ Transplantation: An Analysis of United Network for Organ Sharing Registry Data.

Cai, Junchao; Terasaki, Paul

DOI: 10.1097/TP.0b013e3181fecfcb

Relative risks of graft failure of the most commonly used induction protocols in kidney transplantation (***PP<0.05). Adjusted 5-year graft survival rates of the most commonly used induction protocols in kidney transplantation.
Acute Rejection in the first year after Kidney Transplantation

<table>
<thead>
<tr>
<th>Transplant Year</th>
<th>Living Donor</th>
<th>Deceased Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>SE</td>
</tr>
<tr>
<td>1987-1990</td>
<td>54.2</td>
<td>1.7</td>
</tr>
<tr>
<td>1991-1994</td>
<td>44.9</td>
<td>1.5</td>
</tr>
<tr>
<td>1995-1998</td>
<td>33.0</td>
<td>1.4</td>
</tr>
<tr>
<td>1999-2002</td>
<td>21.9</td>
<td>1.3</td>
</tr>
<tr>
<td>2003-2006</td>
<td>12.8</td>
<td>1.3</td>
</tr>
<tr>
<td>2007-2010</td>
<td>8.6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

NAPRTCS 2010
NAPRTCS 2014 – Time to first rejection in index transplants
Randomized Controlled Trial of Tacrolimus versus Cyclosporine in Children-2003

- 6 month randomized open parallel group study - 18 centers and 9 European countries
- Decrease in acute rejection rate 37% Tacro versus 59% CYA
- Decrease in corticosteroid resistant rejection
- Better graft survival in the first year of transplantation

Evolution of maintenance and induction immunosuppression use 1998–2012

a
Immunosuppressive regimen within the last 10 years (N=864)

Induction therapy stratified by substance

Comparison of Induction therapies
Unweighted Kaplan–Meier overall graft survival estimates in deceased donor renal transplantation (DDRT) recipients maintained on tacrolimus (TAC)/mycophenolic acid (MPA)/steroids by induction types.
Comparison of outcomes with low-dose anti-thymocyte globulin, basiliximab or no induction therapy in pediatric kidney transplant recipients: A retrospective study

ATGI-12
Basiliximab- 29
No antibody Induction- 47
Maintenance immune suppression
CYA MMF Prednisone
TAC MMF prednisone
Lymphocyte-depleting induction therapy lowers the risk of acute rejection in African American pediatric kidney transplant recipients

Crowson CN et al. Pediatric Transplantation, Volume: 21, Issue: 1, First published: 03 October 2016, DOI: (10.1111/petr.12823)
Impact of Induction therapy on delayed graft function

- Definition: Need for dialysis within 1 week of transplantation
- Complicates care especially with calcineurin inhibition
- Makes the diagnosis of acute rejection difficult
- 76 patients with mated deceased donor kidneys were randomized to either thymoglobulin or basiliximab for induction
- Patients who received thymoglobulin had decreased odds of having DGF

Induction therapy in pediatric kidney transplant recipients discharged with a triple drug immunosuppressive regimen - 3 year survival.
Addition of anti-CD25 to thymoglobulin for induction therapy: delayed return of peripheral blood CD25-positive population.

University of Miami Protocol

- Induction therapy
- 3 doses thymoglobulin
- 2 doses basiliximab
- Steroids discontinued in 5-7 days
- Maintenance with mycophenolate and tacrolimus (levels 6-8ng/ml first 3 months and then 5-7ng/ml)
How much immune suppression does a patient need?

Degree of Immune suppression

Monitoring drug levels
Optimal level defined by transplant center

Host factors - determining net state of immune suppression
Assessment of risk status for decision making

- Young age of recipient – stronger immune response
  - Adolescents or young adults >50% risk of nonadherence
- High panel reactive antibody
- Delayed graft function
- Cold ischemia time >24 hours
- >3 HLA mismatches
- African American ethnicity
- Steroid avoidance

Pratschke et al. Transplantation Reviews. 2016; 30(2)77-84
Assessing risk of rejection-influence of age

Pratschke et al. Transplantation Reviews. 2016; 30(2)77-84
Maintenance therapy
• Steroids
• calcinuerin inhibition-tacrolimus (higher trough levels 10-20 ng/ml for 1 mth) cyclosporine (trough 150-250 ng/ml for 1 mth)
• Anti-metabolite – mycophenolate or azathioprine

No Induction

Induction therapy
IL2RA
Alemtuzumab
Anti-thymocyte globulin (rATG)

Maintenance therapy
• Steroid based calcinuerin inhibition-tacrolimus (lower trough levels)
• Anti-metabolite – mycophenolate or azathioprine
• No steroids
• Calcinuerin inhibition-tacrolimus
• Anti-metabolite – mycophenolate or azathioprine
Possible approaches based on current knowledge

<table>
<thead>
<tr>
<th>Risk of rejection</th>
<th>Possible Initial Approach</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low immunological risk</td>
<td>No induction</td>
<td>Steroid based with tacrolimus and mycophenolate</td>
</tr>
<tr>
<td></td>
<td>Basiliximab</td>
<td>Steroid free with tacrolimus and mycophenolate</td>
</tr>
<tr>
<td>High immunologic risk</td>
<td>Thymoglobulin or alemtuzumab</td>
<td>Steroid based with tacrolimus and mycophenolate</td>
</tr>
<tr>
<td>Non-adherent adolescent</td>
<td>Consider induction</td>
<td>Consider belatacept if seropositive for EBV if patient is older</td>
</tr>
</tbody>
</table>
Conclusions

- The optimal approach to post transplant immunosuppression is yet to be defined, especially in children.
- Induction therapy with monoclonal or polyclonal antibodies are being considered by many transplant centers.
- May be strongly considered in steroid free maintenance immunosuppressive protocols.
- Individualized decision making based on recipients immunological profile may optimize outcomes.
Mindful approach

- The magnitude of immune suppression is dose dependent-avoid excessive use of depletional antibodies
- Antibodies can develop to chimeric monoclonal and polyclonal antibody therapies
- Multi-center trial evaluating the immunologic consequences of each induction and maintenance protocol will be helpful