

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

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

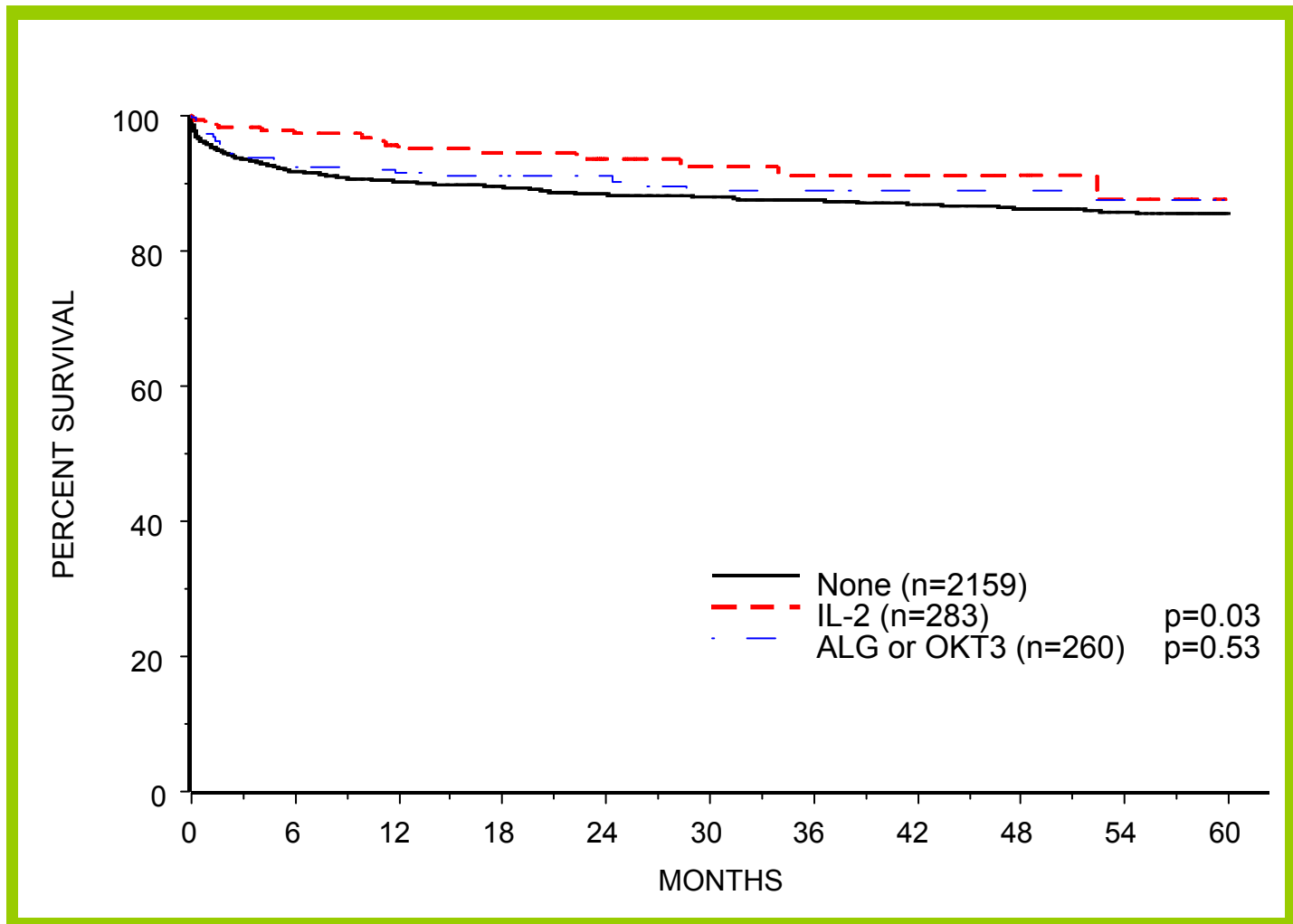
– Acute rejection

- 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



SPLIT analysis 2007 – presented at annual meeting, Nashville, Oct 2007

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

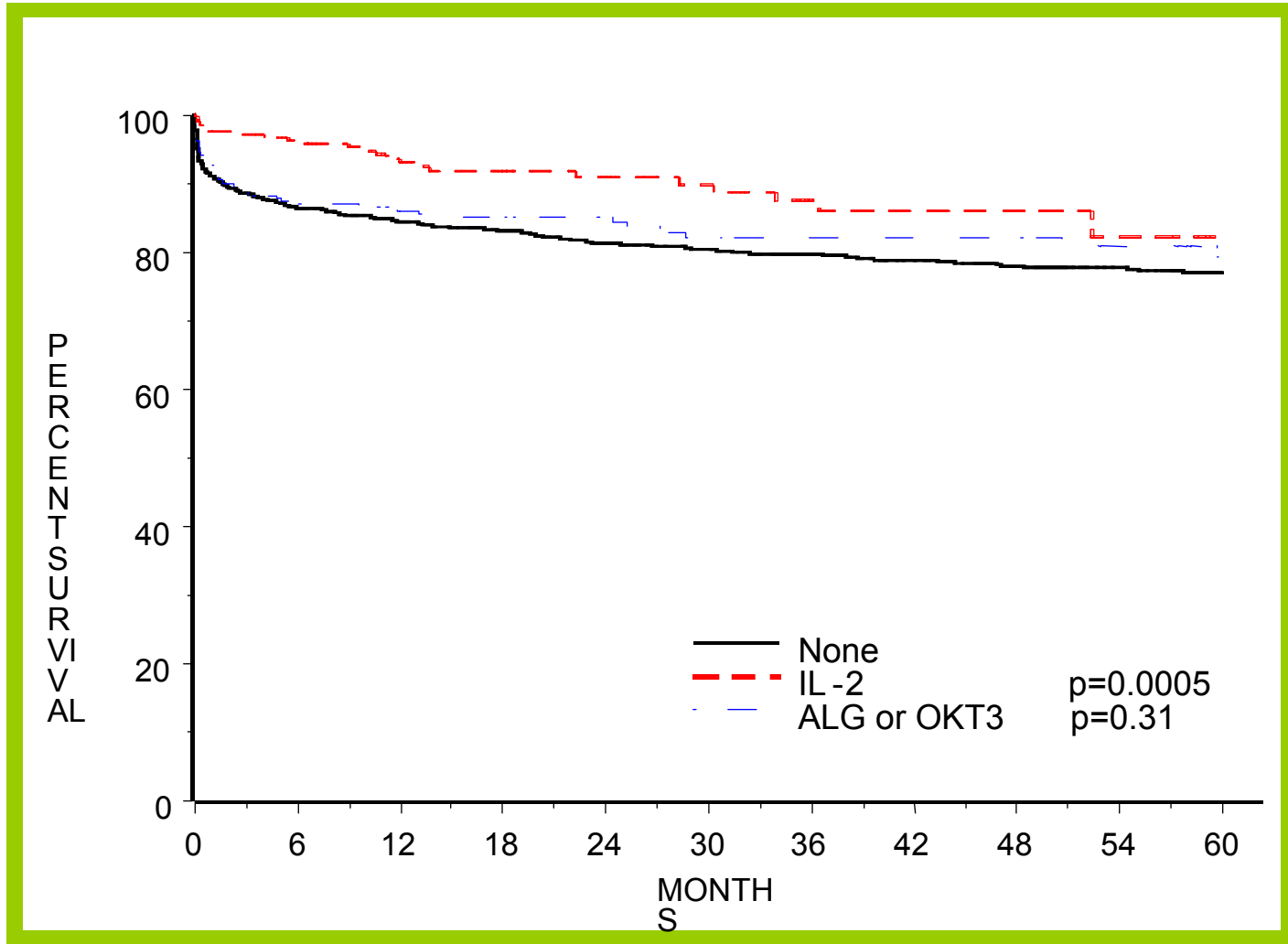
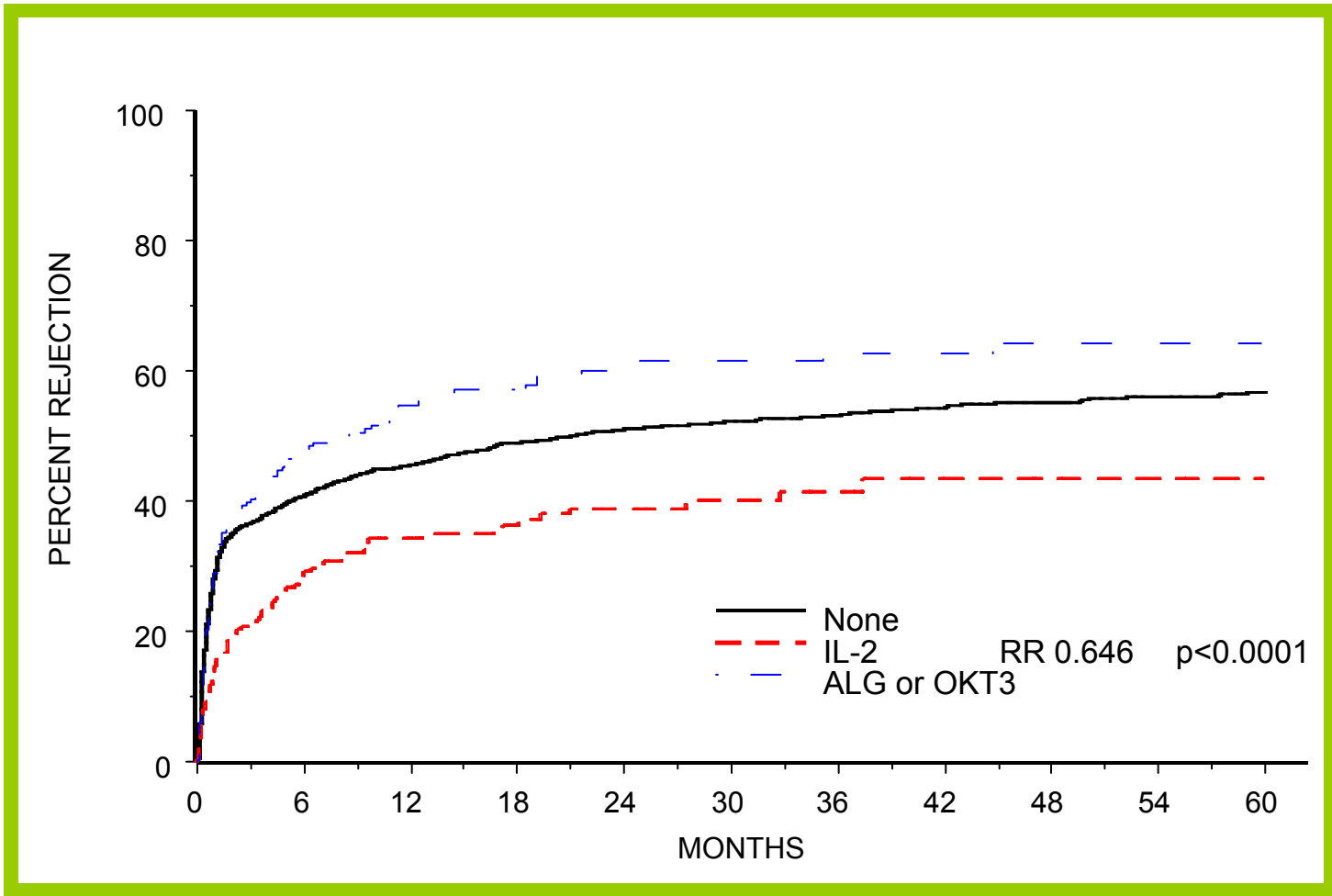


Figure 3: K-M Analysis of Time to First Rejection By Induction Therapy



Induction Agents - Conclusion

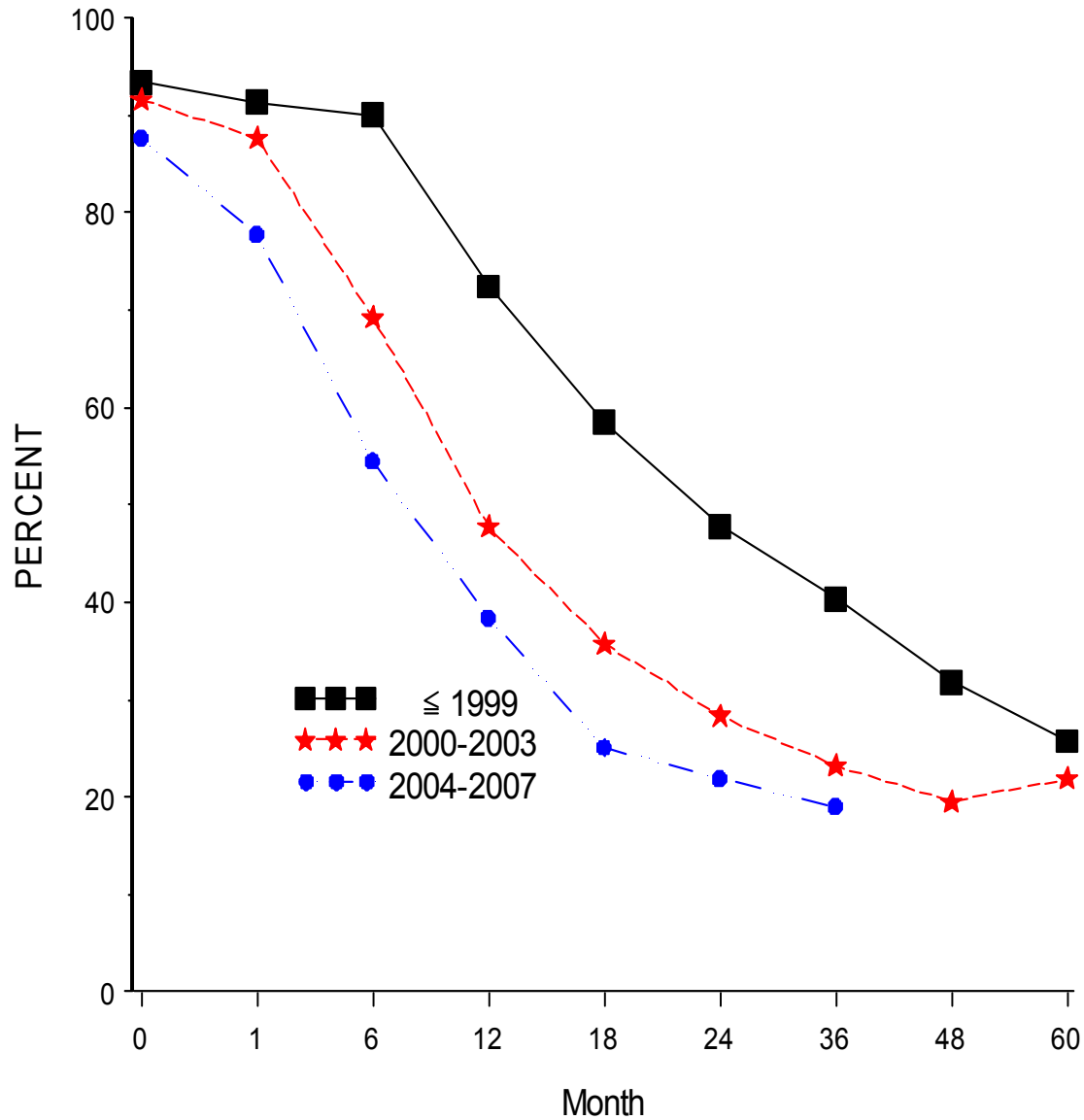
- Induction with IL-2R antagonist improves graft and patient survival and reduces incidence of early acute rejection**
- Agents well tolerated and not associated with significant increase in complications**
- Freedom from early rejection should enable more aggressive weaning of other immunosuppressive 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 Long Term Follow-Up (1992 – 2006)

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

Protocol Withdrawal

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

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

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

- Depleting protocols
- Costimulatory 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