Transplant Immunosuppression in 2017

Hepatobiliary Liver Transplant Symposium 2017

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Transplant Immunosuppression in 2017

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Immunosuppression in the pediatric transplant recipient

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Immunosuppression in Pediatric Liver Transplant Recipients: Unique Aspects

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Solid organ transplantation

Medical field most dramatic developments last decade with advances

- Surgical technique
- Graft preservation
- Critical care management
Solid organ transplantation

- Increased understanding of the immune response
- Improved immunosuppression management
- Improved outcomes and long-term survival
Goal transplant immunosuppression

Prevent

• Allograft rejection
• Immune mediated graft injury

By

• Altering / inhibit the normal host immune response to foreign antigen
Ideal transplant immunosuppression

- Create allograft-specific nonresponse

- Maintain immunocompetence against other potential pathogens and conditions
Ideal transplant immunosuppression

Desired level of immunosuppression a balance

• Prevention acute rejection
• Excess immunosuppression increased risk
  – infection
  – malignancy
  – drug-specific toxicities
Current strategies vary

- Different centers
- Organ transplant types

Protocols

- Combination of drugs
- Organ-specific planned tapering of medication and doses over time
- Active surveillance emerging viral infections / other signs over-immunosuppression
Historical Perspective
Era of solid organ transplantation

• Early 20th century xenotransplantation attempted
• World War I skin allografts were implemented to treat injured
• Theory immune mediated rejection developed
Peter Medawar

- Serial full-thickness skin allografts in cattle rejected more vigorously
- Grafts between monozygotic twins promptly thrived and tolerated
- ALLOGRAFT REJECTION IMMUNOLOGIC PHENOMENON WITH THE CLASSIC IMMUNE PROPERTIES
  - SENSITIZATION
  - MEMORY AND TOLERANCE
- CONCEPT PILLARS TRANSPLANTATION SCIENCE
1954        Kidney transplant
1960 ‘s       Liver, heart, pancreas transplants
1980’s      Lung and intestinal transplants
1963        Paediatric liver transplant
1984        Paediatric heart transplant

Success limited surgical technique and lack of adequate immunosuppression
1930’s  
Immunosuppression by total body irradiation

1970’s  
Steroids and Azathioprine
Outcome dismal 15% one year survival liver transplant

1980’s  
Cyclosporin
Transplantation clinical reality
One year survival 80%

1990’s  
Surge availability new agents
Tacrolimus
Refinement protocols to prevent and treat long term rejection
Variability different regimens centers
Aim standardize care and achieve excellent graft and patient survival
Pharmacology of Immunosuppression
Paediatric perspective

• Significant developments in immunosuppression management past 60 years
• Use new agents limited lack pharmacokinetic data
• Children as vulnerable population often excluded from studies of new regimens due to safety concerns
Important challenges medication

- Medications must be dispensed in liquid form
  - Find compounding pharmacies
  - Pertinent pay attention to exact medication concentrations, as compounded suspensions vary (1mg/ml vs 0.5 mg/ml)
  - Remember volume rather than concentration
Important challenges medication

• Suspensions unpalatable, toddlers refuse to take
  – Nasoenteric, percutaneous gastric tube placement
• Consistent administration, trough levels may change switch suspension / pill
• Interaction nutrition, medication, supplements significant
• Certain suspensions refrigerated
  – Travel etc
• Suspensions shaken before administration
Important challenges medication

• Some medications may clog feeding tubes – routine flushing
• Suspension more expensive than pill form
  – often not covered medical aids
  – add financial burden
Important challenges medication

- Young patients dependent caregiver administration
  - All individuals involved educated
  - Information not transmitted visits
- Parental anxiety and family instability risks errors
- Adverse drug reactions significant morbidity and mortality children
  - Exponential risk multiple medications
  - Pharmacodynamics / Pharmacokinetics
  - Dedicated transplant pharmacist
Pharmacokinetics substantially different

- Metabolize drugs more rapidly - increased hepatic enzyme activity
- Changes in hepatic blood flow, which generally decrease with age, may affect drug extraction and clearance
- Differences body surface area
- Shortened bowel length, decreased area drug absorption
- Slower gastric emptying <6m
- Slower intestinal transit time <12y
Differences particularly important paediatric transplant recipient

- Tacrolimus dosages 2-5x higher to achieve same levels in adults

- Partial liver graft from adult donor: pharmacokinetic pattern of tacrolimus retains the characteristics of the age of the donor, not the recipient
Variations gastric pH alters absorption

- Gastric environment
  - Neutral neonate
  - Acid production adult levels 3y
- Co-administration antacids common
- Chelation co-administration
  - Milk
  - Antacids
  - Iron supplements
Absorption further altered

• Co-administration prokinetic agents
• Variations cytochrome P450 enzyme activity
• Immaturity pancreatic and biliary function
• Intestinal microbiome
• Presence of food alter rate/extent of absorption
  – Tacrolimus/MMF empty stomach, GIT S/E with food
  – consistent administration with / without food
  – Challenge toddlers!
Drug distribution

- Water 70% body mass newborn
- Adult levels 55-60% around 1-2 years
- First few months Extracellular fluid↓ intracellular fluid↑
- Affect drug distribution and lower plasma levels drug administered on weight basis
Pharmacodynamics

• Bone marrow suppression
• Nephrotoxicity
  – Avoid nephrotoxic drugs, adjusted doses
• QTc prolongation – ECG
• Bone disease – Ca, Vit D levels, supplement
• GIT disturbances
  – Separate administration times other drugs GIT effect
• Photosensitivity
  – Tacrolimus, Bactrim, voriconazole
  – Skin protection and avoidance long direct sunlight exposure
Pharmacodynamics

- Neuropsychological deficits and lower cognitive function – mild functional impairment 79% after LT
  - Pre-existing deficits
  - Prolonged exposure developing paediatric brain immunosuppression
NEUROTOXICITY

Minor
- tremor
- headache
- insomnia
- parasthesia

Major
- encephalopathy
- seizures
- polyneuropathy
- Speech disorder
Host immune response: Graft foreign
Destructive T-lymphocyte mediated immune response
Goal immunosuppression

- Inhibit the antigen-induced T-lymphocyte activation and cytokine production
- to interrupt allo-major histocompatibility complex recognition
- or to block effector responses
Accomplish while preserving immunocompetence to maintain adequate host response to infections
Immunosuppressive protocols

- Induction, maintenance, treatment of rejection
- Combination of medications
- Induction immunosuppression
  - Used varying frequency different organs
  - Given at time of transplant to rapidly create a state of immunologic unresponsiveness of the recipient to donor antigens
Induction immunosuppression

1. Induction agent use for pediatric heart, kidney, and liver transplant recipients.

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Acute rejection

- Still occurs in significant number of patients
- Studies of Pediatric Liver Transplantation (SPLIT) registry
  - 1902 patients
  - AR most often first 3 months (45%)
  - 59% at 24 months
  - Less rejection age < 6m and LRD grafts
  - No evidence less rejection episodes better HLA compatibility liver transplant recipients – same protocols
  - Tacrolimus vs cyclosporin less rejection episodes at 6 months, final time of follow up no significance difference
Acute rejection treatment

• Short course high-dose steroids
  – Bolus several days with rapid taper to baseline therapy successful 75-80%
• SPLIT registry: steroid resistant rejection 11%
  – Uncommon
  – Problematic to treat
  – Poly- and monoclonal antibodies, increased risk infection and PTLD
• Refractory / recurrent rejection anti-lymphocytic therapy with poly/monoclonal antibody therapy can be successful
• Bilirubin >10mg/dl – successful control resistant rejection unlikely
• Late acute rejection
  – different prognosis
  – associated low levels immunosuppression and non-adherance
  – Response to steroids suboptimal
  – Increased risk chronic rejection
Immunosuppressive agents
Induction agents

**Polyclonal antibodies**
- Anti-thymocyte globulin

**Monoclonal antibodies**
- Muronomab-CD3
- Basiliximab
- Daclizumab
- Alemtuzumab
ATG (Thymoglobulin)

- Rabbit polyclonal antibody directed against human lymphocytes
- Potent modulator immune response
- 3 Hypotheses mechanism of action
  - Classic complement mediated cell lysis CD2, CD3, CD4, CD8, CD11a, CD25, CD40, CD54
  - Uptake opsonized T cells by RES
  - Modulation essential surface receptors on lymphocytes that remain in circulation but function is blocked
- Create profound lymphocyte depletion (actual or functional)
ATG (Thymoglobulin) Uses

• *Induction agent at time of transplant*
  – Suppress host immune system
  – Allow use CNI several days after transplant
  – CNI side effects exacerbated hemodynamic changes around Tx minimized

• *Steroid resistant rejection*

• *Steroid sparing protocols*
Symptoms ATG administration

- Incidence and severity varied
- Related cytokine release IL1, IL6, TNF
- Cytokine storm
  - Fever, chills, diarrhoea, serum sickness, seizures, anaphylaxis
- Dose dependent thrombocytopenia and leucopenia
- CMV prophylaxis
- CVP – chemical phlebitis
Muronomab CD3 (Orthoclone OKT-3)
- Liver transplantation
- Cytokine release syndrome
- CD3 pos T cells fall 60% to <5% 24-48h
- Voluntarily withdrawn decreased utilization

Basiliximab (Simulect) and daclizumab (Zenepax)
Humanized antibody IL-2 receptor
- Target proliferative T-cell response
- Prevent rejection pediatric Tx patients
- Do not trigger cytokine release syndrome, better tolerated
- Basiliximab induction reduced acute rejection rate after paediatric liver transplant
- Rate steroid refractive and chronic rejection remained the same

Alemtuzumab target CD52 surface protein
- Most recent effective monoclonal Ab adult liver Tx
- Not widely implemented paediatric use
Maintenance of Immunosuppression
Corticosteroids

• First anti-rejection drugs used SOT
• Used varying degrees in most immunosuppressive regimens
Mechanism of action

• Suppress antibody production

• Suppress cytokine synthesis (IL-1, 2, 6, IFN-Υ)

• Bind glucocorticoid receptors in cytoplasm, translocate to the nucleus, decreased proliferation of T cells and B cells
Corticosteroids

• Compromise important role SOT:
  Effective prevention and treatment acute rejection

• Well-known adverse effects children
  – SPLIT study 23% 10 year survivors liver transplant impaired linear growth

• Paediatric programs
  – Steroid withdrawal
  – Steroid minimization
  – Steroid free immunosuppressive protocols
Corticosteroids

2. Steroid use at transplant and 1-year posttransplant for pediatric heart, kidney, and liver transplant recipients.

Other adverse effects

- Increased infection rates
- Osteoporosis
- Metabolic derangements
  - Glucose intolerance
  - Weight gain
- Psychiatric disturbances
Long term steroid therapy

- Avoided
- Current practice of steroid withdrawal variable
  - 3 m, start weaning at 3m or at 12m
- Steroid-free immunosuppressive protocols
  adults promising
  - Most benefit low risk rejection, high risk DM / HT
- Large multicenter trials children lacking
- Clearest contraindication weaning AIH
Calcineurin inhibitors (CNI)

- Cyclosporine and Tacrolimus
- Backbone immunosuppression past 4 decades
- Dramatically improved transplant survival 1980’s
Mechanism of immunological action

• Complex with intracellular proteins
  – Cyclosporin – cyclophilin
  – Tacrolimus – tacrolimus binding protein FKBP12
• Inhibit calcineurin enzyme to dephosphorylate nuclear regulatory elements
• Interfere with production and release IL-2
• IL-2 required T-cell activation and proliferation
• Tacrolimus 100x more potent
Mechanism of action of cyclosporine or tacrolimus (FK506)

Expert Reviews in Molecular Medicine © 2000 Cambridge University Press
• Cyclosporine mainstay immunosuppression 1983
• Tacrolimus following decade – rescue therapy
• Equal controlled trials patient / graft survival
• Tacrolimus more effective preventing acute and steroid-resistant rejection
Benefits Tacrolimus primary immunosuppression

• Superior efficacy in preventing acute and steroid resistant rejection
• Freedom long-term steroid use
  – Allow steroid withdrawal within 1y without adverse effects
• Single agent
  – Cyclosporin in combination MMF / AZA
Tacrolimus primary immunosuppressive agent paediatric SOT

Fig. 3. Calcineurin inhibitor use for pediatric heart, kidney, and liver transplant recipients.

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Both metabolized liver cytochrome P4503A(CYP3A) system

<table>
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<tr>
<th>Increase level (inhibitors)</th>
<th>Decrease level (inducers)</th>
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<tr>
<td>Antifungals (fluconazole, ketoconazole)</td>
<td>Carbamazepine</td>
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<tr>
<td>Calcium channel blockers (verapamil, diltiazem)</td>
<td>Phenobarbital</td>
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<tr>
<td>Erythromycin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Protease inhibitors (ritonavir, indinavir)</td>
<td>Rifampin</td>
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<tr>
<td>Grapefruit juice</td>
<td>St. John’s Wort</td>
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*This table provides examples and not intended to be an exhaustive list.*

Differences metabolism

• Tacrolimus absorption, unlike cyclosporin, not dependent on bile – more effective cholestasis, draining biliary tube should not affect levels

• Both bind to plastic (gastrostomy tubes, feeding tubes, plastic cutlery) – influence levels

• Diarrhoea reduce cyclosporine levels, increase tacrolimus levels – frequent levels to avoid toxicity
Side effects CNIs

- Nephrotoxicity
- Neurotoxicity
- Infection
- Gastrointestinal disturbances
- Tacrolimus: hyperglycemia, DM but lower incidence hyperkalemia, hypercholesterolaemia and hypertension
- Renal impairment most serious complication both – limit use other nephrotoxic agents
Conversion from twice-daily to once-daily tacrolimus formulation in pediatric liver transplant recipients – a long-term prospective study

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SUMMARY

To assess the safety and efficacy of conversion from twice-daily tacrolimus to once-daily tacrolimus in pediatric liver transplant recipients. Conversion from twice-daily to once-daily tacrolimus was made in stable pediatric liver transplant recipients. Doses and serum levels of tacrolimus, liver, and renal function were recorded on the day before the conversion and at days 5, 30, 90, and 180 postconversion. Patients were controlled every 2–3 months thereafter. Fifty-five patients were enrolled in the study. The mean age at conversion was 10.2 ± 3.6 years. The mean tacrolimus trough level was 4.7 ± 1.9 ng/dl preconversion, followed by a significant decline to 4.2 ± 1.7 30 days after the switch (P < 0.004). Mean daily tacrolimus dose was 0.09 ± 0.046 mg/Kg preconversion with a significant increase to 0.11 ± 0.060 3 months postconversion (P < 0.001). Fifteen patients with calculated glomerular filtration rate between 60 to 80 ml/min/m² preconversion showed a significant improvement one and 3 years after the switch (73 ± 4.1, 83 ± 4.3 and 90.3 ± 7.3 ml/min/m², respectively (P < 0.001). The mean follow-up was 5.2 ± 2.4 years. Conversion to once-daily tacrolimus is safe and effective in a cohort of stable pediatric liver transplant patients.

Transplant International 2017;
Mycophenolate mofetil (MMF)

- Converted in liver to active metabolite mycophenolic acid (MPA)
  - Selectively inhibits ionosine monophosphate dehydrogenase
  - Inhibits synthesis guanosine (purine nucleosides)
  - T and B lymphocytes uniquely dependent on for proliferation
  - Selectively inhibits T- and B-cell proliferation and thus antibody formation
MMF

• Pharmacokinetics does not vary with age
• Effectively reduce incidence rejection adults
• Incorporated in paediatric regimens as CNI sparing agent
• Co-agent Tacrolimus pre-existing renal impairment
• GIT side effects: cramping, vomiting, diarrhoea, pancytopenia
• Start low dose and increase if no side effects
Sirolimus

• Macrolide antibiotic produced by *Streptomyces* species isolated Easter Island 1975
• Originally anti-tumor agent
• Bind mTOR receptor, intracellular regulator of protein kinases
• Inhibit IL-2 production and B and T cell activation and proliferation
Sirolimus

- Initially rescue therapy CNI failure
- Subsequently primary immunosuppression
- Associated poor wound healing and hepatic artery thrombosis liver transplant recipients – recent studies no significant differences cohorts
- Not used first several months post transplant
- Anti-tumor proliferative activity – role hepatic tumors
Sirolimus

- Extensively metabolized liver cytochrome P4503A system
- Extremely long half life 62h
- MULTIPLE DRUG INTERACTIONS – toxicity
- Side effects reversible
  - Bone marrow suppression
  - Hyperlipidaemia
  - Athralgia
  - Oral ulcers
  - Interstitial pneumonitis
  - Diarrhoea
Everolimus

- Sirolimus derivative, mTOR inhibitor
- Rescue therapy rejection and renal insufficiency paediatric kidney, heart, liver Tx
- Retrospective cohort 301 paediatric kidney transplant patients decreased 3y incidence CMV disease high risk donor + recipient – pt: possible direct antiviral effects through mTOR inhibition
- Paediatric heart transplant pt everolimus and MMF improvement GFR without increased rejection
- Safety trials needed paediatrics
Everolimus and reduced calcineurin inhibitor therapy in pediatric liver transplant recipients: Results from a multicenter, prospective study

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Abstract
In a 24-month, multicenter, single-arm, prospective study, 56 pediatric liver transplant patients with or without basiliximab induction were converted at 1-6 months post-transplant from standard calcineurin inhibitor (CNI) therapy (± mycophenolic acid), to everolimus with reduced exposure to CNI (tacrolimus n=50, cyclosporine n=6). Steroid therapy was optional. Recruitment was stopped prematurely due to high rates of PTLD, treatment-related serious infections leading to hospitalization and premature study drug discontinuation. Subsequently, patients aged <7 years reverted to local standard-of-care immunosuppression. Mean tacrolimus concentration was above or near the upper end of the maintenance target range (2-5 ng/mL) until after month 6 post-enrollment. The primary variable, mean (SD) change in eGFR from baseline to month 12 (last observation carried forward), was +6.2 (19.5) mL/min/1.73 m\textsuperscript{2}. Two patients experienced treated biopsy-proven acute rejection. No graft losses or deaths occurred. PTLD occurred in five patients (8.9\%) (3/25 [12.0\%] patients <2 years, 2/31 aged 2-18 years [6.5\%]). Adverse events, serious adverse events, and discontinuation due to adverse events were reported in 100.0\%, 76.8\%, and 44.6\% of patients, respectively. In conclusion, everolimus with reduced CNI improved renal function while maintaining antirejection potency in pediatric liver transplant patients but safety outcomes suggest that patients were overimmunosuppressed.
Operational tolerance

“Acceptance of an allograft by a recipient in the absence of maintenance immunosuppression”

- Long sought paediatric SOT – decades immunosuppression
- Liver relatively immunologically permissive – majority studies liver allograft recipients
Complete Immunosuppression Withdrawal and Subsequent Allograft Function Among Pediatric Recipients of Parental Living Donor Liver Transplants

- < 18y age
- Parental LRD allograft >4y
- Stable allograft function 6m
- No features rejection / significant fibrosis on protocol liver biopsy
Complete Immunosuppression Withdrawal and Subsequent Allograft Function Among Pediatric Recipients of Parental Living Donor Liver Transplants

- Gradual withdrawal 36w
- Frequent labs
- Protocol biopsies 4-8 w, 2y, 4y
- 12/20 (60%) off medications 1 year
Remained tolerant without increased graft fibrosis 5y off immunosuppression
Decreased hypertension, Increased GFR
Similar incidence post transplant metabolic syndrome
Operational tolerance is possible

- Highly selected group of paediatric recipients
- Gradual withdrawal immunosuppression

- Ongoing studies
- Identification biomarkers to refine the process
  - Immunophenotypes of circulating blood
  - Peripheral blood signatures of tolerance
- Operational tolerance possibility beyond liver transplantation
Fingerprints of transplant tolerance suggest opportunities for immunosuppression minimization

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this state may be ~8% in kidney allograft recipients, and even more frequent in pediatric recipients and in liver transplantation: 25% in adult liver allograft recipients and ~60% in pediatric liver allograft recipients. In this review we discuss putative molecular mechanisms, cellular players and correlative biomarkers that have been developed through clinically associative studies of tolerant and non-tolerant patients. Through mechanisms of carefully constructed and monitored randomized, prospective clinical trials, the transplant community stands at the cusp of improved quality of recipient life through educated immunosuppression minimization.
Future directions

• Increasing awareness long-term effects of immunosuppression – changes management
• New approaches induction, maintenance and rejection considered widely
• Paediatric late losses all related to immunosuppression
  – Over treating: infection and malignancy
  – Under treating: acute and chronic rejection
Future directions

• New induction therapies should strive to enough immunosuppression to control rejection and protect graft, without added risks of unnecessary immunosuppression like infection and toxicity

• Ultimate goal: induce donor-specific operational tolerance and allow eventual freedom from immunosuppression and long term toxicities
Thank you