Autoimmunity in PIDD
Hematopoietic Cell Transplant in PIDD

Troy R. Torgerson, MD PhD
Associate Professor, Pediatric Immunology/Rheumatology
Director, Immunology Diagnostic Laboratory (IDL)
Co-Director, Non-Malignant Transplant Program
University of Washington & Seattle Children’s Hospital

Topics

1. Autoimmunity
   A. Theoretical
   B. Practical

2. Hematopoietic Cell Transplant (HCT)
   A. Theoretical
   B. Practical
Immune Dysregulation

A clinical disorder that occurs when normal mechanisms for maintaining immune homeostasis are either absent or are overcome/overwhelmed thus leading to an inappropriate immune response that causes damage to host cells in the form of autoimmunity or inflammation.

Spectrum of Immune Defects

<table>
<thead>
<tr>
<th>PIDD:</th>
<th>PIDD:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections Dominant</td>
<td>Autoimmunity/Autoinflammation Dominant</td>
</tr>
<tr>
<td>May have autoimmunity/autoinflammation</td>
<td>May have infections</td>
</tr>
<tr>
<td>- CVID – Bowel, Lungs, Liver, Skin, etc.</td>
<td>- STAT1-GOF – CMC, Mycobacteria</td>
</tr>
<tr>
<td>- CGD – Bowel, etc.</td>
<td>- CGD – Bowel</td>
</tr>
<tr>
<td>- WAS – Vasculitis, etc.</td>
<td>- WAS – Vasculitis, etc.</td>
</tr>
</tbody>
</table>
Universe of PIRD Disorders

Debris Defects
- Complement deficiency
- Phagocyte Defects
- Interferonopathies
  - DNAse I
  - TREX1 Complex
  - IFIH1/MDA5
  - STING

HLH
- SH2D1A, XIAP
- PRF1
- Degranulation Defects
  - MUNC13-4
  - RAB27A
- LYST
- Signaling
  - ITK
  - MAGT1
- STAT1-GOF

Autoinflammatory
- TRAPS (TNFRSF1A, TNFRSF11A)
- CAPS (NLRP3)
- FMF (MEFV)
- CANDLE – Proteosome-opathies
- DADA2
- DIRA – IL-1 pathologies

Congenital Hypersensitivity Syndromes
- PGM3
- STAT5-GOF
- JAK1-GOF

Treg-Opathies
- IPEX (FOXP3)
- IPEX-Like
  - CD25
  - STAT5B
  - hCTLA4
  - LRBA
  - STAT1-GOF
  - STAT3-GOF
  - IL10R1/2
  - Etc.

HLH
- Infant Onset-IBD
- VEO-IBD
- EO-IBD

Rheumatologic Dz
- JIA, SoJIA, Etc.
- Lupus
- Scleroderma

Non-Malignant Lymphoproliferation
- ALPS (FAS, FASL, etc.)
- ALPS-Like/ALPS-U
  - STAT3-GOF
  - hCTLA4
  - PIK3CD/PIK3R1, etc.
  - RALD

IPEX & IPEX-Like Genotyping

IPEX:
- FOXP3

IPEX-like:
- STAT1-GOF
- STAT3-GOF
- STAT5B
- CTLA4 Haploinsufficiency
- LRBA
- CD25
- TTC37
- TTC7A
- RAG1/2
- DOCK8
- IL10RA/RB
- TNFAIP3
- CARD11
- MYO5B

34% of patients in IPEX-like cohort
Genotypic/Phenotypic Overlap

Leaky SCID / CID

GI Structure / Function

TTC37
MYO5B
TTC7A
RAG1/2
CD25
DOCK8
STAT5B

FOXP3

IPEX
IPEX-Like

LRBA
STAT1-GOF
hCTLA4
STAT3-GOF

CVID
ALPS

Regulatory T Cell Axis

APECED (AIRE)

Treg Generation

GITR
CD25
CD4
CD103
FOXP3
Treg

IPEX (FOXP3)

STAT1-GOF
STAT3-GOF

hCTLA4
LRBA

Treg

Teff

IL-10
IL10RA/RB

TGF-β

Treg Suppression

Treg

Treg

Treg

Treg

Treg

Treg

Treg Expansion, Maintenance, Activation

CD25
STAT5B
Secondary Immune Dysregulation
Checkpoint Inhibition

Topics

1. Autoimmunity
   A. Theoretical
   B. Practical

2. Hematopoietic Cell Transplant (HCT)
   A. Theoretical
   B. Practical
Organ Involvement & Management

• **Heme** – AIHA, ITP, Autoimmune Neutropenia.
• **GI** – Enteropathy, Liver
• **Lungs** – LIP, Follicular bronchiolitis, Granulomas
• **Skin** – Eczema, Psoriasis, Pemphigus nodularis
• **Endocrine** – Thyroiditis, Type I DM, Other

Comparison - B Cell Directed Therapy

Old Standby’s:
- Steroids
- Cyclophosphamide
- High-dose IVIG

Blys/BAFF

Anti-CD22

Anti-CD20

Pro-B cell

Pre-B cell

B cell

Plasma cell

Expression of RAG1 and RAG2
**Time to Response – Rituximab**

*Annals of Internal Medicine*

Systematic Review: Efficacy and Safety of Rituximab for Adults with Idiopathic Thrombocytopenic Purpura

Donald M. Arnold, MD, MSc; Francesco Dentali, MD; Mark A. Crowther, MD, MSc; Ralph M. Meyer, MD; Richard J. Cook, PhD; Christopher Sigounis, MSc; Graeme A. Fraser, MD; Wendy Lim, MD, MSc; and John G. Kelton, MD

**Table 3. Time to Response, Response Duration, and Follow-up of Patients with Idiopathic Thrombocytopenic Purpura Treated with Rituximab**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median</th>
<th>Interquartile Range</th>
<th>Range</th>
<th>Contributing Reports (Patients), n (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to response, wk</td>
<td>5.5</td>
<td>3.0-6.6</td>
<td>2.0-18.0</td>
<td>6 (123)</td>
</tr>
<tr>
<td>Response duration, mo</td>
<td>10.5</td>
<td>6.3-17.8</td>
<td>3.0-20.0</td>
<td>16 (252)</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>9.5</td>
<td>6.0-21.3</td>
<td>2.0-25.0</td>
<td>10 (187)</td>
</tr>
</tbody>
</table>


---

**Time to Response – Rituximab**

*Acta Derm Venereol 2015; 95: 928–932*

**SPECIAL REPORT**

**Efficacy of Rituximab for Pemphigus: A Systematic Review and Meta-analysis of Different Regimens**

Hsiang-Han WANG1, Chieh-Wei LIU1, Yu-Chuan LI1 and Yu-Chen HUANG3

1Department of Dermatology, Wen Fang Hospital, Taichung Medical University, and 3Department of Surgery, Cathay General Hospital, Taipei, Taiwan

**Table 1. Key issues**

1. Rituximab is efficacious and well-tolerated in patients with pemphigus.
2. Complete remission rate after 1 cycle of Rituximab was 76% (Mean time to complete remission was 3.8 months, complete remission duration 14.5 months and overall relapse rate 40%). Eighteen patients (3.3%) developed major adverse effects.
3. High-dose (≥2,000 mg) Rituximab was associated with longer complete remission compared with low-dose Rituximab (<1,500 mg).
4. No significant difference in time to complete remission, complete remission or relapse rates between the high-dose and low-dose Rituximab. No superiority of lymphoma protocol over rheumatoid arthritis in all outcomes.
5. Immunoadsorption combined regimens resulted in the fastest control of disease before completion of Rituximab therapy.
6. Choice of optimal regimen may depend on the overall condition of the individual patient.
Comparison - B Cell Directed Therapy

Old Standby’s:
• Steroids
• Cyclophosphamide
• High-dose IVIG

Bortezomib

- An N-protected di-peptide with a boronic acid instead of carboxylic acid at C-term
- Given IV on days 1, 4, 8, and 11 of a 21 day cycle – 8 cycles for MM
- Short half-life: 9-15 hours
- Side effects: Peripheral neuropathy in 30%, myelosuppression (neutropenia, thrombocytopenia), Shingles.
Comparison - B Cell Directed Therapy

Old Standby's:
- Steroids
- Cyclophosphamide
- High-dose IVIG

Bly/BAFF

Anti-CD20

Anti-CD22

Bortezomib

Plasmapheresis

Eculizumab

Classical Pathway (Immune Complexes)

Lectin Pathway (Pathogen Oligosaccharides)

Alternative Pathway (Pathogen Surfaces)

C1q C1r C1s

C2 C4

MBL MASP

C3b

Factor B Factor D

Membrane Attack Complex (MAC)

Complement Proteins (MAC)
Organ Involvement & Management

- **Heme** – AIHA, ITP, Autoimmune Neutropenia.
- **GI** – Enteropathy, Liver
- **Lungs** – LIP, Follicular bronchiolitis, Granulomas
- **Skin** – Eczema, Psoriasis, Pemphigus nodularis
- **Endocrine** – Thyroiditis, Type I DM, Other

General Management

Be aggressive about supportive care!!

Get tissue whenever possible – you learn a lot from the pathology – Inflammatory vs. Autoimmune.
Nodular Lymphoid Hyperplasia

• Watery diarrhea
• Often quite responsive to steroids – can use non-absorbable
• Responsive to Rapamycin

General Management (Cont.)

Nutrition (Cont.):
• Check nutrition labs early – Electrolytes, Ca++, Mg++, Phos, Zinc, Micronutrients, Albumin, Pre-Albumin, AST/ALT, Clotting (Vit. K).
• You might need to enlist the help of a nutritionist – ask for consultation.
• Ask diet questions and try a change in diet (Cow- or soy-based formulas ➔ partially digested or elemental formula).
General Management (Cont.)

Nutrition (Cont.):

• Some patients just don’t tolerate oral feeds – profuse diarrhea or vomiting. Start TPN and put patient on full bowel rest if needed.

• If patients are severely malnourished, sometimes improving nutritional status alone with parenteral nutrition will allow them to re-grow villi and begin to absorb so enteral feeds can be re-started.

Organ Involvement & Management

• **Heme** – AIHA, ITP, Autoimmune Neutropenia.

• **GI** – Enteropathy, Liver

• **Lungs** – LIP, Follicular bronchiolitis, Granulomas

• **Skin** – Eczema, Psoriasis, Pemphigus nodularis

• **Endocrine** – Thyroiditis, Type I DM, Other
**Follicular Bronchiolitis & Granulomas**

Light microscopy: Expansion of alveolar septa by multifocal dense nodular and diffuse interstitial infiltrates composed of mature lymphocytes and plasma cells. Multiple lymphoid aggregates with active germinal centers also seen.

**Lymphoid Follicles**

Adriano Aguzzi, Mario Nuvolone & Caihong Zhu

*Nature Reviews Immunology* 13, 888–902 (2013)
Rituximab in CVID GLILD

Use of Combination Chemotherapy for Treatment of Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD) in Patients with Common Variable Immunodeficiency (CVID)

Key Point:
• Lung biopsy is essential to make sure you know what you are dealing with
• Rituximab + Azathioprine

Organ Systems

- **Heme** – AIHA, ITP, Autoimmune Neutropenia.
- **GI** – Enteropathy, Liver
- **Lungs** – LIP, Follicular bronchiolitis, Granulomas
- **Skin** – Eczema, Psoriasis, Pemphigus nodularis
- **Endocrine** – Thyroiditis, Type I DM, Other
Common Skin Diseases

Initial Management

Aggressive Supportive Care:

- Nutritional support, Parenteral nutrition if needed
- Topical therapies – involve wound care/burn team if needed
- May need systemic therapy – Rituximab (Pemphigus), Others
**Organ Systems**

- **Heme** – AIHA, ITP, Autoimmune Neutropenia.
- **GI** – Enteropathy, Liver
- **Lungs** – LIP, Follicular bronchiolitis, Granulomas
- **Skin** – Eczema, Psoriasis, Pemphigus nodularis
- **Endocrine** – Thyroiditis, Type I DM, Other

**Follicular Inflammation – IPEX Pancreas**
Initial Management

Aggressive Supportive Care:

- Nutritional support, Parenteral nutrition if needed
- Insulin, Thyroid hormone, etc.
- Consider systemic therapies – Tacrolimus, Rapamycin, Rituximab, etc.

Targeted Treatments

Immunosuppression –

*Seems counterintuitive/uncomfortable*

*Be as targeted as possible*

*Watch for side effects*

- Cyclosporine, FK506, Sirolimus (IPEX, CTLA4-h, etc.)
- CTLA4-Ig (LRBA, CTLA4-h)
- JAK inhibitors (STAT1-GOF, STAT3-GOF, Interferonopathies, etc.)
- PI3 Kinase Inhibitors (PIK3CD, PIK3R1 - ????)
- Others
CTLA-4 Haploinsufficiency - Clinical Phenotype

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea/enteropathy</td>
<td>11/14 (78%)</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>10/13 (77%)</td>
</tr>
<tr>
<td>Granulomatous lymphocytic interstitial lung disease</td>
<td>8/12 (66%)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>8/14 (57%)</td>
</tr>
<tr>
<td>Organ infiltration (bone marrow, kidney, brain, liver)</td>
<td>7/14 (50%)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>6/12 (50%)</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia</td>
<td>5/14 (35%)</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>4/14 (28%)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>4/14 (28%)</td>
</tr>
<tr>
<td>Psoriasis and other skin diseases</td>
<td>3/14 (21%)</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>2/13 (15%)</td>
</tr>
<tr>
<td>Autoimmune arthritis</td>
<td>2/14 (14%)</td>
</tr>
<tr>
<td>Solid cancer</td>
<td>1/14 (7%)</td>
</tr>
</tbody>
</table>

T cell Co-Stimulation – Signals 1, 2, 3

Signal #1: Antigen presentation

Signal #2: Co-stimulation

Signal #3: Inflammatory cytokines

IFN-α/β, IL-12, IL-1

APC

MHC molecule

Antigenic peptide

T cell receptor (TCR)

CD28

CD80/86

T cell
STAT1-GOF

- Chronic Mucocutaneous Candidiasis (CMC)
- Cutaneous Staph infections (less common)
- Mycobacterial or other fungal infections (less common)
- Autoimmunity (enteropathy, endocrinopathies (thyroiditis or diabetes), eczema, etc. – IPEX-like)

Modified from Schindler, C.
**STAT1-GOF Disease**

**Treatment:**

Jakafi (Ruxolitinib – JAK 1/2 inhibitor) highly effective in anecdotal cases. Not much pediatric dosing guidance. Usual adult dose is 20 mg po BID. Thrombocytopenia most common side effect. Risk for Herpes viral infections.

---

**IL-10 Receptor Deficiency**

**IL10 Receptor Deficiency**

- Mutations identified in both IL10R1 (2 patients) and IL10R2 (2 patients)
- Bone marrow transplantation effective
- Other immunosuppressants ineffective

**IL10 Deficiency**

- 2 unrelated patients with a similar clinical phenotype but lacking mutations in IL10R1 or IL10R2
- Bone marrow transplantation effective
BMT for IL-10 Receptor Deficiency

PRE

D+10

D+30

D+100

Treatment of IL-10R Deficiency with IL-1 Blockade

Pre-anakinra

Post-anakinra
Summary

1. Autoimmunity is the dominant feature of PIRDs and is common in PIDDs
2. Need to treat autoimmunity and inflammation aggressively – Uncomfortable!
3. If you can find a genetic defect – targeted therapies are available.

Topics

1. Autoimmunity
   A. Theoretical
   B. Practical

2. Hematopoietic Cell Transplant (HCT)
   A. Theoretical
   B. Practical
Hematopoietic Cell Transplant – The 5 Key Things to Know

- **Conditioning Regimen** – Drugs, Radiation (TBI), Antibodies (ATG, Alemtuzumab, etc.)
- **Donor Source** – MRD, MUD, MMRD, Cord, etc.
- **Graft Type** – Bone marrow vs. PBSC
- **Graft Manipulation** – T cell depletion, CD34 selection, *in vivo* Cytoxan, etc.
- **GvHD Prophylaxis** – Tacrolimus, Rapamycin, MTX, MMF, etc.

### Conditioning Regimens

1. No Conditioning – mostly SCID
2. Minimal Intensity Conditioning (MIC)
3. Reduced Intensity Conditioning (RIC)
4. Myeloablative Conditioning (MAC)
Conditioning Regimen Intensity

No Conditioning
2 Gy TBI Fludarabine
4 Gy TBI Fludarabine
Treosulfan Fludarabine
Treosulfan + Fludarabine + ATG
Treosulfan + Fludarabine + ATG + 2-3 Gy TBI
Busulfan Cyclophosphamide ATG

TBI = Total Body Irradiation
ATG = Anti-Thymocyte Globulin

Immunosuppressive intensity
Myeloablative intensity (Regimen Toxicity)

Donor Source

1. Matched Related Donor (MRD)*
1. Matched Unrelated Donor (MUD)*
2. Cord Blood Donor (Cord)
   **Need more aggressive conditioning
3. Haploidentical Donor (Haplo / MMRD)

*Bone Marrow vs. PBSC
Topics

1. Autoimmunity
   A. Theoretical
   B. Practical

2. Hematopoietic Cell Transplant (HCT)
   A. Theoretical
   B. Practical

Transplant – Burning Questions

• When do I transplant (Timing)?
• How do I transplant (Regimen)?

• Disease and complication specific
• Changes with new data & experience
• Outcomes often poor to moderate in first experience & reports
Timing of Transplant - CGD

287 patients from 244 kindreds

Residual NADPH Oxidase and Survival in Chronic Granulomatous Disease

Douglas B. Kuhns, Ph.D., W. Gregory Ahord, Ph.D., Theo Heller, M.B., Ch.B., Jordan J. Feld, M.D., M.P.H., Kristen M. Pike, M.S., Beatriz E. Marciano, M.D., Gulhus Uzel, M.D., Suk See DeFazio, M.D., Ph.D., Debra A. Long Pron, M.S., Benjamin P. Soule, M.D., Kol A. Zarember, Ph.D., Harry L. Malech, M.D., Steven M. Holland, M.D., and John J. Gallin, M.D.

NEJM 363:2600-10 (2010)
Seattle Approach to IPEX HCT

Matched Related or Unrelated Donor

- Few Comorbidities
  - IPEX
    - Treo/Flu/rATG (RIC/RT-MAC)
    - BM or PBSC
  - Flu/4 Gy TBI (MIC)
    - PBSC

Significant Comorbidities

Alternative donor: Cord vs Haplo

Conditioning Regimen
U.S. Treosulfan Study: BM/PBSC

- FLU 150 mg/m²
- TREO 42 g/m²
- BM or PBSC
- rATG 6 mg/kg
- Methotrexate
- Tacrolimus
### IPEX - Treosulfan-Based HSCT (n=10)

<table>
<thead>
<tr>
<th>Cell Source</th>
<th>% Chimerism</th>
<th>GVHD</th>
<th>Clinical Response</th>
<th>F/U (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM</td>
<td>100 CD3</td>
<td>Acute</td>
<td>-</td>
<td>Remission</td>
</tr>
<tr>
<td>BM</td>
<td>100 CD3</td>
<td>Chronic</td>
<td>-</td>
<td>Remission*</td>
</tr>
<tr>
<td>BM</td>
<td>98 CD3</td>
<td>II</td>
<td>-</td>
<td>Remission*</td>
</tr>
<tr>
<td>BM</td>
<td>100 CD3</td>
<td>-</td>
<td>-</td>
<td>Remission</td>
</tr>
<tr>
<td>BM</td>
<td>100 CD3</td>
<td>-</td>
<td>-</td>
<td>Remission</td>
</tr>
<tr>
<td>BM</td>
<td>93 CD3</td>
<td>II</td>
<td>-</td>
<td>Remission</td>
</tr>
<tr>
<td>BM</td>
<td>32 CD3</td>
<td>-</td>
<td>-</td>
<td>Remission*</td>
</tr>
<tr>
<td>BM</td>
<td>5 CD3</td>
<td>II</td>
<td>Rejection s/p 2nd BMT</td>
<td>&gt;7</td>
</tr>
<tr>
<td>DCB</td>
<td>96 CD3</td>
<td>III</td>
<td>+</td>
<td>Remission*</td>
</tr>
<tr>
<td>CB</td>
<td>60 CD3</td>
<td>III</td>
<td>-</td>
<td>Remission</td>
</tr>
</tbody>
</table>

* Persistent IDDM

### Conclusions:

**Treosulfan-Based Approach**

- Well tolerated with low regimen related toxicity
  - 9/10 alive
- Successful engraftment
- Low incidence of severe acute & cGVHD
- Disease responses seen in majority of patients
  - Full donor chimerism is not required
- Late effects research needed
Seattle Approach to IPEX HCT

Matched Related or Unrelated Donor

- Few Comorbidities
  - IPEX
  - Treo/Flu/rATG (RIC/RT-MAC)
  - BM or PBSC

- Significant Comorbidities
  - Flu/4 Gy TBI (MIC)
  - PBSC

Alternative donor: Cord vs Haplo

Nonmyeloablative Approach

Flu/2-4 Gy TBI (n=5)

- IPEX (n=5)
- Median age 17 (range, 0.8-28) years
- Conditioning/Stem Cell Source:
  - Flu/2 Gy TBI: MRD Cord Blood (n=1)
  - Flu/4 Gy TBI: MRD BM (n=1), MURD PBSC (n=3)
- GVHD Prophylaxis:
  - CSP/MMF (n=4)
  - Sirolimus/MMF (n=1)
## Nonmyeloablative Approach

**Flu/2-4 Gy TBI (n=5)**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Donor</th>
<th>% Chimerism</th>
<th>GVHD Acute</th>
<th>GVHD Chronic</th>
<th>Clinical Response</th>
<th>F/U (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>MRD Cord</td>
<td>1</td>
<td>84</td>
<td>N/A</td>
<td>N/A</td>
<td>Rejection s/p 2nd BMT</td>
</tr>
<tr>
<td>17</td>
<td>MRD BM</td>
<td>33</td>
<td>60</td>
<td>II</td>
<td>-</td>
<td>Remission*</td>
</tr>
<tr>
<td>0.8</td>
<td>MUD PBSC</td>
<td>99</td>
<td>100</td>
<td>II</td>
<td>+</td>
<td>Remission*</td>
</tr>
<tr>
<td>24</td>
<td>MUD PBSC</td>
<td>99</td>
<td>100</td>
<td>III</td>
<td>+</td>
<td>Remission</td>
</tr>
<tr>
<td>28</td>
<td>MUD PBSC</td>
<td>73</td>
<td>100</td>
<td>III</td>
<td>+</td>
<td>Remission*</td>
</tr>
</tbody>
</table>

Persistent IDDM: Burroughs, et. al, BMT 2007 & JACI 2010

## Conclusions:

**Nonmyeloablative Approach**

- Reasonable approach for high-risk patients unable to tolerate more aggressive conditioning
- Full donor chimerism not required for disease amelioration
- Low toxicity/mortality in high-risk patients
- GVHD remains a challenge
HCT for CTLA4 Haploinsufficiency

- 8 patients (Newcastle & Seattle)
- Male: 5  Female: 3
- Age at transplant 10-32 years
- Mutation known in 1 patient at transplant
- MIC & RIC regimens
- 6 of 8 alive and well – disease in remission
- 2 deaths – DKA & GvHD


HCT for STAT1-GOF

- 15 patients (Worldwide)
- Male: 9  Female: 6
- Age at transplant 1-33 years
- Mutation known in 1 patient at transplant
- RIC & MAC regimens
- MUD, MRD, and Cord donors
- 6 of 15 alive and well – disease in remission
- 8 of 15 with primary or secondary graft loss
- Death due to infections & HLH (2 pts). IPEX-like phenotype had best outcomes

HCT for STAT3-GOF

- 12 patients (Worldwide)
- Male: 5  Female: 7
- Age at transplant 1.5-20 years
- Mutation known in 3 patients at transplant
- RIC & Reduced toxicity MAC regimens
- 7 of 12 alive and well – disease in remission but no improvement in growth
- 5 deaths – Infections & GvHD

Forbes L et al., Blood submitted (2017)

HCT for LRBA Deficiency

- 12 patients (European)
- Age at transplant 3-15 years
- Mutation known in 3 patients at transplant
- Various RIC regimens
- 8 of 12 alive – 3 in complete remission, 3 in good partial remission of IS, 2 in partial remission on IS.
- 4 deaths – All early (infections?)

HCT for CVID

- 25 patients (European)
- Age at transplant 8-50 years
- Mutation known in 3 patients at transplant
- RIC & MAC regimens
- Overall survival 48%, survival if transplant for lymphoma 83%.
- 13 deaths – 9 infections, 2 cGvHD, 1 VOD, 1 lymphoma recurrence.


Summary

1. Transplant is a viable option for many PIDD & PIRD disorders
2. Timing of transplant remains a challenge for most diseases
3. Many unanswered questions regarding best regimen, pre-transplant immune suppression, etc.
# Acknowledgements

**Torgerson Lab Core Team**  
Stacey Rylaarsdam  
Jesus Lopez-Guisa  
Gesmar Segundo  
Sandro Perrazio  
Stephanie Anover  
David Hagin  
Sarah Baxter

**Key Contributors**  
Lauri Burroughs  
Jennifer Leiding  
Lisa Forbes  
Jennifer Heimall  
Satoshi Okada  
Tomohiro Morio  
Tiphanie Vogel  
Mary Slatter  
Andy Gennery  
Tom Walsh  
Liliana Bezrodnik  
Mikko Seppänen