How I Treat ALPS

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Disclosures for David T. Teachey

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<td>Employee</td>
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Presentation includes discussion of the following off-label use of a drug or medical device: Sirolimus (Rapamycin, Rapamune), mycophenolate mofetil (cellcept)
Autoimmune Lymphoproliferative Syndrome (ALPS)

- Disorder of disrupted lymphocyte homeostasis
- Defects in Fas apoptotic pathway
  - Abnormal lymphocyte survival
  - Chronic lymphoproliferation
  - Autoimmune manifestations
  - Secondary malignancies
Old diagnostic criteria

• Mandatory
  – Lymphoproliferation
  – Elevated DNTs
  – Defective Fas mediated apoptosis

• Supporting
  – Autoimmunity
  – Neoplasia
  – Genetic mutation
Clinical Findings: ALPS

- Lymphoproliferation 100%
  - Chronic (> 6 months)
  - Adenopathy and/or splenomegaly
  - Median age 11.5 months
  - No constitutional symptoms
  - May improve or worsen with infection
  - Often worsens at puberty
  - Often improves in young adulthood
Clinical Findings: ALPS

- Autoimmune Hematologic  75%
  - Usually presents after lymphoproliferation
  - Less likely to “burn out”

- Other Autoimmune  10-20%
  - Similar to SLE: Any organ system

- Neoplasia  ?? (10%)
  - EBER+ NHL and HD
  - Increased risk unaffected family members
Double Negative T cells

- CD 3+
- CD 4,8-
- TCR a/b +
- Normal persons <1% (but laboratory dependent)
Fas Apoptosis Assay
Fas Apoptosis Assay

A

- Untreated
- Anti-Fas
- Ceramide
- Dexamethasone

B

- Untreated
- Anti-Fas
- Ceramide
- Dexamethasone
ALPS: genetics

- ALPS-FAS (formally Ia) (~70%)
  - TNFRSF6 germline
- ALPS-sFAS (formally Im) (~10%)
  - TNFRSF6 somatic
- ALPS-FASLG (formally Ib) (<1%)
  - TNFSF6
- ALPS-CASP10 (formally II) (~2%)
  - Caspase 10
- ALPS-U (formally III) (~20%)
  - No known mutated gene
- ALPS-like
  - CEDS and RALD
Evans Syndrome

- Characterized 1951
- R.S. Evans
- Patients with multiple autoimmune cytopenias
- Diagnosis of exclusion
- Can have lymphoproliferation and secondary malignancies
- We hypothesized a number of patients with Evans have ALPS
ALPS vs Evans Syndrome

DNTs

0% 2% 4% 6% 8% 10% 12%

Patient ID

0% 2% 4% 6% 8% 10% 12%

2.6%

18 13 39 11 6 5 2 44 3 1 38 33 17 43

DNTs

Normal  Defective
ALPS vs Evans syndrome

- ALPS assay negative
- ALPS assay positive

Sensitivity 100%
Negative predictive value 100%
Specificity 95%
Positive predictive value 93%
## 2010 Revised Diagnostic Criteria

### Required Criteria

- Chronic non-malignant lymphoproliferation
- Elevated peripheral blood DNTs (>=1.5% of total lymphocytes or 2.5% of CD3+ cells)

### Accessory Criteria

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<th>Primary</th>
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<tr>
<td>- Defective lymphocyte apoptosis</td>
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<td>- Somatic or germline pathogenic mutation in FAS, FASLG, CASP10</td>
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<th>Secondary</th>
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<tr>
<td>- Elevated plasma sFASL (&gt;200pg/ml) OR vitamin B12 (&gt;1500ng/L) OR IL-10 (&gt;20pg/ml) OR IL-18 (&gt;500pg/ml)</td>
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<td>- Immunohistologic findings on tissue</td>
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<td>- Autoimmune cytopenias &amp; elevated IgG</td>
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<td>- Positive family history</td>
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### Diagnosis

**Definitive**: Required plus a primary accessory

**Probable**: Required plus a secondary accessory
Multi-lineage autoimmune cytopenias

- ALPS
- SLE
- CVID
- Evans

Therapies:
- Steroids
- IVIgG
- Rituximab
- MMF
- Sirolimus
- MTX
- Cytoxan
- Rituximab
What I do

- Patients with chronic single lineage or multiple lineage autoimmune cytopenias
  - Flow cytometry for double negative T cells (ALPS)
  - ANA (SLE)
  - Anti-phospholipid antibodies
  - Quantitative immunoglobulins (CVID)
    - Consider specific antibody titers (CVID)
  - T cell subsets (CD3/CD4, CD3/CD8)
  - HIV (adolescents)
Treatment

- Primarily directed at autoimmune manifestations
- Occasionally organ compromise from bulky lymphadenopathy
- First line treatments
  - Corticosteroids
  - IVIgG

- Second Line Treatments: Avoid
  - Rituximab
  - Splenectomy
Treatment

- **Second Line Treatments**
  - Mycophenolate mofetil
    - 12/13 patients with refractory cytopenias responded
    - 26/30 patients in follow-up study
    - Many partial response
    - No change in lymphoproliferation
    - Many relapsed
  
  - Sirolimus
  
  - Fansidar (Pyrimethamine/Sulfadoxine)
    - 6/7 patients with refractory cytopenias or toxicity from corticosteroids responded
    - F/U study NIH: Did not work
  
  - BMT
mTOR inhibitors

- Sirolimus (Rapamycin)
- Initially developed as anti-fungal
- Found to have immunosuppressive and antiproliferative properties
- Well tolerated
- Hypothesis: mTOR Inhibitors may be effective in ALPS
  - Induces apoptosis in B and T lymphocytes
  - Aberrant mTOR signaling found in a number of lymphoid diseases
- Effective in lymphoid malignancies
PI3K/Akt/mTOR signaling pathway
Sirolimus in MRL-\textit{lpr} mice

- Tx Day 0
- Tx Day 28
- Control Day 0
- Control Day 28
Sirolimus effective in human ALPS

Week 0 = sirolimus started
Arrows = steroids stopped
Sirolimus effective in human ALPS
Sirolimus decreases DNTs

[Graph showing comparison of DNTs before and after treatment with Sirolimus.]

- Pre-Treatment
- On Treatment with Sirolimus

Percent DNTs%
Sirolimus for children with ALPS

- > 40 children treated worldwide
  - By report majority CRs (BUT NOT ALL)
- 15 children treated on study at CHOP
- Ages at enrollment: 18 months to 19 years
- Indication for treatment:
  - Autoimmune cytopenias
    - 10 patients: CR
  - Other autoimmunity
    - 2 patients: 2 PRs
  - Lymphoproliferation
    - 3 patients: 2 CR, 1 NCR
- Overall responses
  - Autoimmune cytopenias: 15 CR
  - Lymphoproliferation: 11 CR, 3 NCR, 1 NR
Sirolimus for children with ALPS

- **Side effects:** Mild
  - Mucositis, hyperlipidemia, HA, diarrhea
  - Mucositis
    - Typically worst during first month and goes away
  - Hypertriglyceridemia
    - Treat with fish oil
  - Hypercholesterolemia
    - Crestor preferred as no drug-drug interactions and may improve triglycerides too

- **Goal sirolimus trough 5-15 ng/ml (Daily dosing)**
- **Watch for drug-drug interactions**
### Laboratory Monitoring

<table>
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<tr>
<th>Laboratory Monitoring</th>
<th>Baseline and first 6 months</th>
<th>Long term</th>
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<tr>
<td>CBC, retic</td>
<td>Weekly if weaning off other medicine. Otherwise every 2 weeks until improvement and then every 4-8 weeks</td>
<td>As clinically indicated. Minimum every 3 months</td>
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<tr>
<td>BMP, LFTs</td>
<td>Baseline, 2 weeks after starting, then monthly</td>
<td>As clinically indicated. Minimum every 3 months</td>
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<tr>
<td>Cholesterol/triglycerides</td>
<td>Baseline then monthly</td>
<td>As clinically indicated. Minimum every 3 months</td>
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<tr>
<td>Trough Sirolimus level</td>
<td>Day 3-5, Day 7-10 and twice weekly until therapeutic then monthly</td>
<td>Every 3 months AND with any medication change</td>
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<tr>
<td>Quantitative immunoglobulins (IgG, A, M)</td>
<td>Baseline and every 2-3 months</td>
<td>Every 6 months</td>
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<tr>
<td>T cell subsets (CD3/4, CD3/8)</td>
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Sirolimus: ALPS sFAS

- 11 yo female dx somatic ALPS
- Presented 1 year of age
  - Profound autoimmune cytopenias
  - Massive Lymphoproliferation
  - Off and on steroids, VCR, Fansidar
  - Lymphopenic: Chronic IVIgG
- 2007: Started MMF
  - Marked improvement in cytopenias
  - NO change DNTs
  - NO change lymphoproliferation
  - Remains lymphopenic on IVIgG
Sirolimus: ALPS sFAS

- 2010: Splenomegaly worsening
  - Hg: 8-11gm/dl; Plt 30-80,000/mm3; ANC 500-1000/mm3; ALC <500/mm3
  - Sirolimus
    - Within 3 weeks: Normal WBC, ANC, Hg, plt, retic for first time since 1 year of age
    - Within 4 weeks: Marked reduction in splenomegaly
    - DNTs: cellcept: 20.8%; week 4 sirolimus 4.2%
    - Within 8 weeks: Resolution of lymphopenia
    - Spaced off IVIgG, including normal response to revaccination
  - Somatic variant – possibility of cure?
Picture tells a 1000 words
MTIs: ALPS vs non-ALPS
mTOR signaling activated in DNTs
How I Treat ALPS

1. **Prednisone**
   - 1 mg/kg BID

2. **Mycophenolate mofetil**
   - 600 mg/m² BID
   - Intolerant or refractory (moderate disease)

3. **Sirolimus**
   - 2 mg/m² daily (goal trough 5-15 ng/ml)
   - Intolerant or refractory

4. **3rd LINE**
   - Vincristine 1.5 mg/m² weekly, or
   - Methotrexate 20 mg/m² weekly or
   - Mercaptopurine 75 mg/m² daily or
   - Pyrimethamine/sulfadoxine 12.5-25mg/250-1000mg weekly
   - Intolerant or refractory

5. **4th LINE**
   - Rituximab 375 mg/m² weekly
   - Splenectomy
   - Combination therapy

6. **Intolerant or refractory (severe disease)**
Important points/Summary

- Diagnostic criteria recently changed
- If concerned for ALPS
  - Screening: DNTs, vitamin B12, IgG
  - Confirmation (If needed)
    - FAS mutation analysis – if negative then
    - Cytokines, sFASL – if negative then
    - Consider somatic FAS mutation analysis – if negative then
    - Consider FASL, CASP10, apoptosis assay
Important points/Summary

- **ALPS treatment**
  - Avoid chronic corticosteroids
  - Avoid rituximab
  - Avoid splenectomy
  - MMF and sirolimus agents of choice
Thanks

- Stephan Grupp
- Catherine Manno
- Alix Seif
- Jack Bleesing
- Koneti Rao
- Kathleen Sullivan
- Jim Bussel
- Susan Travis
- John K. Choi
- Kim Smith-Whitley
- Steve Reiner
- John Maris
- Shannon Maude
- Tiffaney Vincent
- Junior Hall
- Theresa Ryan
- Dan Wechsler

Grant Support

- NIH
- Partnership for Cures
- Goldman Philanthropic Partnership
- Rockefeller Brothers
- Larry and Helen Hoag Foundation
- ASCO
- Leukemia and Lymphoma Society
- United States Immunodeficiency Network
- Foerder-Murray
- Longest Day of Golf