Emerging Medical Therapies for Vascular Anomalies:

*Is Sirolimus the New Propranolol?*

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Disclosures

• No financial conflicts of interest related to content
• Off-label use of medications
Outline

• From case report to practice change
• Lessons from propranolol use
• Lessons from NEJM case reports
• Goals for medical therapies
• Sirolimus for vascular anomalies
Thoughts on propranolol explosion

- 7 years from initial case report to report of phase 3 registration trial and FDA approval
- Off label use outpaced research – equipoise erosion
- Was comparison to placebo the right question?
Propranolol and Lymphatic Anomalies

<table>
<thead>
<tr>
<th>Reference</th>
<th>N/disease</th>
<th>Dose/Duration</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nir et al <em>Pediatr Pulmonol</em> 2014</td>
<td>1 GLA</td>
<td>1 mg/kg/d 15 months</td>
<td>Improved thoracic mass w/in 1 mo</td>
<td>18yo; “Gorham-Stout”</td>
</tr>
<tr>
<td>Akyuz et al <em>Pediatr Blood Cancer</em> 2014</td>
<td>1 LM (tongue)</td>
<td>2 mg/kg/d 1.5 mo</td>
<td>None</td>
<td>10yo; then sirolimus response</td>
</tr>
<tr>
<td>Maruani et al <em>Periatr Derm</em> 2013</td>
<td>2 LM (head/Neck)</td>
<td>2 mg/kg/d 3 months</td>
<td>None</td>
<td>17mo and 3.5yo</td>
</tr>
<tr>
<td>Ozeki et al <em>Tohoku J Exp Med</em> 2013</td>
<td>6 LM (head/neck)</td>
<td>2 mg/kg/d 24 weeks</td>
<td>2 partial (22-30%) 2 minimal 2 none</td>
<td>10mo-19yo; VEGF-A/D decrease</td>
</tr>
<tr>
<td>Leboulanger et al <em>Arch Otolarygol Head Neck Surg</em> 2011</td>
<td>4 LM (tongue)</td>
<td>2 mg/kg/d 4-10 months</td>
<td>3 partial, rapidly (days to weeks) 1 none</td>
<td>31mo-11yo Rebound after stopping &lt;6mo</td>
</tr>
<tr>
<td>Ozeki et al <em>New Engl J Med</em> 2011</td>
<td>1 Pleural effusion</td>
<td>4 mg/kg/d 10 months</td>
<td>Improved in 3-6 months</td>
<td>11yo; GLA?; s/p IFN</td>
</tr>
</tbody>
</table>
Propranolol for Lymphatic Anomalies
Conclusions (2015)

• Several case reports reports benefit, while others deny benefit
• Variable natural history confounds interpretation of case reports
• Well-tolerated
• Reasonable to consider for low acuity cases (safe enough to try), but not as first line for high acuity cases
Sildenafil for Cystic Lymphatic Malformations

- Single patient with lymphatic malformation and pulmonary HTN
- Reported without long-term follow-up
- Two additional cases with multiple therapies including sildenafil
- Wide-spread off-label use
- Led to pilot study at Stanford
  - 7 pts – equivocal results
- 18 head & neck pretreated microcystic lymphatic malformations
  - No benefit
- 14 referral cases without benefit

NEJM 2012;366:384-6
Int J Pediatr Otorhinolaryngol. 2015 Apr 9
Pediatr Blood Cancer. 2015 May 15
Classification of Vascular Anomalies

Please now refer to ISSVA Classification
www.issva.org

Tumors vs. Malformations

• Proliferative lesions
• Medical therapies are the mainstay
  – Steroids/Propranolol
  – Interferon
  – Vincristine
  – Cyclophosphamide
  – Anti-angiogenic drugs
  – Tyrosine-kinase inhibitors
  – mTOR inhibitors
  – Anti-platelet therapy
  – Anti-fibrinolytic therapy

• Embryologic malformation of vessels
• Likely form in utero
• Persist lifelong
• Hematologic/coagulation complications
• Most therapy is surgical/interventional
• Few medical therapies
  – Emerging exceptions
Medical Therapies: Known and Unknown Targets

• VEGF
  – VEGF-A: corticosteroids, bevacizumab
  – VEGFRs: sorafenib, sunitinib, pazopanib…
  – mTOR/PI3K/Akt: sirolimus, everolimus…

• Angiogenesis
  – Interferon
  – Thalidomide, lenalidomide, pomalidomide

• Osteoclast inhibition
  – bisphosphonates, desotinab

• Anti-proliferative
  – Vincristine
  – Cyclophosphamide
  – Anthracyclines
  – Taxols

• Vasoactive/Unclear
  – Propranolol
  – Sildenafil (?)
Patient-specific risk analysis

Safety

• Total number of patients exposed
• Symptomatic or not
• Reversibility
• Long-term use experience
• Common vs. rare
• Severe

Efficacy

• How many patients like me
• What signs/symptoms have improved
• Location of disease
• Patient age
• Prior therapies
# Approaches to Therapies

<table>
<thead>
<tr>
<th>Rationale</th>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype</strong> (e.g. PIK3CA mutation)</td>
<td>Molecular/logical Targeted therapies</td>
<td>Availability of genotyping</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor genotype:phenotype correlation</td>
</tr>
<tr>
<td><strong>ISSVA Diagnosis</strong> (e.g. Kaposiform lymphangiomatosis)</td>
<td>Consistent diagnosis</td>
<td>Range of severity within diagnoses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some boundaries unclear/unstable</td>
</tr>
<tr>
<td><strong>Phenotype</strong> (e.g. pleural effusions)</td>
<td>Treating the problem(s) at hand</td>
<td>Varied pathophysiology may lead to same symptoms</td>
</tr>
</tbody>
</table>
The best target for therapies is the patient’s chief complaint
Spectrum of KHE/TA
<table>
<thead>
<tr>
<th>Severity</th>
<th>Risk:Benefit</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MINOR:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal platelets</td>
<td>Low Risk</td>
<td>Observe</td>
</tr>
<tr>
<td>No pain</td>
<td>Unsure Efficacy</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Stable disease</td>
<td></td>
<td>Topical therapy</td>
</tr>
<tr>
<td>Superficial</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MODERATE:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild KMP</td>
<td>Low Risk</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Some pain</td>
<td>Some efficacy</td>
<td>Propranolol?</td>
</tr>
<tr>
<td>Muscle involvement</td>
<td></td>
<td>(vincristine or sirolimus if insufficient)</td>
</tr>
<tr>
<td><strong>SEVERE:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KMP + low fibrinogen</td>
<td>Some Risk</td>
<td>Steroid + vincristine</td>
</tr>
<tr>
<td>Progressive</td>
<td>Need efficacy</td>
<td>2\textsuperscript{nd} line: sirolimus, IFN</td>
</tr>
<tr>
<td>Infiltrative</td>
<td></td>
<td>(&gt;1yo), embolization, XRT</td>
</tr>
</tbody>
</table>
Receptor Tyrosine Kinases (EGFR, VEGFR)

Cell Membrane

PTEN-associated vascular malformations

PTEN

PTEN

TSC1

TSC2

TS-associated angiofibromas

Ras Raf

CLOVES

Rasa1

Multiple CMs, CM-AVM, Parkes-Weber

Multiple venous malformations

PI3K

Akt/PKB

Tie-2

mTOR

S6

↑ protein synthesis

eIF-4E

Hif-1

VEGF

Slide courtesy of Dr. Denise Adams
Sirolimus for PTEN-hamartoma

BEFORE
Painful
Limited function

AFTER 1 YEAR
Pain free
Full ROM

Sirolimus for venolymphatic malformations

BRBNS = Blue Rubber Bleb Nevus Syndrome

Pediatrics. 2012 Apr;129(4):e1080-4
Sirolimus in Kaposiform Hemangioendothelioma

Before Sirolimus

10 months of Sirolimus

Experimental therapy informing clinical trial development

Safety and Efficacy Study of Sirolimus in Complicated Vascular Anomalies

This study is ongoing, but not recruiting participants.

Sponsor:
Children's Hospital Medical Center, Cincinnati

Information provided by (Responsible Party):
Children's Hospital Medical Center, Cincinnati

ClinicalTrials.gov Identifier:
NCT00975819

First received: September 10, 2009
Last updated: April 11, 2014
Last verified: April 2014

History of Changes
PATIENT ELIGIBILITY

Diagnosis:
• Kaposiform Hemangioendothelioma with Kasabach-Merritt Phenomenon
• Kaposiform Hemangioendothelioma without Kasabach-Merritt Phenomenon
• Tufted Angioma with Kasabach-Merritt Phenomenon
• Tufted Angioma without Kasabach-Merritt Phenomenon
• Capillary Lymphaticovenous Malformation (CLVM)
• Venous Lymphatic Malformation (VLM)
• Microcystic Lymphatic Malformation (MLM)
• Multifocal Lymphangiomatosis and Thrombocytopenia (MLT)/Cutaneovisceral Angiomatosis and Thrombocytopenia (CAT)
• Capillary Lymphatic Arterial Venous Malformations (CLAVM)
• PTEN Overgrowth syndrome with vascular anomaly
• Lymphangiectasia Syndromes

Complications:
• Coagulopathy
• Chronic pain
• Recurrent cellulitis (>3 episodes/year)
• Ulceration
• Visceral and/or bone involvement
• Cardiac dysfunction
Disease Response (3, 6 & 12 months)

- Imaging
- Quality of Life
- Clinical criteria and functional impairment

**Complete Response (CR):**
- No evidence of disease on MRI and,
- No evidence of organ dysfunction due to disease
- Normalization of QOL criteria

**Partial Responses (PR):**
- >20% reduction of target vascular lesion evident on radiographic imaging, or
- Improvement in target organ dysfunction by at least one Grade, or
- Improvement of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 compared to baseline; FACT-G by >3.99

**Progressive disease (PD):**
- >20% increase of target vascular lesion evident on radiographic imaging, or
- Worsening in target organ dysfunction by at least one Grade, or
- Worsening of self-report PedsQL by >4.4 or Peds proxy-report PedsQL by >4.5 compared to baseline; FACT-G by >3.99

**Stable disease (SD):**
- None of the above
## Overall Response

<table>
<thead>
<tr>
<th></th>
<th>Course 6 N=57</th>
<th></th>
<th>Course 12* N=53</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) [95% CL]</td>
<td></td>
<td>N (%) [95% CL]</td>
<td></td>
</tr>
<tr>
<td><strong>Complete Response (CR)</strong></td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
<td>47 (82.5%; [70.1%, 94.8%])</td>
<td>45 (84.9%; [73.1%, 96.8%])</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progressive Disease (PD)</strong></td>
<td>7 (12.3%; [1.6%, 23.0%])</td>
<td>8 (15.1%; [3.2%, 26.9%])</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stable Disease (SD)</strong></td>
<td>3 (5.3%; [0.0%, 12.5%])</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*1 patient removed at physician discretion; 1 patient removed for incorrect diagnosis; 2 patients removed for intolerable toxicity; 1 patient lost to follow up; 2 patients withdrew consent
# Course 12 Adverse Events (n=57)

## Table of Toxicity Category by Grade and Attribution

<table>
<thead>
<tr>
<th>Toxicity Category</th>
<th>Maximum Grade</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Possible</td>
<td>Probable</td>
<td>Definite</td>
<td>Possible</td>
<td>Probable</td>
<td>Definite</td>
<td></td>
</tr>
<tr>
<td>Blood/Bone Marrow</td>
<td>10 (17.5%)</td>
<td>1 (1.8%)</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1 (1.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>1 (1.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lymphatics</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Metabolic/Laboratory</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pulmonary/Upper Respiratory</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Initial Strata</td>
<td>Updated Strata</td>
<td>Response (53 evaluable)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
<td></td>
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</tr>
<tr>
<td>Microcystic Lymphatic Malformation (21)</td>
<td>Generalized Lymphatic Anomaly (7) Gorham’s syndrome (2) Kaposiform Lymphangiomatosis (7) MLM (5)</td>
<td>PR 7 (100%) PR 1 (50%), PD 1 (50%) PR 6 (86%), PD 1 (14%) PR 2 (50%), PD 2 (50%) (1 NE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>KHE with KMP (10)</td>
<td></td>
<td>PR 10 (100%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KHE without KMP (3)</td>
<td></td>
<td>PR 2 (66%), PD 1 (33%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillary venous lymphatic malformation (12)</td>
<td>Capillary lymphatico/venous malformation (12)</td>
<td>PR 11 (100%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lymphangiectasia (3)</td>
<td>Abnormalities of the central conducting lymphatic channels (ACCLC) (3)</td>
<td>PD 3 (100%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PTEN with vascular anomaly (6)</td>
<td>PTEN/AVM (2) PTEN/overgrowth/VA (4)</td>
<td>PR 1 (100%) (1 LTF) PR 3 (100%) (1 NE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous lymphatic malformation (2)</td>
<td>Venous lymphatic malformation (2)</td>
<td>PR 2 (100%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL 57</td>
<td>57</td>
<td>PR 45 (85%), PD 8 (15%)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

RESPONSE: **CR**= Complete Response, **PR**= Partial Response, **PD**= Progressive Disease, **SD**= Stable Disease
STATUS: **NE**= Non Evaluable, **LTF**= Lost to Follow Up, **NC**= Not Yet Completed
KHE – hematologic response

**Platelet**

![Graph showing Platelet levels over time]

**Fibrinogen**

![Graph showing Fibrinogen levels over time]

**D-Dimer**

![Graph showing D-Dimer levels over time]
CLOVES syndrome with rapidly enlarging mediastinal mass

### Hemoglobin

<table>
<thead>
<tr>
<th>Date</th>
<th>Value (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>7.5</td>
</tr>
<tr>
<td>2013</td>
<td>9.0</td>
</tr>
<tr>
<td>2014</td>
<td>10.0</td>
</tr>
<tr>
<td>2015</td>
<td>11.0</td>
</tr>
<tr>
<td>2016</td>
<td>12.0</td>
</tr>
<tr>
<td>2017</td>
<td>13.0</td>
</tr>
</tbody>
</table>

### D-Dimer

<table>
<thead>
<tr>
<th>Date</th>
<th>Value (mg/L FEU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>30</td>
</tr>
<tr>
<td>2013</td>
<td>25</td>
</tr>
<tr>
<td>2014</td>
<td>20</td>
</tr>
<tr>
<td>2015</td>
<td>15</td>
</tr>
<tr>
<td>2016</td>
<td>10</td>
</tr>
<tr>
<td>2017</td>
<td>5</td>
</tr>
</tbody>
</table>

### Infections

<table>
<thead>
<tr>
<th>Period</th>
<th># Infections</th>
<th>Hosp Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE</td>
<td>8</td>
<td>51</td>
</tr>
<tr>
<td>1st 6 months POST</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>2nd 6 months POST</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Sirolimus - mucosal lymphatic vesicles

**BEFORE**

![Image of mucosal lymphatic vesicles before treatment](image1)

**4 WEEKS**

![Image of mucosal lymphatic vesicles after 4 weeks](image2)

**10 WEEKS**

![Image of mucosal lymphatic vesicles after 10 weeks](image3)

**10 MONTHS**

![Image of mucosal lymphatic vesicles after 10 months](image4)
Sirolimus for Vascular Anomalies

**Likely Beneficial**
- KHE (especially if KMP)
- Leaky cutaneous lymphatic vesicles
- Oral mucosal lymphatic vesicles
- Recurrent infections (esp. if related to above)
- Pleural effusions
- Lymphedema-associated pain
- GI bleeding in BRBNS and KT-S
- Possibly for bony and cystic lymphatic diseases
- Progressive PTEN lesions

**Benefit Unclear**
- Lipomatous overgrowth
- AVMs
- Venous malformations?
- Capillary malformations?
Sirolimus for capillary malformation

- Pulse-dye laser of Laser Only sites
- Sirolimus 2mg daily
  - Started 4 weeks after Laser Only
  - Started 7 days prior to Laser + RPM
  - Stopped 4 weeks after laser

Topical sirolimus + PDL

- RCT of 1mo placebo vs. 1% topical sirolimus +/- pulse dye laser
- Topical sirolimus improves response to laser and may decrease number of sessions needed.

Evolving Referral Landscape for Medical Therapies

Procedural Therapies Exhausted

Multimodal Therapies

Rational Protocols with Neo-adjuvant or Adjuvant Use of Medical Therapies
Vision of the near future

• Improved natural history and outcomes data from observational studies
  – Sirolimus Off-Label Use
    • PI: Adrienne Hammill (CCHMC)
  – Lymphatic Anomalies Registry
    • PI: Cameron Trenor (BCH)
    • www.lymphaticregistry.org

• Emerging animal models and biology studies

• Expanded trials of sirolimus
  – Specific diagnoses
  – Combination therapies
  – Biomarkers of sirolimus response
  – Late effects and durability of sirolimus response
  – Topical sirolimus studies?
Summary

• “Everything works once” – caution with case reports
• Sirolimus is permeating across the spectrum of vascular anomalies
• Monitoring is critical to safety margin and possibly efficacy
• Define goals of treatment and align with chief complaint

• cameron.trenor@childrens.harvard.edu