Sirolimus for the Medical Management of Vascular Anomalies

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Disclosures

• I will be discussing off-label use of sirolimus
  – There are no FDA-approved medications for the diagnoses we will be discussing today

• Pfizer, which previously held the patent on Rapamune, has provided drug for 3 clinical trials in which I have been involved
  – No financial compensation
One patient with KHE...

7 months old

11 months
Medical Treatment of KHE

• There is no standard of care for medical treatment
  – Steroids
  – Chemotherapy: Vincristine, Cytoxan, combinations
  – Interferon
  – Anti-platelet agents + chemo
  – Anti-fibrinolytic agents + chemo

• Expert consensus
  – Steroids + vincristine if complicated
How one patient changed our thinking…

Vincristine/Steroids
Cyclophosphamide
Amicar
Interferon
Avastin
The mTOR pathway

Receptor Tyrosine Kinases (EGFR, VEGFR)

Cell Membrane

PI3K

Ras

Raf

PTEN

Akt/PKB

TSC2

TSC1

mTOR

↑ protein synthesis

↑ cell growth & proliferation

↑ angiogenesis

Sirolimus
Sirolimus (aka Rapamycin)

- Specific and potent inhibitor of mTor
- Inhibition mediated through binding to the cellular protein receptor FKBP512
- Exact mechanism unknown, likely involves disruption of an effective multi-protein signaling complex
- Effective and safe in both adult and pediatric populations in setting of solid organ transplant
Patient 1: Kasabach-Merritt Phenomenon
Patient 1: KHE

Starting sirolimus therapy  
21 months on  
18 months off  
Recent
Sirolimus for the Treatment of Complicated Vascular Anomalies in Children

Adrienne M. Hammill, MD, PhD, 1,2* MarySue Wentzel, RN, 1 Anita Gupta, MD, 1,3 Stephen Nelson, MD, 4 Anne Lucky, MD, 1,5 Ravi Elluru, MD, PhD, 1,6 Roshni Dasgupta, MD, 1,7 Richard G. Azizkhan, MD, 1,7 and Denise M. Adams, MD 1,2

Background. Vascular anomalies comprise a diverse group of diagnoses. While infantile hemangiomas are common, the majority of these conditions are quite rare and have not been widely studied. Some of these lesions, though benign, can impair vital structures, be deforming, or even become life-threatening. Vascular tumors such as kaposiform hemangioendotheliomas (KHE) and complicated vascular malformations have proven particularly difficult to treat. Procedure. Here we retrospectively evaluate a series of six patients with complicated, life-threatening vascular anomalies who were treated with the mTOR inhibitor sirolimus for compassionate use at two centers after failing multiple other therapies. Results. These patients showed significant improvement in clinical status with tolerable side effects. Conclusions. Sirolimus appears to be effective and safe in patients with life-threatening vascular anomalies and represents an important tool in treating these diseases. These findings are currently being further evaluated in a Phase II safety and efficacy trial. Pediatr Blood Cancer 2011;57:1018–1024.

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Key words: vascular anomalies; vascular malformations; kaposiform hemangioendothelioma; Kasabach–Merritt phenomenon; lymphatic malformation; rapamycin; sirolimus
Phase II: Safety and Efficacy of Sirolimus for Complicated Vascular Anomalies

- FDA funded, drug supplied by Pfizer
- Initially single institution (CCHMC)
  - Second site 2012 (BCH)
- Children and young adults with complicated vascular anomalies (0-31 years)
- **Primary Aims**
  - Establish Safety
  - Determine Efficacy
- 60 patients
- Oral sirolimus therapy
  - Rapamune (1mg/ml solution) starting at 0.8mg/m²/dose BID with subsequent target trough of 10-15 ng/mL
Clinical Trial: Eligibility

Diagnosis:
• Kaposiform Hemangioendotheliomas +/- Kasabach-Merritt Phenomenon
• Tufted Angioma +/- Kasabach-Merritt Phenomenon
• Capillary Lymphatico-Venous 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
Clinical Trial: Response Assessment

Response was established by change in at least 1 of these parameters

CR
No evidence of disease on radiologic imaging and
No evidence of organ dysfunction due to disease and
Normalization of quality of life criteria

PR
>20% reduction in size of target vascular lesion evident on radiologic imaging or
Improvement in target organ dysfunction by at least 1 grade or
Improvement of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 compared with baseline;
FACT-G by >3.99

Progressive disease
>20% increase of target vascular lesion evident on radiologic imaging or
Worsening in target organ dysfunction by at least 1 grade or
Worsening of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 compared with baseline;
FACT-G by >3.99

Stable disease
None of the above

FACT-G, Functional Assessment of Cancer Therapy—General; PedsQL, Pediatric Quality of Life Inventory 4.0.
Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies

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Clinical Trial: Conditions Enrolled

<table>
<thead>
<tr>
<th>Initial Enrolling Diagnosis</th>
<th>Updated Diagnosis Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcystic lymphatic malformation (n = 22)</td>
<td>Generalized lymphatic anomaly (n = 7)</td>
</tr>
<tr>
<td>KHE or TA with KMP (n = 10)</td>
<td>Gorham syndrome (n = 3)</td>
</tr>
<tr>
<td>KHE or TA without KMP (n = 3)</td>
<td>Kaposiform lymphangiomatosis (n = 7)</td>
</tr>
<tr>
<td>Capillary venous lymphatic malformation (n = 13)</td>
<td>Microcystic lymphatic malformation (n = 5)</td>
</tr>
<tr>
<td>Lymphangiectasia (n = 3)</td>
<td>KHE with KMP (n = 10)</td>
</tr>
<tr>
<td>PTEN with vascular anomaly (n = 6)</td>
<td>KHE without KMP (n = 3)</td>
</tr>
<tr>
<td>Venous lymphatic malformation (n = 3)</td>
<td>Capillary lymphatico/venous malformation (n = 13)</td>
</tr>
<tr>
<td>Multifocal lymphangioendotheliomatosis with thrombocytopenia/cutaneovisceral angiomatosis with thrombocytopenia (n = 0)</td>
<td>Abnormalities of the central conducting lymphatic channels (n = 3)</td>
</tr>
<tr>
<td>Capillary lymphatic arterial venous malformation (n = 0)</td>
<td>PTEN/AVM (n = 2)</td>
</tr>
<tr>
<td></td>
<td>PTEN/overgrowth/VA (n = 4)</td>
</tr>
<tr>
<td></td>
<td>Venous lymphatic malformation (n = 3)</td>
</tr>
<tr>
<td></td>
<td>Multifocal lymphangioendotheliomatosis with thrombocytopenia/cutaneovisceral angiomatosis with thrombocytopenia (n = 0)</td>
</tr>
<tr>
<td></td>
<td>Capillary lymphatic arterial venous malformation (n = 0)</td>
</tr>
</tbody>
</table>

Diseases were initially stratified on the basis of the ISSVA classification reported in 1997; lesions were then recategorized based on the revised 2014 ISSVA classification.
# Clinical Trial: Safety

<table>
<thead>
<tr>
<th>Toxicity Category</th>
<th>Possible</th>
<th>Probable</th>
<th>Definite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood/bone marrow, (%)</td>
<td>17 (28)</td>
<td>11 (18)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Cardiac general, (%)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Constitutional symptoms, (%)</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatology/skin, (%)</td>
<td>3 (5)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal, (%)</td>
<td>12 (20)</td>
<td>18 (30)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Infection, (%)</td>
<td>9 (15)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphatics, (%)</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolic/laboratory, (%)</td>
<td>5 (8)</td>
<td>6 (10)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Musculoskeletal/soft tissue, (%)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain, (%)</td>
<td>5 (8)</td>
<td>5 (8)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pulmonary/upper respiratory, (%)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Total participants = 60.
Clinical Trial: Overall Response

<table>
<thead>
<tr>
<th>Overall Response</th>
<th>Course 6, ( n = 57 )</th>
<th>Course 12, ( N = 53 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>47 (83) [70–95]</td>
<td>45 (85) [73–97]</td>
</tr>
<tr>
<td>PD</td>
<td>7 (12) [2–23]</td>
<td>8 (15) [3–27]</td>
</tr>
<tr>
<td>SD</td>
<td>3 (5) [0–13]</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are presented as \( n \) (%) [95% CI].
### Clinical Trial: Response

**TABLE 5** Disease Response at EOC 6 and 12

<table>
<thead>
<tr>
<th>Initial Enrolling Diagnosis</th>
<th>Updated Diagnosis Classification</th>
<th>Efficacy Presented According to Vascular Anomaly Diagnosis Following 6 Courses: Response (57 Evaluable)</th>
<th>Efficacy Presented According to Vascular Anomaly Diagnosis Following 12 Courses: Response (53 Evaluable)</th>
</tr>
</thead>
</table>
| Microcystic lymphatic malformation (n = 22) | Generalized lymphatic anomaly  
Gorham syndrome  
Kaposiform lymphangiomatosis  
Microcystic lymphatic malformation | PR 7 (100%) | PR 7 (100%) |
| KHE with KMP (n = 10)  
KHE without KMP (n = 3) | | | |
| Capillary venous lymphatic malformation (n = 12)  
Lymphangiectasia (n = 3) | Capillary lymphatico/venous malformation  
Abnormalities of the central conducting lymphatic channels | PR 11 (100%) (1 NE) | PR 11 (100%) (1 NE) |
| PTEN with vascular anomaly (n = 6)  
Venous lymphatic malformation (n = 3) | PTEN/AVM  
PTEN/overgrowth/VA  
Venous lymphatic malformation | PR 2 (100%) | PR 1 (100%) (1 LTFU) |
| | | PR 3 (75%), stable disease 1 (25%) | PR 3 (100%) (1 NE) |
| | | PR 3 (100%) | PR 2 (100%) |
| | | PR 47 (82%), stable disease 3 (5%), progressive disease 7 (12%) | PR 45 (85%), progressive disease 8 (15%) |

AVM, arteriovenous malformation; LTFU, lost to follow-up; NE, not evaluable; VA, vascular anomalies.

* Participants were removed from study treatments for reasons other than progressive disease.

* Participant did not return for end of study visit at EOC 12.
KHE with KMP: Hematologic response to sirolimus
KHE Response to Sirolimus: Skin Changes

Prior to sirolimus

End of Course 12
KHE Response to Sirolimus: Skin Changes

Prior to sirolimus

End of Course 9
KHE Response to Sirolimus: MRI Changes

Prior to starting sirolimus

End of Course 6
Lymphatic Anomalies

• Lymphatic malformations
• Generalized Lymphatic Anomaly
• Kaposiform Lymphangiomatosis
• Combined lesions – CLVM
  – CLOVES Syndrome
  – Klippel-Trenaunay Syndrome
GLA: Pleural Effusion

Prior to sirolimus

On sirolimus for 2 months
GLA: Pleural Effusion

End of sirolimus therapy

Infection, 5 months off sirolimus
CLVM: Lymphatic Blebs

Start of sirolimus

On sirolimus for 7 months
CLVM: Lymphatic Blebs

2 years on sirolimus therapy

2 weeks off sirolimus therapy
Venous Malformations

- Venous Malformations
  - For pain and coagulopathy
- Blue Rubber Bleb Nevus Syndrome
  - For pain, coagulopathy, anemia
Indications for Medical Management

• Life threatening lesion
• Persistent pain
• Coagulopathy
• Recurrent infections/ cellulitis
• Multifocal or diffuse
• Interfering with function
Our Obstacles

• Few standardized treatments, fewer prospective studies
  – Heterogeneous group of disorders
  – Small numbers of patients that need treatment
  – Limited funding
  – No animal models

• Need better drugs
  – Identify promising targets through disease registries, tissue repositories, and biomarker analyses

• Need to tailor the order of treatments to the patient
CLVM – Multimodal therapy

- Hip dislocation
- Extensive pelvic involvement, partly macrocystic
- Required:
  - Rectal Tube
  - Suprapubic catheter
- Bacteremia – E. coli
CLVM – Multimodal therapy

- 1 month: Drainage of pelvic macrocyst
- 4 months: Sclerotherapy to thigh/buttocks
CLVM – Multimodal therapy

- 4 months: sclerotherapy with doxycycline to thigh/buttocks
- Started on sirolimus clinical trial
CLVM – Multimodal therapy

- Completed study (1yr) and continued on
- Hip dislocation resolved
- Discoloration lightened

15 months on sirolimus
CLVM – Multimodal therapy

- Still with episodes of cellulitis in buttock/thigh
- 2 additional sclerotherapies at age 2yo
CLVM – Multimodal therapy

3 years old
• 3 sclerotherapies
• Almost 3 years on sirolimus
• Soft, functional leg and hip
• But clear overgrowth and asymmetry
CLVM – Multimodal therapy

- Surgical Debulking of buttock and thigh
- Resection of residual capillary/lymphatic blebs
CLVM – Multimodal therapy

- Multiple sclerotherapies
- Sirolimus (ongoing)
- Surgical debulking
CLOVES – Multimodal therapy
CLOVES – Multimodal therapy

• Ray amputation and debulking of feet at 9 months old
CLOVES – Multimodal therapy

- Enrolled on sirolimus trial at 20 months
- Partial response at EOC 3
- Withdrew at EOC 4
- Restarted lower dose within 1 week!
CLOVES – Multimodal therapy

- Large ectatic veins left leg
- Unable to stand without compression
- Lightheaded getting into the bathtub
- Underwent vein ligation and radiofrequency ablation at 5 yo
CLOVES – Multimodal therapy

- Debulking of buttocks
CLOVES – Multimodal therapy

- Multiple sclerotherapies
- Radiofrequency ablation of ectatic embryonic veins
- Sirolimus (ongoing)

- Multiple surgeries
  - Hydrocele repair
  - Inguinal hernia repair
  - Amputation/debulking feet
  - Debulking buttocks
  - More to come…
    - R hip dysplasia
    - Epiphysiodesis
Our HVMC Multidisciplinary Team

- Interventional Radiology
  Manish Patel, DO
- Hematology-Oncology
  Adrienne Hammill, MD, PhD
  Kiersten Ricci, MD
  Carol Chute, CNP
  Saulius Girnius, MD (adult)
- Pediatric Surgery
  Roshni Dasgupta, MD
- Otolaryngology
  Charles Myer IV, MD
- Pulmonary
  Chris Towe, MD
- Orthopedics
  James McCarthy, MD
  Joel Sorger, MD
- Plastic Surgery
  John van Aalst, MD
- Genetics
  Katie Wusik-Healy, Genetic Counselor
- Behavioral Medicine
  Aimee Thompson, PhD
  Lauren Szulczuski, PsyD
- Pathology
  Anita Gupta, MD
  Sara Szabo, MD
- Radiology
  Carl Merrow, MD
- Compression (PT/OT)
  Kathleen Baumhardt, OT
  Paige Boppel, OT
  Kathy Neff, PT
- Clinical Research
  Paula Mobberley-Schuman, Project Specialist
  Megan Chute, Clin Research Coordinator
- Support
  Melissa Schrinner, Program Coordinator
  Mary Bishara, RN
  Amy Schmidt, RN
  Leah Baker, RN
  Christine Miller, Social Work
  Melissa Morris, Manager
  Katie Napier, Intake Coordinator
  Brionne Moore, CSR
  Mike Snyder, Photographer

Boston Collaborators: Denise Adams, MD
Cameron Trenor, MD