Sirolimus Eluting Collagen Implant to improve AV Fistula Outcomes

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Hemodialysis Access at the VEITH Symposium
New York November 21st 2015

Sirolimus and the Cell Cycle

Cell Cycle

Sirolimus – Anti-Proliferative Action

Sirolimus – Anti-Proliferative Action

Harnessing the Anti-proliferative Action of Sirolimus via Local Vascular Delivery

Why Don’t Fistulae Mature?

Juxta-anastomotic stenosis (JAS; red arrows) resulting from Neointimal Hyperplasia at and around the anastomosis of the fistula (yellow arrow) is an important cause of fistula failure

Sirolimus is a clinically proven anti-proliferative

Sirolimus-eluting Collagen Implant

* Large body of experience
* Wide Therapeutic Window
* Anti-proliferative effect independent of
  » Age
  » Gender
  » Diabetes
  » Diffuse vs. Focal
* Anti-proliferative effect maintains vascular lumen patency
* Reduces need for supplementary interventions

Ultrasound of the Fistula at 6 weeks

> 50% of Fistula Non Maturation
Flow limiting Stenosis at the JAS

No Treatment available (Unmet Clinical Need)

Sirolimus-eluting Collagen Implant

* Dry state – Flat, rectangular. Self curls upon hydration
* Hydrated membrane maintains curvature without need for sutures
* Thin, supple, does not tear
* Drug starts eluting soon after implantation
* Lipophilic, partitions into RBC’s
* Bioabsorbable – approximately 12 weeks post implantation
VT 303: Hemodialysis AV Fistula

- N= 30
- Phase 2
- Open label
- Single Arm (Non Randomized)
- Radiocephalic (wrist; n=22) and Brachiocephalic (n=08)
- Two sites; two surgeons
- 12 month Follow up (100%)

VT-303 AV Fistula Study (N=30)

22 Radiocephalic and 8 Brachiocephalic Fistulae

VT-303 -- Demographics

<table>
<thead>
<tr>
<th>N=30</th>
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<tbody>
<tr>
<td>Age (years), Mean ± SD</td>
<td>50.8±14.8</td>
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<tr>
<td>Gender (N, %)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (60.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (40.0%)</td>
</tr>
<tr>
<td>ESRD on Hemodialysis</td>
<td>29 (97.0%)</td>
</tr>
<tr>
<td>CKD Stage 5</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>6 (20.0%)</td>
</tr>
<tr>
<td>History of Smoking</td>
<td></td>
</tr>
<tr>
<td>Previous Smoker</td>
<td>12 (40.0%)</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>5 (16.7%)</td>
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Usefulness Assessment -- (VT-303)

<table>
<thead>
<tr>
<th>N=30</th>
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<tbody>
<tr>
<td>Thrombosis (within 2 weeks of surgery)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Maturation</td>
<td>29 (87%)</td>
</tr>
<tr>
<td>Mean time to maturation (KDOQI Criteria)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Fistula successfully cannulated for dialysis</td>
<td>29 (87%)</td>
</tr>
<tr>
<td>Mean time to first cannulation</td>
<td>7 weeks</td>
</tr>
<tr>
<td>Late Failures</td>
<td>3</td>
</tr>
<tr>
<td>Ipsilateral Central Vein occlusion (n=1)</td>
<td></td>
</tr>
<tr>
<td>Pseudoaneurysm (n=1)</td>
<td></td>
</tr>
<tr>
<td>Treatment Failure (n=1)</td>
<td></td>
</tr>
<tr>
<td>Primary (Unassisted) patency at 6-months</td>
<td>22/29* (76%)</td>
</tr>
<tr>
<td>Primary (Unassisted) patency at 12-months</td>
<td>20/27** (74%)</td>
</tr>
<tr>
<td>Whole blood mean peak sirolimus level (ng/ml)</td>
<td>4.13</td>
</tr>
</tbody>
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No Risk of Systemic Immunosuppression

Mean Whole Blood Sirolimus Concentration (ng/mL) Following
implantation

No Problems with Wound Healing or Infections
**Protocol VT-304 (The ACCESS Study)**
- **N = ~315**
- Randomized, Prospective, Controlled
- Multicenter
- United States
- **Key End Points**
  - Time to First Dialysis
  - Fistula Suitability for Dialysis
  - Enrollment is ongoing

**Study Design**
- ~315 Subjects Enrolled
- ~15 Run-in Subjects (1 per site)
- ~300 Subjects Randomized
- ~150 Subjects Randomized to Control
- ~150 Subjects Randomized to SECM

**Key Study Points**
- Randomization in the operating room AFTER successful fistula creation
- Roughly equal number of control and treatment per surgeon
- Patients already on Dialysis – no preemptive fistulae
- Study processes mimic current standard of care
- End points are clinically important and relevant
  - Time to First Dialysis
  - Fistula Suitability for Dialysis
- Functional (can it be used for dialysis) NOT Anatomical (is it patent or not) End Points

**Fistula: Anatomical Patency vs. Functionality**
- ALL Functionally Useful are Anatomically patent
- ALL Anatomically patent are NOT Functionally useful
Thank you.