Treatment of AV Fistulae with DCBs: Advantages of Sirolimus Over Ptx

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Employment in industry: No

Honorarium:
Amgen; Abbott Vascular; Biosensors; Boston Scientific; Celonova; Cook Medical; CSI; Lutonix Bard; Sinomed; Terumo Corporation.

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Owner of a healthcare company: No

Stockholder of a healthcare company: No
Introduction

Despite the introduction of new fistula surgical techniques and locations over the last fifty-four years, AVFs are mired by high primary failure rates.

Pathophysiology of stenosis in AVF and AVGs is very different from after angioplasty

It is believed that ongoing NIH proliferation in AVFs and AVGs is due to non-physiologic flow dynamics that develop when there is a direct anastomosis of a high-pressure arterial system into a low-pressure venous one.

Mechanical factors contribute to ongoing NIH, including repetitive needle punctures that can lead to both endothelial disruption and fibrotic wall changes.

Following observations from traumatic arteriovenous fistulas caused by mechanical injuries, Dr. Brescia, Cimino and Hurwich first described the creation of a radial cephalic AVF in the forearm forming a side-to-side anastomosis between the cephalic vein and radial artery in 1966; thereby revolutionizing care for hemodialysis patients.
Costs of Maintaining Vascular Access

• Costs of treating patient who has failure of HD access graft is significantly higher ($62,000 per year) than costs of treating patient who does not have access failure

• Multiple percutaneous techniques and tools have been used to treat neointimal stenosis that develop at the site of venous anastomoses of AVG

• At best, secondary patency of arteriovenous grafts (i.e., patency after an intervention) is 50% at 3 years after the creation of the vascular access; typically, multiple interventions are required to maintain patency
Drug Coated Balloon Devices for AVF stenosis

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Coating</th>
<th>Drug dose (µg/mm²)</th>
<th>CE mark*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In.Pact™ Admiral,</td>
<td>Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.5</td>
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<tr>
<td>Lutonix® 035 DCB</td>
<td>BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel–polysorbate/sorbitol</td>
<td>2.0</td>
<td>Yes</td>
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</table>


Scott O. Trerotola et al. CJASN 2018;13:1215-1224
Why We Need a Sirolimus DCB?

- Sirolimus is the standard for coronary artery disease treatment via DES and proven to be safe and effective.
- Ptx modifications (crystalline form) means coating integrity and transfer are variable with substantial portion lost downstream into blood and tissues.
- Loss of Ptx into body remains a significant safety concern which was further exacerbated by Katsanos analysis in published in JAHA.
Ptx Safety Concerns Persist

**FDA Says Newer Paclitaxel Data Are ‘Comforting’ but Limited**

Acknowledging the recent, reassuring SWEDEPAD data, the agency says it’s not yet ready to update its advice to doctors.

*By L.A. McKewon | January 12, 2021*

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**Total Dose of Ptx Delivered on In.Pact Balloon**

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Length</th>
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<tbody>
<tr>
<td></td>
<td>80mm</td>
</tr>
<tr>
<td>20mm</td>
<td>1.1mg</td>
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<td>40mm</td>
<td>1.5</td>
</tr>
<tr>
<td>60mm</td>
<td>1.9</td>
</tr>
<tr>
<td>80mm</td>
<td>2.3</td>
</tr>
<tr>
<td>100mm</td>
<td></td>
</tr>
<tr>
<td>120mm</td>
<td></td>
</tr>
</tbody>
</table>

*Source: IFU for IN.PACT*


**Sirolimus offers potential benefits over Paclitaxel**

Common anti-proliferative drug for DCB is currently **PACLITAXEL**, however, **SIROLIMUS** (rapamycin) offers potential benefits over Paclitaxel.

<table>
<thead>
<tr>
<th></th>
<th>SIROLIMUS (OR ANALOGS)</th>
<th>PACLITAXEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of SMC proliferation</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Inhibition of SMC migration</td>
<td>+ +</td>
<td>+</td>
</tr>
<tr>
<td>Inhibition of EC proliferation</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>Pro-apoptotic effects</td>
<td>(+)</td>
<td>+ +</td>
</tr>
<tr>
<td>Therapeutic range</td>
<td>WIDE</td>
<td>NARROW</td>
</tr>
<tr>
<td>Safety margin</td>
<td>10’000 fold</td>
<td>100 fold</td>
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<tr>
<td>Anti-Restenotic impact</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Anti-inflammatory properties</td>
<td>+ +</td>
<td>(+) / -</td>
</tr>
<tr>
<td>Tissue Absorption</td>
<td>SLOW</td>
<td>FAST</td>
</tr>
<tr>
<td>Tissue Retention</td>
<td>SHORT</td>
<td>LONG</td>
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</tbody>
</table>

Sirolimus Coated Balloons – Technical challenges

• **Enhance tissue absorption**
  • Difficult to get sirolimus to enter into arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of “instant glue” is required to transfer the drug from the balloon to the tissue efficiently

• **Extend tissue retention**
  • Sirolimus must be continuously delivered over time, so some form of “time release mechanism” must be employed to maintain therapeutic levels
Arterial Wall Sirolimus (ng/g tissue) after MagicTouch

<table>
<thead>
<tr>
<th>Time</th>
<th>1 hour</th>
<th>24 hours</th>
<th>3 days</th>
<th>14 days</th>
<th>30 days</th>
<th>60 days</th>
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<td>1301.2</td>
<td>309</td>
<td>108</td>
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<td>BLQ</td>
<td>BLQ</td>
<td>BLQ</td>
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<tr>
<td>1541.3</td>
<td>1586.4</td>
<td>432.9</td>
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<td>114</td>
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<tr>
<td>3147.3</td>
<td>1013.7</td>
<td>632.2</td>
<td>193.7</td>
<td>26.7</td>
<td>12.54</td>
<td>BLQ</td>
<td>BLQ</td>
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<tr>
<td>1791.7</td>
<td>1255.4</td>
<td>327.3</td>
<td>76.4</td>
<td>56.6</td>
<td>14.33</td>
<td>BLQ</td>
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<td>1158.5</td>
<td>406.6</td>
<td>293.1</td>
<td>18.3</td>
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<td>BLQ</td>
<td>BLQ</td>
<td></td>
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<tr>
<td>1613.9</td>
<td>2444.4</td>
<td>351.7</td>
<td>143.4</td>
<td>10.2</td>
<td>10.21</td>
<td>6.94</td>
<td>4.43</td>
<td></td>
</tr>
</tbody>
</table>

BLQ = Below Limit of Quantification
MAGICTOUCH – Sirolimus Coated Balloon

- MAGICTOUCH® – SCB is Sirolimus Coated Balloon to treat coronary artery disease
- Delivers drug in 60 seconds
- Sub-micron phospholipid particles

Nothing Leaves Behind
Raman imaging – free vs encapsulated sirolimus

Preliminary results
(1) Raman maps were evaluated by TCA with the reference components for sirolimus and the nanocarrier-encapsulated drug
(2) Mean GVI were determined for Raman images of free and encapsulated sirolimus

TCA: true component analysis
GVI: gray value intensity
28 Day Histology

MagicTouch

POBA
AV Fistula Model
What Histological Markers Indicate Safety and Efficacy?

a. Endothelial cell loss
b. Inter-strut SMC density
c. Fibrin deposition
d. Medial SMC Loss (Depth and Circumference)
e. Medial Proteoglycan/Collagen replacement
Downstream Sampling for Histopathology Assessment

*Evaluated skeletal muscle and coronary band for potential embolic changes*
Ptx DCB in swine AV-shunt model

Anastomosis

Distal Femoral Vein
Proximal Femoral Artery
Distal Femoral Artery

60-day result

Distal vein

DCB
POBA
MagicTouch at 60 Days Histology in AVF Model
Conclusions

• Sirolimus is the preferred drug for intravascular interventions

• Ptx coated balloons are limited by high rate of distal embolization and loss of Ptx into the body—these concerns were only heightened by the analysis of Katsanos and may be a concern with treatment of AVF where embolization to venous system and lungs are a potential concern

• MagicTouch SCB demonstrated successful drug transfer for the arterial wall out to 60 days
  • ISR study at 30 days in porcine model showed no evidence of toxicity

• This is a promising new technology for the treatment of AVF and AVG stenosis
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