Regional Photodynamic Therapy for Vulnerable Plaque Stabilization: Antrin

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Photodynamic Therapy

Cell death occurs only if both light and drug present
Antrin® (Motexafin Lutetium)

- Selective accumulation in atherosclerotic plaques
- Rapid clearance from plasma and normal tissues
- Light activation produces singlet O₂ (very short path length) causing cell death
- Activation at 732 nm penetrates blood and tissue better than other photosensitizers in development
- Fluorescence detected at 750 nm with 460-480 nm excitation
Antrin® Photodynamic Therapy

Antrin (Motexafin Lutetium) Diffusing Fiber

Diode Laser

Diffusing Fiber

IV or Local Delivery

Optical Selectivity

Focal or Regional (multivessel) treatment

Mid LAD Stenosis

Tip of Transit

Fiber markers
Intracellular Localization of Antrin

Mitochondria (green)  Antrin (red)  Overlay

Human Macrophages

HCASMC

Woodburn et al., ACC 2002
Lysosomal Instability after Phototherapy

THP-1 Macrophages + Acridine Orange

Pre-treatment

Post-PDT @ LD_{50}

Woodburn et al., ACC 2002
Antrin Phototherapy Induces Apoptosis in Human Macrophages

Cytochrome C immunoreactivity assay in human THP-1 cells

Control  20 ug/ml Antrin  2 J/cm² Light  Antrin + Light

Woodburn et al., ACC 2002
Antrin Biolocalization in Atheromatous Plaque

NZW Rabbit aorta, 10 mg/kg iv administration, analysis at 24h

Rockson SG et al., Circulation 2000; 102:591-6
Texaphyrin Uptake in Rabbit Atheromas

B/W image

Fluorescence

RAM-11 (macrophage)

Oil Red O (neutral lipids)
Antrin Phototherapy (PT) depletes vascular macrophages in NZW rabbit injury model, local Antrin

Macrophage depletion in Fat-Fed New Zealand White (NZW) Rabbit; iv Antrin

Macrophage Burden as % of total intima and media

Intraballooon Illumination

Bare Fiber Illumination

YP Sun, ACC 2003 Poster Presentation
Reduces cell density post-Antrin PT

NZW injury model, 7d after PDT

Hamblin, et. al, Wellman Labs, MGH, Boston
Preclinical Findings

- Antrin localizes intracellularly in mitochondria and lysosomes
- Antrin is selective to plaques rich in macrophages and neutral lipids
- **Antrin Phototherapy:**
  - Reduces macrophages in all rabbit models studied
  - Produces significant plaque accellularity within days post-PT
  - Downregulates cytokines involved in monocyte migration
  - Appears to maintain or increase smooth muscle area
  - Suggests some collagen remodeling of PT lesion
  - Does not traumatize normal vessel walls.
  - Potentially remodels and stabilizes unstable plaque
- Allows both focal and regional treatment of diseased vessels.
Antrin Clinical Development

Peripheral Arterial Disease (PAD)


Phase II: Multi-center, double-blind, randomized trial for prevention of restenosis and treatment of de novo lesion. Study Completed. No adverse safety signals.

Coronary Arterial Disease (CAD)

Antrin Phototherapy
Phase 1 Coronary Artery Disease
Angiographic Results

- Enrollment: 79 patients
- Design: Drug and light dose escalation for safety
- Safety: No serious adverse effects
- Results: Optimum regimen identified
- Publication: Kereiakes, et. al. Circulation 2003; 103:1310

“The present phase 1 coronary study supports the apparent safety and tolerability of this treatment and materially extends our understanding of this emerging therapy in several ways.”
Phase I CAD
Participating Investigators & Centers

Dean Kereiakes
*The Lindner Center, Cincinnati*

Daniel Simon
*Brigham and Women’s Hospital, Boston*

Arthur M. Szyniszewski
*Micigan Heart & Vascular, Ann Arbor*

Alan Yeung
*Stanford Medical Center, Palo Alto*

Paul Kramer
*Mid-America Heart Institute, Kansas City*

Howard Herrmann
*Hospital of the University of Pennsylvania*

Wendy Shear
*Minneapolis VA Medical Center*

Jeffry Popma
*QCA Core Lab, Boston, MA*

Peter Fitzgerald
*IVUS Core Lab, Stanford, CA*
CAD Phase I Design

Dose-escalation safety trial in subjects with CAD undergoing PCI with stent placement

Eligibility: Patients With Coronary Arterial Disease

Design: IV ANTRIN Followed 18-24 Hours Later by Phototherapy.
   Drug escalation (0.05 – 4 mg/kg)
   Light escalation (100-600 J/cm²)

Safety Objectives:

* Extent of restenosis in Antrin PT-treated lesions (QCA, IVUS)
* Pharmacokinetics in this CAD pop.

Primary Outcome Variables

* Dose-limiting toxicities associated with Antrin Injection and/or illumination
* Phototherapy-related procedural adverse events
* Death, Stroke, CK or CK-MB > 3 x ULN
CAD Phase I Design

Secondary Outcome Variables
* Late lumen loss/index (QCA; IVUS) at 6 months
* Angiographic restenosis rate (> 50%)
* TLR, TVR, TVF
* Pharmacokinetics

Inclusion Criteria:
* Target lesion stenosis >50% needing PCI
* Target lesion for PCI ≤ 30 mm long
* Men or women ≥ 18 yrs old
* Give informed consent

Exclusion Criteria:
* Target lesions with previously placed stent
* Target lesions involving left main or ostial left anterior descending arteries
Angiographic Analysis Plan
BWH Angiography Core Lab – J. Popma

Normal 1
Proximal Edge
Stent
Balloon
Illumination
Entire Analysis

Normal 2
Distal Edge
## CAD Phase I Study
### Demographics (n=79)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, yrs</td>
<td>64.0 (43-85)</td>
</tr>
<tr>
<td>Men, %</td>
<td>70.9%</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>20.3%</td>
</tr>
<tr>
<td>Prior PCI, %</td>
<td>16.5%</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>51.9%</td>
</tr>
<tr>
<td>NYHA Class I, %</td>
<td>31.6%</td>
</tr>
<tr>
<td>NYHA Class II, %</td>
<td>68.4%</td>
</tr>
</tbody>
</table>
CAD Phase I Study
Target Vessel Characteristics

Target Vessel, %

- LAD 40 %
- LCX 28 %
- RCA 32 %

Stent Diameter (mm; mean) 3.33

Stent Length (mm; mean) 19.1
# CAD Phase I Study

## Procedure and Device Performance

<table>
<thead>
<tr>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Success*</td>
<td>100%</td>
</tr>
<tr>
<td>Procedural Success**</td>
<td>96.2%</td>
</tr>
<tr>
<td><strong>Interrupted Illumination</strong></td>
<td>0%</td>
</tr>
<tr>
<td>Fiber could not be delivered</td>
<td>0%</td>
</tr>
<tr>
<td>Bailout procedure</td>
<td>3.8%</td>
</tr>
<tr>
<td>[left main disease; angioplasty dissection] (n=3)</td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa Use</td>
<td>51%</td>
</tr>
</tbody>
</table>

*Successful delivery of the illuminating fiber when attempted*

**No in-hospital MACE**
## CAD Phase I Study
### Preliminary Acute Safety (30 days)

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergent CABG</td>
<td>0 %</td>
</tr>
<tr>
<td>Death</td>
<td>0 %</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 %</td>
</tr>
<tr>
<td>Total CK Elevation (&gt;3xULN)</td>
<td>1.3 %</td>
</tr>
<tr>
<td>Total CK-MB Elevation (&gt;3xULN)</td>
<td>10.3 %</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>1.3 %</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>0 %</td>
</tr>
</tbody>
</table>
## Antrin CAD Phase I Study

### Infusion Related Events

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>N</th>
<th>Peripheral Paresthesia*</th>
<th>Rash*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>5</td>
<td>1 (20.0%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.15</td>
<td>5</td>
<td>0 (0%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.50</td>
<td>6</td>
<td>0 (0%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1.00</td>
<td>6</td>
<td>1 (16.7%)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>2.00</td>
<td>21</td>
<td>10 (47.6%)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>3.00</td>
<td>26</td>
<td>14 (53.8%)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>4.00</td>
<td>10</td>
<td>6 (60.0%)</td>
<td>3 (30.0)</td>
</tr>
</tbody>
</table>

* Rashes were not phototoxic reactions. Duration of paresthesias and rashes ranged from 0-46 days, and 0-51 days, respectively. All were mild to moderate in severity.
Antrin (MLu) Pop Pharmacokinetics
Rapid Clearance from Plasma

Across all drug doses: 0.05-4 mg/kg

Functional $T_{1/2} = \sim 25$ min
(Based on 48h sampling)

95% cleared from plasma
Follow-Up Angiography
Quantitative Results

There were no clinically significant differences between the stent, balloon injury, illumination and analysis segments.

<table>
<thead>
<tr>
<th>Segment</th>
<th>Overall % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stent Segment</strong> (Binary Restenosis)</td>
<td>24/71, 33.8 % (23.0, 46.0)</td>
</tr>
<tr>
<td>Stent Segment MLD (mm)</td>
<td>1.75</td>
</tr>
<tr>
<td>Stent Segment Late lumen loss (mm)</td>
<td>1.02</td>
</tr>
<tr>
<td><strong>Edge segments</strong></td>
<td>2/70 (2.9 %) (0.3, 9.9)</td>
</tr>
<tr>
<td>Pre-PCI % stenosis (median)</td>
<td>66.0 %</td>
</tr>
<tr>
<td>Post-PCI % stenosis (median)</td>
<td>6.8 %</td>
</tr>
<tr>
<td>Pre / Post- ref. vessel diameter (mean)</td>
<td>2.93 / 2.94 mm</td>
</tr>
</tbody>
</table>
Mean (SE) late lumen loss by quantitative coronary angiography stratified by study stage, MLu dose, and light fluence.
Qualitative Assessment by IVUS (N=39)

- **Incomplete apposition**
  - Preserved incomplete apposition: 2
  - Resolved incomplete apposition: 1
  - Late incomplete apposition: 0

- **Stent edge dissection**
  
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Intraluminal thrombus**
  
<table>
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<th>Baseline</th>
<th>6-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Hongo, et. al., manuscript under preparation
Quantitative Assessment by IVUS (N=39)

Percent Neointima Volume Obstruction

<table>
<thead>
<tr>
<th>Light (J/cm-fiber)</th>
<th>MLu (mg/kg)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.05-1.0</td>
<td>(9)</td>
</tr>
<tr>
<td>100</td>
<td>2.0-4.0</td>
<td>(7)</td>
</tr>
<tr>
<td>200-600</td>
<td>2.0-3.0</td>
<td>(23)</td>
</tr>
</tbody>
</table>

Hongo, et. al., manuscript under preparation
Quantitative Assessment by IVUS (N=39)

Percent Change in Plaque Volume

<table>
<thead>
<tr>
<th>Light (J/cm-fiber)</th>
<th>100</th>
<th>100</th>
<th>200-600</th>
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<td>MLu (mg/kg)</td>
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</tr>
<tr>
<td>N</td>
<td>(9)</td>
<td>(7)</td>
<td>(23)</td>
</tr>
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</table>

Hongo, et. al., manuscript under preparation
Safety Summary - CAD

- ANTRIN Phototherapy is feasible, well-tolerated and safe in >250 trial patients to date.
  - No drug/light dose-limiting toxicities
  - Self-limited paresthesias with > 2.0 mg/kg
  - Successful and safe intravascular light delivery

- Absence of late incomplete stent apposition with PT

- Very low incidence of geographical miss

- No evidence of deleterious edge effects

- No reported treatment-related aneurysms

- No observed subacute stent thrombosis or proliferative fibrosis within the reference segment
Vulnerable Plaque
Native CAD vs SVG?