Photoangioplasty for Human Peripheral Atherosclerosis
Results of a Phase I Trial of Photodynamic Therapy With Motexafin Lutetium (Antrin)

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Background—In photoangioplasty, light activation of a photosensitive drug offers the potential for treatment of long segments of vascular disease. This is a brief description of a study designed to evaluate the safety and tolerability of a new photosensitizer, Antrin (motexafin lutetium), in the endovascular treatment of atherosclerosis.

Methods and Results—An open-label, single-dose, escalating drug- and light-dose study was performed in patients with atherosclerotic peripheral arterial insufficiency. Clinical evaluation, serial quantitative angiography, and intravascular ultrasonography were performed. Therapy was well tolerated, and only minor side effects were observed. Treatment produced no deleterious vascular effects. Although this study was not designed to examine clinical efficacy, several secondary end points suggested a favorable therapeutic effect.

Conclusions—This phase I study demonstrates that photoangioplasty with motexafin lutetium is well tolerated and safe. Preliminary efficacy data suggest a future role for the treatment of flow-limiting atherosclerosis.

Key Words: atherosclerosis • peripheral vascular disease • catheters

Photodynamic therapy (PDT) is an emerging treatment method for atherosclerosis that has possible therapeutic implications in restenosis treatment and prevention. PDT utilizes light energy to activate a photosensitive drug. Long segments of vascular disease can be treated with cylindrical light-emitting fiberoptic catheters. The administration of a photosensitive drug with subsequent percutaneous, endovascular light activation, called photoangioplasty, is a novel therapeutic approach for atherosclerosis.

The texaphyrins are a new, recently described family of photosensitizing compounds. These porphyrin-related compounds specifically localize within tumors and atheromatous plaque. During photoactivation with far-red light (720 to 760 nm), they absorb light energy and are thereby converted to an excited state. Far-red-light energy sufficiently penetrates tissues to activate the texaphyrins, even in the presence of flowing blood. Singlet oxygen, released by photoactivation, produces a cytotoxic cellular effect within the plaque while sparing normal, surrounding vascular tissues.

This report represents a brief description of a clinical trial performed primarily to evaluate the safety of photoangioplasty with Antrin (motexafin lutetium) in human peripheral arterial atherosclerosis. The goals of this study were to assess tolerability and secondarily to obtain a preliminary assessment of the therapeutic potential of this approach for the treatment of human peripheral atherosclerosis.

Methods

An open-label, single-dose, escalating drug- and light-dose study was performed in patients with symptomatic atherosclerotic peripheral arterial insufficiency.

Study Population

The study population consisted of patients with symptomatic claudication and objectively documented peripheral arterial insufficiency. Inclusion required an ankle/brachial index (ABI) of ≥0.85 in at least 1 lower extremity, either at rest or after treadmill exercise, or an ipsilateral toe pressure <60 mm Hg. Photoangioplasty of a single atherosclerotic lesion was performed in the external iliac, common femoral, or superficial femoral artery. Many patients had multisegmental disease; the illuminated lesion was chosen on the basis of accessibility and was not necessarily the most flow-limiting stenosis. Exclusion criteria included myocardial infarction within the preceding 6 months, New York Heart Association class III or IV congestive heart failure, inadequate angiographic runoff, or a history of porphyria.

Experimental Design

This study utilized a 2-part experimental design. The first phase (Table 2, part 1) sought to define the maximum tolerated dose of motexafin lutetium. Cohorts of patients received a standard light

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fluorescence of 400 J/cm fiber. The drug dose was escalated, by patient cohort, from 1 to 5 mg/kg. In the second phase (Table 1, part 2), a combination of escalating drug and light dosages was used. The former ranged from 2 to 4 mg/kg; light fluences of 500, 625, and 781 J/cm fiber, respectively, were used. Each patient received a single dose of drug and light, respectively, as predetermined by the enrollment cohort. Each cohort consisted of at least 3 patients; additional patients were enrolled within a cohort if additional safety data were required for that particular drug-light dose combination.

Photoangioplasty Protocol
On day 0, ~24 hours before photoangioplasty, the patient received a single intravenous dose of motexafin lutetium. Angiography was performed on day 1. Iliofemoral arterial dimensions were measured with the QCA Plus System (Sanders Data Systems). Reference and minimum diameters were used to calculate the percent stenosis at the level of photoactivation. Intravascular ultrasonography (IVUS) was performed before intervention. The commercial IVUS system (CVIS/Boston Scientific Corporation) was composed of a single-element 30- or 40-MHz transducer mounted on the tip of a flexible shaft rotated at 1800 rpm within a 3.2F short monorail polyethylene imaging sheath. Automated motorized transducer pullback was performed at a fixed speed of 1 mm/s. Ultrasound images were recorded on videotape for offline analysis.

After IVUS acquisition, a fiberoptic catheter was coaxially positioned under fluoroscopic guidance. Laser light energy was delivered through a 3-cm diffuser fiber at the fixed wavelength of 730±6 nm with either the Laserscope 600 series RTP-primed dye laser or the Diomed PDT diode laser. Endovascular illumination was performed for 941 seconds at the predetermined light fluence rate.

Clinical reassessment was performed on days 2, 7, 14, and 28. Angiographic and IVUS reevaluations were performed either on day 14 (the first 8 paired examinations) or on day 28.

Analysis
The objective clinical response to photoangioplasty with motexafin lutetium was assessed through serial measurement of the ABI. Overall clinical assessment was based on the Rutherford-Becker standardized classification of clinical outcomes. Summary measures included point and 95% CI estimates for the median effect on angiographic stenosis and ABI.

Results
There were 51 photoangioplasty procedures performed in 47 patients. Of these 34 men and 13 women, 4 patients received drug but did not undergo photoactivation because vascular anatomy precluded safe completion of photoangioplasty. These 4 patients completed the safety follow-up. Two additional patients underwent the photoangioplasty procedure but failed to complete the protocol with follow-up imaging of the treated vascular segment. The age range of the patient population was 45 to 87 years (mean, 65.5±8.7 years). At baseline, the median resting ABI was 0.74 (interquartile range, 0.62 to 0.85).

Therapy was well tolerated throughout the dose range of motexafin lutetium (1 to 5 mg/kg) and light (400 to 781 J/cm fiber) tested. The infrequent side effects were limited to transient paresthesias and minor, transient, self-limited cutaneous eruptions (Table 2). Skin rashes were not limited to light-exposed regions of the skin. No phototoxic manifestations were observed. There were no clinically relevant hematologic or serum chemistry abnormalities. Procedural complications included chiefly groin hematomas. One instance of bilateral, distal athereomobolism was judged a complication of diagnostic catheter manipulation and not ipsilateral endovascular illumination. One arterial dissection, noted after angiography and IVUS (before photoangioplasty), required stent placement in the superficial femoral artery. One procedure was complicated by a prototype device failure that did not influence the clinical outcome of the procedure. There were no procedural complications directly ascribed to the experimental photoangioplasty. Serial IVUS disclosed no evidence of vascular damage, thrombus, hemorrhage, dissection, or increase in calcium deposition in the vascular segments treated. Furthermore, no deleterious effects were observed in the adjacent, untreated segments of the vessel wall. Serial quantitative angiography disclosed no evidence of adverse vascular responses.

Although this study was neither designed nor statistically powered to assess the clinical efficacy of photoangioplasty with motexafin lutetium, several secondary end points lent themselves to examination. Forty-three paired angiographic assessments were available. The median change in arterial stenosis was −4.0%, based on percent change from the baseline stenosis (95% nonparametric CI −10.4% to 1.9%) (Figure 1). Similarly, analysis of paired ABIs in the 47 patients treated with motexafin lutetium photoangioplasty showed a median improvement in percent change from baseline ABI of 3.6% (95% CI −1.0% to 9.4%) (Figure 2).

Finally, the standardized classification of clinical outcomes (based on the Rutherford-Becker classification2) for the 47 patients at follow-up showed improvement in 29 (62%), no change in 17 (36%), and moderate worsening in 1 (2%). The percent change in the ABI of the treated leg correlated significantly with the clinical outcome (Spearman correlation coefficient 0.372, P=0.01).

**Table 1. Design of Study Cohorts**

<table>
<thead>
<tr>
<th>Drug Dose, mg/kg</th>
<th>Rate, mW/cm Fiber</th>
<th>Fluence, J/cm Fiber</th>
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<tbody>
<tr>
<td>Part 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>425</td>
<td>400</td>
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<tr>
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<tr>
<td>Part 2</td>
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<td>2</td>
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<td>500</td>
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<tr>
<td>2</td>
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<td>3</td>
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**Table 2. Observed Side Effects After Antrin Photoangioplasty**

<table>
<thead>
<tr>
<th>Dose, mg/kg</th>
<th>Paresthesias, n</th>
<th>Skin Rash, n</th>
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<tr>
<td>1</td>
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<tr>
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<td>5</td>
<td>2/3</td>
<td>0/3</td>
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The current phase I study tests the concept that the texaphyrins might circumvent the limitations of earlier photoactivated agents. Motexafin lutetium, a water-soluble photosensitizer, is currently in clinical trials for the treatment of advanced cancers. Early animal model studies of atherosclerosis suggest that photoangioplasty with motexafin lutetium may induce atherosclerotic plaque regression. Efficient reduction of atherosclerotic plaque burden has been demonstrated after in vivo PDT with motexafin lutetium in animals. Histological analysis of the posttreatment specimens reveals selective reduction in plaque area in a hypercholesterolemic rabbit model; furthermore, balloon-injury models of atherosclerosis reportedly respond to photoangioplasty with a significant reduction in macrophage density within the treated lesions.

In the 47 patients treated with motexafin lutetium photoangioplasty in this study, there was no evidence of significant, dose-limiting systemic toxicity. Adverse reactions were limited to infrequent, transient, self-terminating episodes of paresthesias and minor skin eruptions. There was no angiographic or ultrasonographic evidence of embolization, vascular trauma, or disease progression that could be ascribed to the experimental treatment.

Although this study was designed to investigate safety and was not statistically powered to assess efficacy, the paired observations of ABI and quantitative angiography suggest potential for a therapeutic effect of photoangioplasty with motexafin lutetium. The classification of clinical outcomes describes a trend toward clinical improvement that correlates with the observed changes in the ABI.

In summary, this phase I study of photoangioplasty with motexafin lutetium demonstrates that it is safe and well tolerated. Further placebo-controlled trials are clearly warranted. Preliminary efficacy data suggest that the approach holds promise as an alternative intervention for flow-limiting atherosclerosis.

Acknowledgments

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References

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