Phase I Drug and Light Dose-Escalation Trial of Motexafin Lutetium and Far Red Light Activation (Phototherapy) in Subjects With Coronary Artery Disease Undergoing Percutaneous Coronary Intervention and Stent Deployment

Procedural and Long-Term Results

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Background—Motexafin lutetium (MLu; Antrin) is a photosensitizer that is taken up by atherosclerotic plaque and concentrated within macrophages and vascular smooth muscle cells. After photoactivation with far red light, MLu facilitates production of cytotoxic oxygen radicals that mediate apoptosis. We assessed the safety and tolerability of phototherapy (PT) with MLu in patients undergoing percutaneous coronary intervention with stent deployment.

Methods and Results—An open-label, phase I, drug and light dose-escalation clinical trial of MLu PT enrolled 80 patients undergoing de novo coronary stent deployment. MLu was administered to 79 patients by intravenous infusion 18 to 24 hours before procedure, and photoactivation was performed after balloon predilatation and before stent deployment. Clinical evaluation, serial quantitative angiography, and intravascular ultrasound were performed periprocedurally and at 6 months follow-up. MLu PT was well tolerated without serious dose-limiting toxicities, and side effects (paresthesia and rash) were minor. No adverse angiographic outcomes were attributed to phototherapy.

Conclusions—This study demonstrates that coronary MLu PT seems safe, and the maximum well-tolerated MLu dose and range of tolerated light doses were identified. These data can be used in phase II efficacy trials of MLu PT for the treatment of coronary atherosclerosis or vulnerable plaque. (Circulation. 2003;108:1310-1315.)

Key Words: motexafin lutetium ■ phototherapy ■ atherosclerosis ■ restenosis

Inflammation is implicated in the pathogenesis of acute coronary syndromes and the vascular response to percutaneous coronary intervention (PCI), particularly stent deployment. After coronary stent deployment, monocyte-macrophage infiltration is prevalent in the stented segment and is directly correlated with the degree of neointimal proliferative response.1,2 Motexafin lutetium (MLu, Antrin) belongs to a class of compounds termed texaphyrins, which are synthetic expanded porphyrins that localize in diseased tissue and alter intracellular oxidation-reduction balance.3–5 MLu selectively targets and accumulates in metabolically active inflammatory cells, such as macrophages in atheromatous plaque, likely in part by LDL-receptor–mediated mechanisms.6–12 Animal studies have shown that after photoactivation (ie, phototherapy) by far red light (732-nm wavelength), MLu facilitates absorbed energy transfer with the generation of cytotoxic oxygen (eg, singlet oxygen) radicals, which mediate macrophage and smooth muscle cell apoptosis.8,11,12 We assessed the clinical safety and tolerability as well as the coronary arterial effects of phototherapy (PT) with MLu as part of a....
Study Population

The study population comprised 80 patients who satisfied inclusion criteria, which included being ≥18 years of age with a target stenosis ≥50%, target lesion length ≤30 mm, and ability to provide informed consent. Exclusion criteria included a target lesion within a previously placed stent (in-stent restenosis) or involving the left main or ostial left anterior descending, angiographic evidence of thrombus, aneurysm, diminished (TIMI grade ≤1) coronary flow, or marked (>45-degree) target site vessel angulation; hepatic or renal insufficiency; history of stroke (within 6 months), porphyria, or myocardial infarction (within 48 hours); left ventricular ejection fraction <30%; target vessel <2.5 or >4.5 mm diameter; white blood cell count <3000; platelet count <100,000; alanine aminotransferase, or alkaline phosphatase >3× upper limit normal; and allergy to aspirin, clopidogrel, or heparin.

Experimental Design

This study was designed in 2 stages to assess sequential MLu and light dose escalation, as follows.

Stage 1

MLu dose escalation was performed in 7 sequential cohorts of ≥5 patients, each beginning at 0.05 mg/kg and ending with 4.0 mg/kg MLu (Figure 1). The far red laser light dose was held constant at 100 J/cm-fiber in this stage.

Stage 2

MLu was administered sequentially in doses of 2 and 3 mg/kg, and light dose escalation was performed (200, 400, and 600 J/cm-fiber) in cohorts of ≥5 patients at both MLu dose levels administered. Each patient cohort was individually assessed by the steering committee of the trial for safety and tolerability before enrolling subsequent patient cohorts.

Study Objectives

The primary objective of this study was to evaluate the safety and tolerability of MLu PT in subjects undergoing PCI with stent deployment. The primary outcome variables assessed included dose-limiting toxicities associated with MLu injection or subsequent endovascular illumination and PT procedural adverse events, including death, stroke, or myocardial infarction. Myocardial infarction was defined as either Q-wave (development of new, pathologic Q-waves in ≥2 continuous ECG leads with postprocedural CK or CK-MB levels close to normal or non-Q-wave (CK or CK-MB ≥3× upper limit of normal in the absence of new Q-waves). Secondary objectives included the evaluation of the extent of restenosis in the PT-treated lesion and exploration of MLu pharmacokinetics in this patient population. Secondary end points assessed included late coronary lumen loss/loss index by quantitative coronary angiography (QCA) or intravascular ultrasound (IVUS) at 6 months and binary (>50%) QCA restenosis and target lesion and target vessel restenosis as well as target vessel failure. The institutional review boards of all participating institutions approved this protocol, and all patients signed informed consent before participation.

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MLu Administration

MLu was administered by intravenous infusion over 10 to 20 minutes at least 18 hours and no longer than 24 hours before the PCI procedure. Patients were observed clinically for 2 hours after MLu infusion and were instructed to avoid direct, intense sunlight exposure for 1 week after MLu administration.

PCI Procedure

PCI was performed from the femoral artery approach using ≥6F guide catheters per routine of the participating institution. Adjunctive platelet GP IIb/IIIa inhibitor therapy was administered at the discretion of the investigator, and intravenous heparin was administered to achieve a target in-laboratory ACT of >200 seconds (in conjunction with GP IIb/IIIa blockade) or >250 to 300 seconds (no GP IIb/IIIa blockade). All patients received oral clopidogrel 300 mg on the day before PCI and 75 mg daily thereafter in addition to aspirin 325 mg daily throughout the study. The target lesion was predilated to facilitate laser fiber endovascular illumination after administration of intracoronary nitroglycerin (≥100 μg). IVUS was performed before and after balloon predilatation as well as after subsequent stent deployment using a commercial system (CVIS, Boston Scientific Corporation) using a motorized pull-back technique (0.5 mm/s). Ultrasound images were recorded on videotape for subsequent core laboratory analysis. After the endovascular illumination procedure, stent deployment was performed according to institutional standards and was followed by final IVUS and QCA evaluation. Both IVUS and QCA analyses were performed by central core laboratories (IVUS-Standard University; QCA-Brigham and Women’s Hospital). The IVUS findings of this study are the subject of a separate report.

Endovascular Illumination

After predilatation, a flexible optical fiber (0.018-inch OD), with a distal active illumination length of 30 or 50 mm from which light emission is circumferential and uniform, was delivered under fluoroscopic guidance through a Transit catheter (2.5F; Cordis Corporation). Light at a wavelength of 732 ±6 nm was produced by a 730/6 class IV diode. Illumination lasted 12 minutes, after which the laser fiber was removed and stent deployment was followed. The timing of PT relative to MLu administration (18 to 24 hours after) was chosen to allow MLu clearance from plasma, thus minimizing circulating MLu that could impede light delivery to the vessel wall. Power densities delivered by fluence rates administered are shown in Table 1. Device success was defined as successful delivery of the optical fiber when attempted, and PT procedural success was defined as device success without the occurrence of a major adverse cardiovascular event (death, myocardial infarction, or requirement for urgent surgical or percutaneous repeat revascularization) in hospital.

Pharmacokinetics

Blood samples were obtained for pharmacokinetic analysis at baseline (pre-MLu infusion) and at 5 minutes, 3, 5 to 12, 17 to 24, and 36 to 60 hours, and 6 days after termination of MLu infusion. Pharmacokinetic parameters were estimated using noncompartmental methods.
TABLE 2. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Stage I (n=44)</th>
<th>Stage II (n=35)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>64.2 (9.3)</td>
<td>63.5 (10.4)</td>
<td>63.9 (9.8)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>28 (63.6)</td>
<td>28 (80.0)</td>
<td>56 (70.9)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>7 (15.9)</td>
<td>9 (25.7)</td>
<td>16 (20.3)</td>
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<tr>
<td>Prior MI (%)</td>
<td>20 (45.5)</td>
<td>21 (60.0)</td>
<td>41 (51.9)</td>
</tr>
<tr>
<td>NYHA angina class I (%)</td>
<td>15 (34.1)</td>
<td>10 (28.6)</td>
<td>25 (31.6)</td>
</tr>
<tr>
<td>Class II (%)</td>
<td>29 (65.9)</td>
<td>25 (71.4)</td>
<td>54 (68.4)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>28 (63.6)</td>
<td>22 (62.9)</td>
<td>50 (63.3)</td>
</tr>
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MI indicates myocardial infarction.

Statistical Analysis

Statistical analyses included descriptive summaries of baseline characteristics, procedural data, and all safety variables, including adverse events, terminations, vital signs, and clinical laboratory results. In addition, an exploratory analysis of QCA and IVUS variables was conducted, with descriptive summaries rather than statistical comparisons. Analyses were performed in SAS (Version 8).

Results

A total of 80 patients were enrolled at 8 clinical sites in the United States, of which 75 patients received the complete MLu-endovascular illumination treatment sequence. Of the 4 MLu-treated patients who did not undergo endovascular illumination, 1 patient had MLu infusion terminated prematurely because of the development of an acute erythematous cutaneous reaction, 1 patient had previously unrecognized left main coronary artery disease on the control guide catheter angiogram, and 2 patients experienced occlusive coronary dissection requiring immediate stent deployment after balloon predilatation in preparation for and before laser fiber delivery. Patient demographics by study stage and in aggregate are depicted in Table 2. The most commonly observed adverse MLu infusion–related events included peripheral paresthesias and rash (Table 3), which were not definitively related to MLu or endovascular illumination, observed in the aggregate study cohort included back pain (28%), chest pain (22%), bradycardia (18%), dyspnea (17%), hypotension (15%), headache (14%), dizziness (13%), and peripheral edema (11%).

Procedural Outcomes

The distribution of target vessels for MLu PT was left anterior descending coronary artery (40%), right coronary artery (32%), and left circumflex coronary artery (28%). The mean (±SD) stent length deployed was 19.1 (7.8) mm, and mean stent diameter was 3.3 (0.4) mm. Optical fibers with 30- or 50-mm diffuser lengths were used in 89% and 11% of procedures, respectively. Adjunctive GPIb/IIa inhibitor therapy was administered in 54.4% of procedures. The optical fiber was successfully delivered in all patients (device success, 100%) in whom endovascular illumination was attempted, and all patients tolerated the 12-minute illumination period without incident. Procedural success was 90% with 8 patients experiencing a periprocedural non-Q-wave myocardial infarction. No patient experienced death, stroke, Q-wave myocardial infarction, urgent repeat revascularization, or stent thrombosis through 30 days follow-up. Beyond 30 days (range, 71 to 189 days), 15 (19%) patients experienced adverse outcomes, including non-Q-wave myocardial infarction (n=6) and symptomatic target lesion revascularization (n=11), with 2 patients experiencing both infarction and revascularization.

Quantitative Coronary Angiography

Core laboratory QCA analysis of stented, injury, illumination zone, and entire (includes 5-mm margins proximal and distal to illuminated segments to assess for edge effect) PT arterial segments was performed (Figure 2). Baseline QCA for the entire study population revealed target lesion eccentricity (24%), calcification (13%), ulceration (7%), and diminished TIMI flow (<3) in 3%. QCA parameters at baseline and after PCI are depicted in Table 4. Follow-up QCA by study stage and segment analyzed is shown in Table 5. The mean length (mm±SD) for each QCA segment analyzed was as follows:

...
Pharmacokinetic Analysis

The maximum plasma concentrations ($C_{\text{max}}$) increased proportionally to the administered dose over the dose range studied. After IV administration, MLu rapidly clears from the plasma, with MLu concentrations declining to 8.9% of $C_{\text{max}}$ by 24 hours after administration of a 3-mg/kg dose. However, the $t_{1/2}$ was dependent on the length of the sample collection period. Collection to 168 hours after dose revealed a slower elimination of MLu ($t_{1/2} = 39.2$ hours) compared with collection to 42 hours after dose ($t_{1/2} = 13.3$ hours). The mean total body clearance was significantly greater ($P<0.05$) with 168-hour sample collection compared with 42-hour collection (1169 versus 791 mL/h, respectively).

Discussion

The promise of PT lies in the ability of a specific photosensitizing agent to selectively accumulate in a target tissue so that subsequent photoactivation of the sensitizer may mediate target tissue damage while sparing surrounding normal tissues. Prior application of PT has been hampered by the poor blood and tissue penetration of shorter light wavelengths ($<700$ nm). MLu is an attractive agent for PT, because uptake by atherosclerotic plaque (relative to adjacent normal vessel wall) occurs at a ratio of 16:1 to 34:1 and its longer wavelength for photoactivation (732 nm) reduces attenuation of light energy by blood and tissues.

A prior phase I study of MLu (doses 1 to 5 mg/kg) PT (light fluence of 400 to 781 J/cm per fiber) in subjects with peripheral arterial insufficiency secondary to stenosis of the iliac, common, or superficial femoral arteries has been reported. In this prior study, MLu PT was performed as a stand-alone intervention (without balloon angioplasty or stent deployment) in large-caliber peripheral arterial vessels, and follow-up angiographic or IVUS assessment was limited to either 14 or 28 days. No evidence of vascular damage, thrombus, or dissection was observed, and minor, self-limited side effects of paresthesia or rash were noted.

The present phase I coronary study supports the apparent safety and tolerability of this treatment and materially extends our understanding of this emerging therapy in several ways. First, MLu PT seems to be well tolerated to MLu doses up to 4 mg/kg. Although dose-related peripheral paresthesia and rash were commonly observed, these side effects were generally mild and self-limited. No serious adverse events definitely related to MLu infusion or endovascular illumination were observed in the present cohort of 79 dosed patients, which represents the largest single clinical experience with PT to date. Second, no adverse angiographic or IVUS outcomes were observed at up to 6 months, the longest follow-up with PT to date. Specifically, no edge stenosis or promotion of restenosis at the margins proximal or distal to the zone of illumination was observed.

The present experience does not provide randomized placebo control groups for either drug or laser light treatment from which to demonstrate the therapeutic effects of PT. Although the numbers of patients analyzed in each treatment cohort are small, no adverse angiographic effects of MLu PT were apparent, and measures of late lumen loss were comparable to those reported from QCA analyses from recent stainless steel stent studies. The binary restenosis rates observed in the present study for the entire arterial segments analyzed (sten+injury+illumination+edge) must be interpreted in the context of the total length of artery assessed. For example, recent QCA analyses evaluating new stent technologies have reported only in-stent or in-segment (includes 3- to 5-mm margin) measurements. By expanding the window of observation to include all portions of the target artery that might have been influenced by any facet of PT (average±SD length of entire segment, 49.8±11.9 mm), the...
opportunity to capture more late stenosis events, whether provoked by PT or not, is intuitively obvious. Furthermore, attempts at comparison of the stent segment analysis from the present study with stent segment analyses from recent registry reports must acknowledge the lack of standardization for stent design or strut thickness and deployment technique in the MLu PT experience. In the context of the above-noted limitations, values for late loss and binary restenosis observed in this phase I MLu PT experience seem comparable with those reported from trials of bare metal stenting alone (no PT).

The present study better defines the range for selection of optimal dose regimens for both MLu and light energy to be used in combination. In addition to confirming safety and tolerability of MLu PT as an adjunct to PCI, this study provides the dose-ranging framework required to design a larger, placebo-controlled randomized trial with adequate statistical power to assess therapeutic efficacy. Furthermore, the pharmacokinetic profile of MLu in patients with atherosclerotic cardiovascular disease has been better delineated and suggests that greater than 90% of MLu is eliminated from plasma by 24 hours after intravenous bolus dose. Although the optimal timing of PCI relative to intravenous MLu administration was not tested, the delay in performance of PCI (18 to 24 hours after dosing) was specifically chosen to allow the major portion of plasma MLu to be cleared so that circulating drug absorbance of red light laser energy and,

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stent Injury Illumination Entire Analysis</th>
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<tbody>
<tr>
<td>MLD, mm</td>
<td>Median 1.52 1.52 1.48 1.43</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) 1.62 (0.79) 1.61 (0.80) 1.52 (0.69) 1.51 (0.68)</td>
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<tr>
<td></td>
<td>95% CI (1.36, 1.88) (1.35, 1.87) (1.30, 1.75) (1.29, 1.73)</td>
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<tr>
<td>Late loss, mm</td>
<td>Median 1.1 0.8 0.6 0.6</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) 1.1 (0.59) 0.9 (0.64) 0.6 (0.48) 0.6 (0.55)</td>
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<tr>
<td></td>
<td>95% CI (0.9, 1.3) (0.7, 1.1) (0.5, 0.8) (0.4, 0.8)</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>Median 42.5 44.0 43.9 44.7</td>
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<tr>
<td></td>
<td>Mean (SD) 42.9 (22.9) 43.4 (23.1) 46.2 (20.2) 46.8 (19.8)</td>
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<tr>
<td></td>
<td>95% CI 35.4 to 50.5 35.9 to 51.0 39.6 to 52.9 40.3 to 53.3</td>
</tr>
<tr>
<td>Binary restenosis (&gt;50%), %</td>
<td>39.5 42.1 42.1 44.7</td>
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<table>
<thead>
<tr>
<th>Stage 2</th>
<th>Stent Injury Illumination Entire Analysis</th>
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<tr>
<td>MLD, mm</td>
<td>Median 2.07 1.99 1.75 1.75</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) 1.90 (0.74) 1.80 (0.72) 1.74 (0.68) 1.72 (0.65)</td>
</tr>
<tr>
<td></td>
<td>95% CI 1.63 to 2.16 1.54 to 2.05 1.50 to 1.98 1.49 to 1.96</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>Median 1.0 0.9 0.6 0.4</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) 0.9 (0.62) 0.9 (0.64) 0.6 (0.58) 0.6 (0.59)</td>
</tr>
<tr>
<td></td>
<td>95% CI 0.7 to 1.2 0.7 to 1.2 0.4 to 0.8 0.4 to 0.8</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>Median 33.4 33.8 39.6 39.6</td>
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<td></td>
<td>Mean (SD) 37.5 (21.3) 40.7 (21.2) 42.5 (19.7) 43.1 (19.0)</td>
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<tr>
<td></td>
<td>95% CI 29.9 to 45.0 33.2 to 48.2 35.6 to 49.5 36.4 to 49.8</td>
</tr>
<tr>
<td>Binary restenosis (&gt;50%), %</td>
<td>27.3 30.3 30.3 30.3</td>
</tr>
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</table>

MLD indicates minimum lumen diameter.

Figure 3. Mean (±SE) late lumen loss by quantitative coronary angiography stratified by study stage, MLu dose, and light fluence.
thus, interference with tissue light dose delivery would be minimized. Another theoretical concern for PT of coronary heart disease, that the depth of light penetration, especially at higher fluences, could result in activation of MLu in the myocardial microvasculature surrounding the illuminated vessel with resultant myocardial necrosis, was also not evident from the present analysis. Indeed, no correlation of periprocedural creatine kinase-MB with either MLu or light energy dose was observed.

Future Directions

The present phase I drug and light dose-escalation study of MLu PT in patients undergoing PCI with stent deployment provides the requisite framework for safe application of this technology in future studies. Although the patient population evaluated (PCI with stent deployment) was selected for expediency as well as to provide IVUS and QCA evidence of safety and toxicity, other patient populations with disease processes for which vascular inflammation is central could be favorably modified by this therapy in future studies. For example, the spectrum of vulnerable plaque, plaque rupture, and acute coronary syndromes seems to be integrally linked by the presence and degree of vascular inflammation.25–28 Indeed, mononuclear cell inflammatory infiltrate in conjunction with monocyte colony stimulating factor has been implicated in the pathogenesis of vascular smooth muscle cell apoptosis, depletion, and subsequent weakening of plaque infrastructural integrity, which precipitates plaque rupture.29 Thus, although the present study defines important parameters for the application of PT therapy, the selection of optimal patient cohorts and the potential utility of PT as a stand-alone therapeutic modality that targets an underlying vascular inflammatory process remains to be investigated. The MLu and light energy doses defined by the present study (MLu, 2 to 3 mg/kg; light fluence, 100 to 400 J/cm-fiber) seem to be safe and well tolerated for future assessments of therapeutic efficacy.

References

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