Motexafin Lutetium Phototherapy Decreases Vascular Inflammation in Rabbit Atheroma: Implications for Vulnerable Plaque Therapy

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Background: Motexafin Lutetium (MLu) is an expanded porphyrin, decreases Mac3 in rabbit atheroma when locally administered and photoactivated. We studied the effect of MLu phototherapY on human macrovascular and the effect of systemic MLu following local photolocalization (723nm) on vascular Mac3 burden, as well as thermal effects of balloon illumination in vivo.

Methods: In vivo human macrovascular (THP-1) were mixed with MLu (10 nM/ml), then photoactivated (2 J/cm²; drug uptake (histofluorescence), growth and differentiation of MLu count) were assessed. In vivo: After 14 hrs on 2% chlo, 48 rabbits were randomazod to 7 groups: (1) Control (5% mannitol); (2) MLu (10 mg/kg); (3) Light (100 J/cm² in balloon, 300 J/cm² with bare fiber); and MLu + light, 10, 30, 100 and 300 J/cm² as groups 4–7. Light was delivered to upper thoracic aorta via a balloon and lower thoracic aortic branch by a bare fiber for 900 seconds, 24 hrs after i.v. MLu. At 2 more weeks, animals were examined for plaque (FM ratio) and Mac3 (PAN-1 stain). Six more animals underwent balloon illumination (30–500 J/cm²) with adventitial temperatures of vessels continuously recorded by an infrared camera. Results in vitro, MLu was taken up by Mac3 90 min post illumination and retained over 24hr. MLu reduced macrovascular monocytes (723nm) to Mac3 (43.6% of control, p=0.01). MLu phototherapY (24h) induced apoptotic death in Mac3 (44.8±3.2% vs control 9.8±1.0%, p<0.01). In vivo, MLu phototherapY at lower light levels reduced vascular Mac3 burden (0% total area from 28.1±1.41 control to 12.0±1.4 to 10 J/cm² and 16.4±2.5 at 30 J/cm² in balloon (p=0.05), and from 8.9±1.6 (control) to 4.4±1.5 at 30 J/cm² and 4.5±2.0 at 100 J/cm² with bare fiber (p=0.05), but did not change plaque burden. Adventitial temperature increased up to 15°C at 300 J/cm² and 3°C at 100 J/cm², with no change at 30 J/cm². Conclusions: MLu phototherapY decreases lower light fluorescence, in the absence of regression, possibly by reduction of macrovascular differentiation and Mac3 apoptosis. Thermal effects at higher light intensity may reduce efficacy. MLu phototherapY may be useful in plaque stabilization.

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Long Term Effects of Ocerotide Therapy: A Somatostatin Analog, on In-Stent Restenosis

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Background: Although somatostatin analogs have been shown to reduce neointimal reaction in animal models but to have no definite good result in human balloon angioplasty, the role of reducing in-stent restenosis (ISR) in human has not been evaluated. Neointimal hyperplasia shown to be decreased by the ocerotide therapy is accepted as the predominant mechanism of ISR in-stent as well as neointimal hyperplasia is only one of the major responsible mechanisms of restenosis after angioplasty. The purpose of this study was to assess the long-term effects of ocerotide on the in-stent restenosis at six-month follow-up coronary angiography.

Methods: In a placebo-controlled, randomized study, of the 176 patients, the finally evaluated 148 patients with significant coronary disease (stenosis > 70%) amenable to stenting were enrolled into ocerotide therapy. ISR was defined as neointimal diameter stenoses > 50% at follow-up angiography. Stenting was considered a failure if the residual diameter stenoses was less than 10%.

Results: There was no significant difference between ocrerotide and placebo groups in the pre (85.6% ± 5.6% and 85% ± 5.4% at 10 J/cm² and 10 J/cm² at 30 J/cm² and 30 J/cm² in balloon (p=0.05), and from 8.9±1.6 (control) to 4.4±1.5 at 30 J/cm² and 4.5±2.0 at 100 J/cm² with bare fiber (p=0.05), but did not change plaque burden. Adventitial temperature increased up to 15°C at 300 J/cm² and 3°C at 100 J/cm², with no change at 30 J/cm². Conclusions: MLu phototherapY decreases lower light fluorescence, in the absence of regression, possibly by reduction of macrovascular differentiation and Mac3 apoptosis. Thermal effects at higher light intensity may reduce efficacy. MLu phototherapY may be useful in plaque stabilization.

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Effect of Simvastatin on the Inflammatory Response to Coronary Angioplasty

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Background: Previous studies have reported treatment with the HMG-CoA reductase (HMG-CoA) inhibitor simvastatin reduces serum C-reactive protein (CRP) levels, suggesting an anti-inflammatory effect that appears to be fully established within 4 weeks of commencing therapy. Coronary angioplasty is associated with an acute increase in serum inflammatory markers which may predict early complications. The effect of simvastatin on this inflammatory marker is unknown. The aim of this study was to determine whether pre-treatment with simvastatin reduces the inflammatory response to coronary angioplasty.

Methods: We studied 92 patients (mean age 60±10 years) randomised to simvastatin (40 mg/day) or placebo (n=46) a median of 11.9 months (IQR 0.9 to 3.6 months) before elective coronary angioplasty. All patients were taking aspirin 150mg/day unless there was a specific contraindication (aspirin use 92% for simvastatin group, 95% for placebo group, p=NS). CRP was measured by high sensitivity immunoassay on serum samples taken immediately prior to and 48 hours after angioplasty.

Results: The CRP (median(IQR) immediately prior to angioplasty was 1.3mg/l (0.71-2.43) for the placebo group, versus 1.46mg/l (0.67-2.14) for the simvastatin group, p=0.79. CRP increased post-PCI for both groups (p=0.001 for both simvastatin and placebo). Simvastatin did not alter this inflammatory response; the increase in CRP (pro-angioplasty to 48 hours post-angioplasty) was not significantly different in placebo patients randomised to simvastatin with 4.68mg/l (1.9 to 10.3) compared to 5.18mg/l (1.2-2.9) for placebo (p=0.95). Exclusion of patients on simvastatin for less than 4 weeks prior to angioplasty did not alter this result.

Conclusion: There was an increase in CRP measured 48 hours after angioplasty, confirming an inflammatory response. Simvastatin did not significantly influence this inflammatory response.

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Neither Periprocedural Pregnancy-Associated Plasma Protein A nor C-Reactive Protein Levels Predict Restenosis

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Background: Matrix metalloproteinases including Pregnancy-Associated Plasma Protein A (PAPP-A) are abundantly expressed at sites of atherosclerotic plaque rupture, are predictive of acute coronary syndromes when circulating levess are elevated, and may play an important role in the development of restenosis following percutaneous coronary intervention (PCI). C-reactive protein (CRP) levels increase following PCI, peaking at 48 to 72 hours, but the effect of this inflammatory response on restenosis is unclear. The aim of this study was to determine whether periprocedural levels of PAPP-A and/or CRP predict restenosis.

Methods: We studied 136 patients with stable angina who underwent elective PCI with stored peri-procedural blood samples and corresponding pre-, post-, and six month coronary angiograms; age (mean±SD) 59±10 yrs, 83% male. siat insertion rate 14%. CRP and PAPP-A were measured by high sensitivity immunoassay on EDTA-plasma samples which had been taken immediately prior to, and 44 hours post PCI. All results are expressed as median (IQR). Restenosis (diameter stenosis >50%) six months after PCI was determined by quantitative coronary angiographic (QCA) analysis. In multi vessel PCI (30% of patients), stenosis was scored on a "poor pattern" basis by averaging the percent diameter stenosis of all lesions.

Results: CRP was associated with a significant rise in both CRP and PAPP-A levels; peak CRP prior to PCI 1.2mg/l (0.7-2.2), post-PCI 6.5mg/l (4.0-13.2), p<0.0001. PAPP-A prior to PCI 4.1IU/l (3.3-5.1), post-PCI 5.8IU/l (4.3-7.2), p=0.0001. The median stenosis at six months was 46% (IQR 34-63%) and the binary restenosis rate was 42%. There were net elevations of CRP, IC-CBS group had an earlier rise in CRP (p=0.002 by 8 hrs) and an earlier peak (16.3 hrs vs 28.1 hrs) compared with the IC-TG group.

Conclusions: Routine IC-CBS use is associated with an earlier rise of CRP enzymes after PCI. This supports the role of CCB as vasodilators of the microcirculation and suggests further avenues for research in enhancing blood flow at the tissue level of the myocardium during PCI.