Phase I/II Study of Simvastatin (Zocor) Therapy in Sickle Cell Disease

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Synopsis:
The numerous clinical complications associated with sickle cell disease (SCD) are primarily attributable to sickle-induced vascular damage. The vasculopathy of SCD is characterized by endothelial injury due to the effects of hypoxia, increased shear stress, abnormal endothelial adherence of sickled RBCs, and inflammation induced by reperfusion injury. Growing evidence indicates that this vasculopathy also promotes angiogenesis, activation of coagulation, and disordered vasoregulation. Therapies targeted at the pathways contributing to endothelial injury may thus ameliorate the progressive vascular damage that occurs in SCD.

The 3-Hydroxy-3-methyl-glutaryl CoA (HMG-CoA) reductase inhibitors, also known as statins, are potent inhibitors of cholesterol biosynthesis and have been used extensively to treat patients with hypercholesterolemia. Recent clinical and experimental data indicate that statins modulate yet other pathophysiologic processes, many of which play a major role in the vasculopathy of SCD. Simvastatin has been shown to be well-tolerated and safe in humans and appears to have significant NO enhancing effects in normocholesterolemic individuals. Numerous studies documenting the vasculoprotective effects of statins, together with preliminary data showing the therapeutic role of NO donors in SCD, provide a compelling rationale to investigate the potential clinical benefit of statins in SCD. We propose the following specific aims:

1. To determine the effect of oral simvastatin (Zocor) on vascular physiology in SCD, as measured by peripheral blood markers of endothelial injury.

2. To assess the safety and tolerability of oral simvastatin in patients with SCD.