Effect of Extended-Release Niacin on Serum Lipids and on Endothelial Function in Adults With Sickle Cell Anemia and Low High-Density Lipoprotein Cholesterol Levels

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Through bound apolipoprotein A-I (apoA-I), high-density lipoprotein cholesterol (HDL-C) activates endothelial nitric oxide synthase, inducing vasodilation. Because patients with sickle cell disease (SCD) have low apoA-I and endothelial dysfunction, we conducted a randomized, double-blinded, placebo-controlled trial to test whether extended-release niacin (niacin-ER) increases apoA-I-containing HDL-C and improves vascular function in SCD. Twenty-seven patients with SCD with levels of HDL-C <39 mg/dl or apoA-I <99 mg/dl were randomized to 12 weeks of niacin-ER, increased in 500-mg increments to a maximum of 1,500 mg/day, or placebo. The primary outcome was the absolute change in HDL-C level after 12 weeks, with endothelial function assessed before and at the end of treatment. Niacin-ER-treated patients trended to greater increase in HDL-C level compared with placebo treatment at 12 weeks (5.1 ± 7.7 vs 0.9 ± 3.8 mg/dl, 1-tailed $p = 0.07$), associated with significantly greater improvements in the ratios of low-density lipoprotein to HDL-C levels (1.24 vs 1.95, $p = 0.003$) and apolipoprotein B to apoA-I levels (0.46 vs 0.58, $p = 0.03$) compared with placebo-treated patients. No improvements were detected in 3 independent vascular physiology assays of endothelial function. Thus, the relatively small changes in HDL-C levels achieved by the dose of niacin-ER used in our study are not associated with improved vascular function in patients with SCD with initially low levels of apoA-I or HDL-C. Published by Elsevier Inc. (Am J Cardiol 2013;112:1499−1504)

Our laboratory has shown that patients with sickle cell disease (SCD) have significantly decreased high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apoA-I) levels.[1,2] We have also demonstrated that among patients with SCD, those with lower apoA-I levels have impaired vasodilatory responses to acetylcholine during forearm blood flow (FBF) strain gauge plethysmography and they tend to have elevated estimated pulmonary artery systolic pressures, an echocardiographic marker of pulmonary hypertension.[1] In support of this finding, in patients with pulmonary arterial hypertension without SCD, plasma HDL-C levels are low and predict clinical worsening and death.[3]

Extended-release niacin (niacin-ER) treatment promotes an increase in HDL-C level containing apoA-I.[4] In particular, niacin-ER inhibits the degradation and hepatic clearance of apoA-I-containing HDL-C, cholesterol ester transport to low-density lipoprotein cholesterol, and also the actions of hepatic lipase.[5] Interestingly, a precursor of niacin, nicotinic acid, was used in a case report in SCD with possible improvement in disease manifestations.[6] We reasoned that niacin-ER administration would increase levels of HDL-C and apoA-I in SCD and improve vascular function and tested this hypothesis in a randomized, double-blinded, placebo-controlled trial. Our primary outcome was an absolute change in HDL-C level, and secondary outcomes included absolute change in apoA-I level and physiologic assessments of improved vascular function.

Methods

This was a prospective, single-center, randomized, double-blinded trial comparing niacin-ER with placebo treatment. The National Heart, Lung, and Blood Institute's Institutional Review Board approved all protocols

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See page 1503 for disclosure information.

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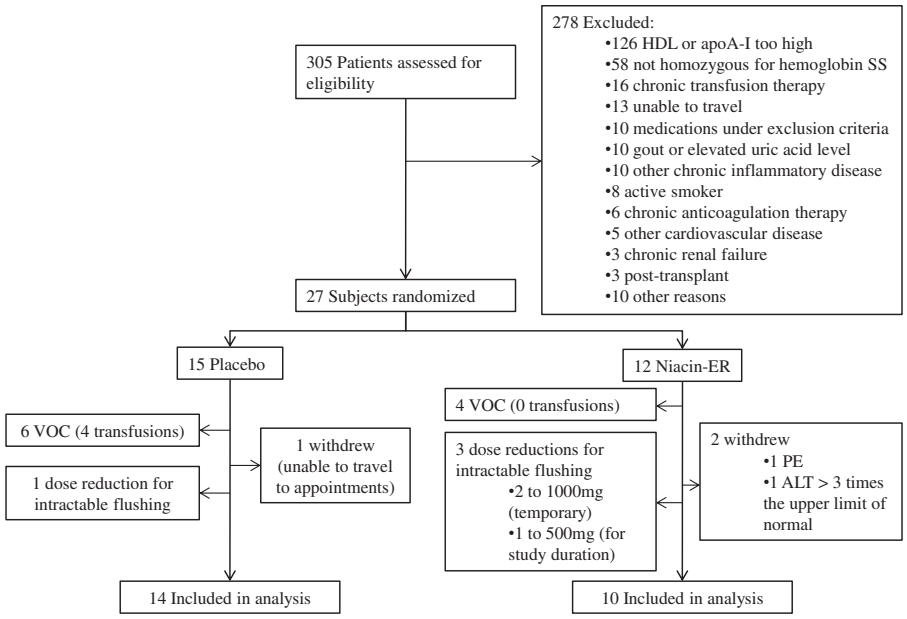

Figure 1. Study assignments and outcomes. Twenty-seven subjects were randomized to niacin-ER or placebo treatment. Fourteen placebo-treated and 10 niacin-ER-treated subjects completed the study; the subsequent analyses are based on these 24 completed cases. ALT = alanine aminotransferase; PE = pulmonary embolism; VOC = vaso-occlusive crisis.

(ClinicalTrials.gov identifier NCT00508989). All subjects provided written informed consent.

Subjects enrolled met all of the inclusion criteria: men or women 18 to 65 years of age, electrophoresis or high-performance liquid chromatographic documentation of homozygous hemoglobin S only phenotype, levels of HDL-C <39 mg/dl or apoA-I <99 mg/dl, level of hemoglobin >5.5 or <9.0 g/dl, and absolute reticulocyte count >95,000/μl. Subjects met none of the exclusion criteria: acute pain crisis requiring intravenous analgesics within 2 weeks before enrollment, women who were pregnant, lactating, or not using birth control at the time of enrollment, and hemoglobin SCD or hemoglobin A >20%. In addition, subjects were excluded if they used aspirin or nonsteroidal anti-inflammatory drugs within 1 week before vascular testing or used caffeine on the day of vascular testing. Pre-existing conditions that may independently affect endothelial function caused subjects to be excluded, including diabetes mellitus, cigarette smoking within 1 month before enrollment, renal failure, gout, and significant cardiovascular disease such as uncontrolled hypertension, peripheral artery disease, or severe hypotension. The use of medications including sildenafil, tadalafil, L-arginine, fibrates, inhaled nitric oxide, or any prostaglandins such as epoprostenol or treprostinil within 1 week before evaluation, or any statin within 4 weeks before enrollment caused subjects to be excluded.

Simple randomization was used to assign subjects to either 12 weeks of placebo or niacin-ER. The medication was incrementally dosed in 500-mg steps every 4 weeks as tolerated, to a maximum dose of 1,500 mg/day. Subjects were withdrawn if they developed: rhabdomyolysis (creatine kinase level of >5× the upper limit of normal), clinically significant myositis, red cell lysis, hepatocellular injury (alanine aminotransferase level of >3× the upper limit of normal or >123 mg/dl), elevated prothrombin time or partial thromboplastin time (to >1.5× control values), or intractable flushing unresponsive to ibuprofen therapy or dose reduction.

Our sample size calculation was based on a previous study of 11 subjects with coronary artery disease and initial HDL-C level of ≤36 mg/dl treated with niacin-ER (doses initiated at 375 mg and titrated up to 1,500 mg) for 12 weeks.[4] The mean HDL-C level in this group increased from 30.1 to 40.5 mg/dl, with SD of 4 mg/dl both before and after treatment.[7] Therefore, with $\alpha = 0.05$ and a 98% power, the sample size needed to detect a mean difference of 10 mg/dl with SD = 4 mg/dl was 13 in each treatment group (JMP version 8.0, SAS Institute Inc., Cary, North Carolina). Our original protocol was designed to enroll 40 subjects with SCD who met eligibility criteria, 20 randomized to niacin-ER, and 20 to placebo. An interim analysis was planned when 12 subjects in each group completed the study.

To measure vascular and/or endothelial function, FBF, flow-mediated dilation (FMD) of the brachial artery, and peripheral arterial tonometry were performed at baseline and after 12 weeks of treatment. FBF was measured similarly to that by Gladwin et al.[8] In brief, brachial artery and antecubital vein catheters were placed in the arm, with the intra-arterial catheter connected to a pressure transducer and an infusion pump that delivered 5% dextrose-in-water at 0.5 ml/min.[8] After 20 minutes of rest, acetylcholine was infused at 7.5, 15, and 30 μg/min, sodium nitroprusside was infused at 0.8, 1.6, and 3.2 μg/min, and N^G-monomethyl-L-arginine was infused at 4 μg/min. Each of the infusions was followed by a 30-minute washout with 5% dextrose-in-water infusion at 0.5 ml/min and repeat of a baseline measurement.[1,9] After 3 minutes of each infusion dose (or 5 minutes for N^G-monomethyl-L-arginine), FBF was measured.[1] Infusions were done with acetylcholine to test endothelium-dependent vasodilation, sodium nitroprusside to test endothelium-independent