Extended-Release Niacin for Dyslipidemic Patients with HIV Infection

Speaker: James H. Stein, MD, Associate Professor, Section of Cardiovascular Medicine, Department of Medicine, University of Wisconsin Medical School, Madison, Wisconsin

Extended-release (ER) niacin (Niaspan, Kos), well known for its value in lowering low-density lipoprotein-cholesterol (LDL-C) and total cholesterol and its ability to increase HDL-cholesterol (HDL-C) in patients with hypercholesterolemia and mixed dyslipidemia, has proved safe, well tolerated, and effective for treating dyslipidemia in patients with human immunodeficiency virus (HIV) infection who are receiving antiretroviral therapy (ART).

A total of 37 patients were initially enrolled into a two-step, open-label, dose-escalating, 48-week, single-arm protocol. All of the patients had triglyceride levels above 200 mg/dl and non–HDL-C levels above 180 mg/dl.

Step one included a four-week lipid-lowering diet, therapeutic lifestyle changes, and an activity guide. In step two, patients received ER niacin 500 mg nightly, titrated every four to six weeks to a target dose of 2,000 mg daily.

The primary endpoint of the study was to evaluate the safety and tolerability of ER niacin therapy over 44 weeks of lipid goal-directed therapy. Secondary endpoints included the product’s efficacy over 20 weeks and 44 weeks in lowering non–HDL-C, raising HDL-C, lowering triglycerides, and bringing about composite lipid goals over 44 weeks.

Of 33 men who entered step 2, 32 completed the study. Although there was some concern about insulin resistance and hepatotoxicity, which are common in HIV-infected individuals receiving niacin, ER niacin at doses up to 200 mg/day was safe and well tolerated. There were no significant changes in uric acid or aminotransferase levels. Although fasting glucose levels increased minimally at week 12 of treatment, the increase was transient, and there were no changes at weeks 24 or 48.

ART regimens were changed for five patients over the course of the study, but these adjustments did not appear to significantly affect the results of their dyslipidemia treatment.

Nearly 25% of patients (7 of 32) met the strict composite lipid goal at week 44, a rate better than that reported in similar statin and fibrate studies. Eight patients met the non–HDL-C criteria, 11 men met the LDL-C criteria, and 27 subjects met the triglyceride criteria.

On the basis of these findings, it was recommended that ER niacin, in combination with other lipid-lowering drugs, be studied in HIV-positive patients.

Long-Term Fenofibrate/Ezetimibe Effective in Mixed Hyperlipidemia

Speaker: James M. McKenney, PharmD, President and Chief Executive Officer, National Clinical Research, and Professor Emeritus, Virginia Commonwealth University School of Medicine, Richmond, Virginia

Long-term coadministration of fenofibrate (Antara, Reliant; TriCor, Abbott) and ezetimibe (Zetia, Merck/Schering-Plough) provided superior lipid-altering effects when compared with fenofibrate monotherapy, and it was well tolerated for up to 48 weeks in patients with mixed hyperlipidemia.

Mixed hyperlipidemia is associated with a high risk of coronary heart disease (CHD). Patients require treatment that effectively lowers LDL-C, triglyceride, and non–HDL-C levels.
while raising HDL-C concentrations. Fenofibrate and ezetimibe offer complementary effects on the lipid profile and together may improve mixed hyperlipidemia.

Researchers decided to compare the long-term safety and efficacy of fenofibrate plus ezetimibe with fenofibrate monotherapy in patients with mixed hyperlipidemia. Initially, 625 patients were enrolled in a 12-week base study and were randomly selected, in a 3:3:3:1 ratio, to receive fenofibrate 160 mg/day plus ezetimibe 10 mg/day (185 patients), ezetimibe 10 mg a day (187 patients), fenofibrate 160 mg a day (189 patients), or placebo (64 patients). Of the 587 patients who completed the 12-week base study, 576 continued into a 48-week extension study, with 340 patients receiving fenofibrate plus ezetimibe and 236 patients receiving fenofibrate monotherapy.

The primary efficacy variable was the percentage of change in LDL-C levels from the baseline of the initial study to the study’s endpoint in the extension, from 0 to 48 weeks. Secondary efficacy endpoints included the percentage of change from the baseline to the study’s endpoint in total cholesterol, LDL-C, triglycerides, non–HDL-C, apolipoprotein B (apo B), apo A-I, and high-sensitivity C-reactive protein (hs CRP).

Coadministration of fenofibrate plus ezetimibe was well tolerated during the 48-week extension study, and the safety profile was similar to that of fenofibrate monotherapy. The fenofibrate/ezetimibe regimen also resulted in significantly greater percentage reductions, compared with fenofibrate monotherapy in LDL-C (–22% vs. –9%), total cholesterol (–23% vs. –14%), TG (–46% vs. –42%) non–HDL-C (–32% vs. –19%) and apo B (–25% vs. –18%). Furthermore, HDL-C was significantly greater (10% vs. 8%), and the differences in hs CRP showed a trend in reduction (–25% vs. –21%). The changes in apo A-1, however, did not differ significantly between the groups (–10% vs. –8%).

**Omega-3 Fatty Acid Supplementation Improves Lipid Profile in Overweight Children**

**Speaker:** Gary A. Mayman, MD, Associate Professor, Cardiology Section, Department of Pediatrics, University of Nevada School of Medicine, and Co-Director, Children’s Heart Center, Las Vegas, Nevada

A group of overweight children who received a dietary supplement of fish oil containing omega-3 fatty acids (Omega RX, Zone Labs), showed a significant improvement in their lipid profiles, in contrast to children who did not receive the supplementation.

In studies of adults, there is growing evidence that diets high in omega-3 fatty acids decrease the risk of fatal ischemic heart disease and that early intervention might reduce the risk of cardiovascular complications later in life. A study was thus designed to assess the effects of dietary fish oil supplementation on the lipid profiles in overweight children and adolescents.

Forty-nine children, enrolled in a medically supervised weight-management program, participated in a 12-week, randomized clinical trial. All of the youngsters, 10 to 18 years of age, had a body mass index (BMI) above the 95th percentile. They received a diet low in glycemic load and participated in a supervised exercise program. They were assigned to a control placebo group or to a group receiving 3 grams of fish oil daily. Fasting blood samples were drawn in the first, sixth, and 12th weeks. A paired t-test for statistical analysis was conducted.

At the first visit, the lipid profiles were similar in both study groups. At week 12, the children receiving fish oil showed significantly improved triglyceride levels (reduced from 157 ± 74 mg/dl at baseline to 120 ± 49 mg/dl), compared with the controls (reduced from 163 ± 118 to 155 ± 77 mg/dl) at the end of the study. For children whose triglyceride/HDL-C ratio was greater than 3, there was a significant increase in HDL-C levels in those who received fish oil supplementation.

In the treated patients, HDL-C levels rose from 37 ± 5 mg/dl at week one to 41 ± 7 mg/dl at week 12. In the control group, HDL-C levels increased from 34 ± 4 mg/dl at week one to 35.6 mg/dl at week 12.

Although the intensive nutritional counseling, exercise, and psychological assistance resulted in improved lipid profiles in both groups of patients, it was the addition of omega-3 fatty acid supplementation that caused a marked improvement in the lipid profile, compared with only diet and exercise.

**Diet/Statin Therapy Reduces Coronary Heart Disease in Mild Hypercholesterolemia**

**Speaker:** Haruo Nakamura, MD, PhD, Emeritus Professor of Medicine, National Defense Medical College, Tokorozawa City, Saitama, Japan, and Study Chair of the MEGA Study

A combination of low-dose pravastatin (Pravachol, Bristol-Myers Squibb) markedly reduced the risk of coronary heart disease (CHD) in people with only moderately elevated cholesterol levels. This is the first time that a low-dose statin reduced the CHD risk in a low-risk population in a manner similar to that reported in statin trials of high-risk populations.

In the **Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trial,** 7,832 patients with mild hypercholesterolemia and no history of CHD were assigned to receive either dietary changes or diet plus pravastatin 10 mg/day in a prospective, randomized, open-label, blinded-endpoint evaluation design. Mild hypercholesterolemia was defined as a total cholesterol level of 220 to 270 mg/dl.

The doses for the active-treatment patients could be titrated to 20 mg/day of pravastatin if their total cholesterol level was above 200 mg/dl at eight weeks after the initial administration.

The follow-up schedule was originally to last for five years. Patients who consented to extend the study at the 60th month were followed for a maximum of 10 years.

Even a small reduction in cholesterol levels brought about significant changes in CHD risk. After an average follow-up period of 5.3 years, there was a 33% decrease in the incidence of CHD in the mildly hypercholesterolemic men and women who received dietary therapy and low-dose pravastatin, compared with the diet-only subjects. There were 3.3 CHD events per 1,000 person-years in the active-treatment patients and 5.5 CHD events per 1,000 person-years in the diet-only patients.

At the start of the study, the average baseline total cholesterol value was 243 mg/dl, and the LDL-C level was 157 mg/dl.
At 5.3 years of follow-up observation, total cholesterol levels in the diet-only patients decreased by 2.1%; for the diet/pravastatin patients, they decreased by 11.5%. LDL-C concentrations decreased by only 3.2% for the diet-alone patients, whereas they were lowered by 18% in those receiving diet plus pravastatin.

The MEGA study suggests that low-risk populations such as the Japanese can significantly reduce their risk for CHD without aggressive lipid-lowering treatment. Whether these results can be applied to statins other than pravastatin is unclear.

**Early Invasive Strategy in Women with Non-ST-Segment Elevation Acute Coronary Syndrome Linked to Aggressive Pharmacotherapy and Better In-Hospital Outcomes**

**Speaker:** William E. Boden, MD, Professor, University of Connecticut School of Medicine, and Director, Division of Cardiology, Hartford Hospital, Hartford, Connecticut

Women who underwent cardiac catheterization with 48 hours of admission for high-risk non-ST-segment elevation acute coronary syndrome (NSTE ACS) were significantly more likely to receive American College of Cardiology/American Heart Association (ACC/AHA) Guideline-driven pharmacology and counseling for therapeutic lifestyle changes during hospitalization and to have lower in-hospital mortality rates than women who underwent delayed or no cardiac catheterization.

It has been suggested that women with NSTE ACS receive less adjunctive pharmacotherapy and are less likely to have cardiac catheterization than men, but it is unclear whether this disparity has a negative effect on clinical outcomes. To answer this question, the study population of the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines) Quality Improvement Initiative were screened and assessed.

Among 119,257 consecutive patients with high-risk NSTE ACS, 33,804 women were identified from January 1, 2001, to October 2005. Of these patients, 15,733 women underwent cardiac catheterization in less than 48 hours, whereas cardiac catheterization was delayed for more than 48 hours or was not received another LMWH. A total of 1,431 patients received UFH.

Treatment with LMWH, compared with UFH, was associated with significantly lower rates of both (1) a closed artery or death or MI before angiography (12.5% vs. 22.5%) respectively, and (2) cardiovascular death or MI through 30 days (6.9% vs. 11.5%), respectively. TIMI major bleeding was similar in the LMWH group and in those receiving UFH (1.6% vs. 2.2%); intracranial hemorrhage was also similar (0.6 vs. 0.8%).

**Pioglitazone Reduces Risk of a Second Myocardial Infarction in Type-2 Diabetes**

**Speaker:** Erland Erdi mann, MD, Professor, University of Cologne, and Director, Third Clinic for Internal Medicine, Cologne, Germany

Pioglitazone (Actos, Takeda), a well-known thiazolidinedione used as an adjunct to diet and exercise in type-2 diabetes mellitus, can significantly reduce the risk of a second myocardial infarction (MI) in patients with type-2 diabetes and a pre-existing MI when compared with placebo.

To determine whether pioglitazone might reduce total mortality and macrovascular morbidity in high-risk patients with type-2 diabetes, researchers conducted a trial entitled The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2,445 Patients with Type 2 Diabetes and Pre-existing Myocardial Infarction: Data from the PROactive (PROspective PioglitAzone Clinical Trial in MacroVascular Events) Study.
This study was a subanalysis of data from the larger PROactive clinical trial, which investigated the effect of pioglitazone on macrovascular disease in type-2 diabetes.

In this multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 clinical trial, approximately 5,000 patients with type-2 diabetes at increased risk of macrovascular disease were randomly selected to use pioglitazone. The dose was increased stepwise from 15 to 30 to 45 mg, depending on tolerability, or placebo daily, given in addition to current antidiabetic drugs and other medications.

In the PROactive trial, pioglitazone reduced the risk of heart attacks, strokes, and premature death by 16%.

In the subgroup analysis, the type-2 diabetic patients with pre-existing MIs were observed for 2.5 years. The investigators calculated that giving pioglitazone to 1,000 patients who had type-2 diabetes and a previous heart attack would prevent 22 recurrent MIs over three years. In addition, there was a 37% decrease in acute coronary syndrome (ACS) with pioglitazone. ACS represents a spectrum of ischemic heart symptomatology ranging from unstable angina to non–STEMI.

Pioglitazone was also well tolerated. The tolerability profile in the subgroup analysis was similar to that observed in the other study, and there were no unexpected adverse events.

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Nesiritide Reduces Mortality Risk in Heart Failure

**Speaker:** Uri Elkayam, MD, Professor, and Director, Heart Failure Program, Los Angeles County University of Southern California Medical Center, Los Angeles, California

Nesiritide (Natrecor, Scios), a recombinant form of human B-type natriuretic peptide (BNP), may diminish the increased acute mortality risk associated with worsening renal function in patients with chronic decompensated heart failure.

Even though nesiritide has been linked to an increased risk of serum creatinine elevations in some patients, the actual effect of nesiritide-associated serum creatinine increases on mortality is unknown.

Pooled data were analyzed from five randomized trials that evaluated the efficacy and safety of nesiritide in 1,248 patients with chronic decompensated heart failure. Mortality was assessed at 30 days in patients whose serum creatinine increases were more than 0.5 mg/dl within 30 days. The hazard ratios associated with these increases were compared in the patients treated with nesiritide and the controls. Patients in the control group were given standard therapy, including inotropes, nitroglycerin, and/or diuretics.

In total, 214 of the 1,248 patients in the pooled study showed serum creatinine increases greater than 0.5 mg/dl—151 of 768 in the nesiritide group (19%) and 63 of 462 in the control group (14%). A serum creatinine increase of greater than 0.5 mg/dl was associated with a 1.1-fold increase in 30-day mortality risk in the patients receiving nesiritide and a 3.4-fold increase in 30-day mortality risk in the controls.

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Early Benefits of Levosimendan for Acute Decompensated Heart Failure

**Speaker:** Alexandre Mebazaa, MD, PhD, Professor, Department of Anesthesiology and Critical Care, Hôpital Lariboisière, Paris, France

An experimental drug in the U.S., levosimendan (Simdax, Abbott) has the dual action of calcium sensitization and potassium adenosine triphosphatase channel opening. When given together with standard therapy, levosimendan showed early benefits in reducing the important heart disease marker B-type natriuretic peptide (BNP). However, the regimen did not meet the overall goal of reducing mortality by 25% in patients with acute decompensated heart failure. BNP was one of several secondary endpoints evaluated.

Investigators randomly assigned 1,327 patients from nine European countries to receive levosimendan as a 12-mcg/kg bolus, followed by a dose of 0.2 mcg/kg per minute, or dobutamine (Dobutrex, Eli Lilly) at 5 mcg/kg per minute, for 24 hours, along with standard therapy. (Dobutamine is commonly used for acute decompensated heart failure, but it is associated with an increased risk of death.) The standard therapy consisted of physician-selected drugs such as diuretics, vasodilators, and inotropes.

The primary endpoint of the study was all-cause mortality during 180 days of follow-up.

There was a clear trend toward all-cause mortality with levosimendan, but the rate was only 15% at 30 days, far short of the study’s goal. However, an important difference was discovered in the activity of levosimendan and dobutamine. Before treatment, BNP levels were equally high in both groups, confirming the presence of heart failure in these patients. After five days of treatment, BNP levels declined by 46% with levosimendan therapy and by only 13% with dobutamine.