Vitamin E May Play a Role in NASH Treatment

BY DIANA MAHONEY

BOSTON — The use of vitamin E supplements by patients with nonalcoholic steatohepatitis was associated with a greater improvement in nonalcoholic fatty liver disease activity scores and cytologic ballooning, compared with the use of pioglitazone or placebo, results from a randomized controlled trial showed.

The investigation was spurred by findings suggesting that oxidative damage and insulin resistance both play a role in the chronic liver disease, Dr. Arun J. Sanyal said at the American Association for the Study of Liver Diseases. He and his colleagues at Virginia Commonwealth University, Richmond, sought to evaluate the role of vitamin E, an antioxidant, and pioglitazone, an insulin-sensitizing agent, in the treatment of nonalcoholic steatohepatitis (NASH).

The 247 patients were randomized to receive 800 IU of vitamin E once daily, 30 mg of pioglitazone once daily, or placebo for 96 weeks. All of the patients had biopsy-proven steatohepatitis with a nonalcoholic fatty liver disease (NAFLD) activity score of 4 or higher within 6 months prior to randomization, Dr. Sanyal said.

The study's primary end point was improvement—defined as a decrease in NAFLD activity score of 2 points or more and a decrease of at least 1 point in cytologic ballooning—and no worsening of fibrosis. Secondary end points included changes in histologic features, liver enzymes, insulin resistance, anthropometric measures, and quality of life, Dr. Sanyal explained.

Because the study encompassed two primary comparisons (vitamin E vs. placebo and pioglitazone vs. placebo) "we prespecified a significance value for the primary end point," he said, noting that a *P* value less than .025 relative to placebo was considered significant.

Compared with placebo, both vitamin E and pioglitazone were associated with liver function improvement, decreased ballooning, and better fibrosis stabilization at 96 weeks, although only vitamin E met the prespecified level of significance for the preliminary end point, Dr, Sanyal said.

Of the 84 patients randomized to vitamin E, 43% demonstrated the predefined composite improvement, compared with 34% of the pioglitazone group and 19% of the placebo group, he said.

The failure of pioglitazone to meet the end point criteria can likely be attributed to the fact that substantially fewer patients in that group had ballooning at baseline "and therefore couldn't demonstrate a reduction with treatment," he said.

Improvement in steatosis as measured by poststudy biopsy, lobular inflammation, ballooning scores, and serum alanine aminotransferase levels were observed in both treatment groups compared with placebo, Dr. Sanyal reported.

Only vitamin E met the prespecified level of significance for the preliminary end point.

DR. SANYAL

Regarding other secondary end points, patients on pioglitazone had greater weight gain (mean 4.7 kg) than did those on vitamin E (0.4 kg) or placebo (0.8 kg), but they also were the only group to demonstrate an improvement in insulin resistance, said Dr. Sanyal, who described that outcome as expected, as previous studies have produced similar results. Neither treatment produced significant changes in quality of life, he said.

Although the study suggests that both vitamin E and pioglitazone can lead to biochemical and histologic improvement in NASH, studies are needed not only to determine the sustainability of the observed histological and clinical outcomes, but also the long-term safety.

With respect to the vitamin E findings in particular, "this should resurrect our efforts to use antioxidants [for NASH] and, more importantly, to develop very potent antioxidants that are well tolerated in these patients," Dr. Scott Friedman, of the Mount Sinai School of Medicine, New York.

The study was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases.

Dr. Sanyal disclosed financial relationships with Amylin Pharmaceuticals, Astellas Pharma Inc., Bayer AG, Exalenz Bioscience Ltd., Gilead, Ikaria Holdings Inc., Intercept, Onyx Pharmaceuticals, Pfizer Inc., Salix Pharmaceuticals, Sanofi-Aventis, Takeda Pharmaceuticals Co., and Vertex Pharmaceuticals. Dr. Friedman disclosed relationships with Angion Biomedica Corp., Axcan Pharma Inc., Celera Corp., Exalenz, Intercept, Sanofi-Aventis, Stromedix Inc., and 7TM Pharma. ■

Gastric Cancer Risk Appears to Rise 200-Fold With Intestinal Metaplasia

BY SHERRY BOSCHERT

SAN DIEGO — The risk for gastric cancer was more than 200 times higher in patients with gastric intestinal metaplasia on initial or repeat upper endoscopy, compared with the control population, in a retrospective study of 11,600 male veterans.

In all, 3% of the cohort (354 veterans) were diagnosed with gastric intestinal metaplasia (GIM) over a 19-year period; the investigators compared their records with those of 355 randomly selected patients who were seen at the GI clinic of the Brooklyn campus of the Veterans Affairs New York Harbor Healthcare System.

Of the veterans with GIM, 6% (21 patients) were diagnosed with gastric cancer, a rate that was 200-fold higher than the gastric cancer rate seen in the control group, Dr. Naveen Anand and his associates reported at the annual meeting of the American College of Gastroenterology.

Half of the cancer diagnoses were made on the initial endoscopy, and half were made on follow-up endoscopy, said Dr. Anand, a chief resident at the State University of New York Downstate Medical Center, Brooklyn. Repeat endoscopies were performed on 53% of the cohort (including 11% who underwent four or more endoscopies), and 47% underwent initial endoscopy only.

Gastric cancer was more likely to be diagnosed in patients with GIM who were older and black, or who had more severe gastritis on histology.

Patients with GIM—especially patients in these higher-risk subgroups—should undergo regular endoscopic surveillance with careful histologic diagnosis of GIM based on biopsies at multiple gastric locations, Dr. Anand suggested.

He acknowledged that increased surveillance has cost implications, but noted that the gastric cancer rate in patients with GIM is similar to that seen in patients with severe dysplasia. "If patients have severe dysplasia on biopsy, we will bring these patients back for follow-up. So, if we're seeing similar rates of progression to cancer from GIM, these patients probably should be followed up.

"We need a prospective study looking at these patients followed over time," he said.

He and his associates were surprised to find that having a history of *Helicobacter pylori* infection did not significantly influence pathology results, compared with patients with no history of *H. pylori*. He attributed that to early intervention (that is, treatment that was initiated whenever *H. pylori* was diagnosed by histology).

Patients with GIM were more likely to be 70-90 years old, whereas those without GIM were more likely to be aged 50-70 years. About half of patients in the GIM and control groups were black and half were white, and there were small numbers of veterans of other races or ethnicities. Because the mean age in blacks was significantly older than in whites (75 vs. 71 years), blacks accounted for 67% of patients who developed gastric cancer, Dr. Anand said.

"We believe there is a long lead time between the premalignant lesion and intestinal metaplasia and intestinal-type gastric carcinoma, similar to what we see in colon cancer and cervical cancer, which gives us an opportunity for possible surveillance and even possible intervention," Dr. Anand said.

The investigators reported no conflicts of interest. ■

Barrett's Esophagus Does Not Alter Survival

BY SHERRY BOSCHERT

SAN DIEGO — Among 366 patients with Barrett's esophagus, 82% were alive 5 years after diagnosis, a rate that was essentially no different than the overall survival rate seen in a matched control group from the general population.

The retrospective study is one of the first on survival in a large cohort of patients with Barrett's esophagus in the United States, Dr. Ganapathy A. Prasad said at the annual meeting of the American College of Gastroenterology.

Among previous studies, some found decreased survival in patients with Barrett's esophagus, compared with matched controls, while others showed comparable overall survival rates.

Those data came predominantly from Europe, said Dr. Prasad of the Mayo Clinic, Rochester, Minn.

Dr. Prasad and his associates identified 401 patients with Barrett's esophagus in the Rochester Epidemiology Project who were diagnosed between January 1976 and January 2007, and excluded 35 who had some evidence of cancer or who developed cancer within 6 months of diagnosis.

The 366 patients in the study were followed for a mean of 7.1 years. They had a mean age of 62 years at baseline, 70% were male, and more than 85% were white.

The investigators compared the study cohort's survival rate with survival data from an age- and gender-matched cohort from the U.S. Census for the white population in Minnesota.

At diagnosis, the mean segment length of the Barrett's esophagus was 4.8 cm, and 59% of patients had long-segment Barrett's esophagus. No dysplasia was apparent in 84% of patients.

The only predictors of death were older age and higher scores on the Charlson Comorbidity Index at the time of Barrett's esophagus diagnosis, a multivariate analysis showed. Neither male gender nor the presence of dysplasia affected survival significantly.

Only 5% of the 104 patients who died during follow-up died of esophageal adenocarcinoma.

Dr. Prasad reported having no conflicts of interest. ■