Vitamin E—therapy for NASH?

Treatment with vitamin E results in a substantial histological improvement in patients with nonalcoholic steatohepatitis (NASH), report Arun Sanyal and colleagues in the *New England Journal of Medicine*. Pioglitazone treatment also has beneficial effects on important histological features of this disease. However, treatment with either drug would probably have to continue indefinitely, as relapse occurs after discontinuation of therapy.

NASH is closely linked with both the metabolic syndrome and oxidative stress. Histologically, NASH is defined by hepatic steatosis, lobular inflammation and hepatocellular ballooning, which progresses to cirrhosis in 15% of cases. In pilot studies, insulin-sensitizing agents (such as the thiazolidinediones, pioglitazone and rosiglitazone) improve the features of NASH. Antioxidants, such as vitamin E, also seem to have positive effects on liver function and histology. "At the time the study was designed," says Sanyal, the available data from small trials constituted "very little … literature to guide the practising physician." These researchers, therefore, aimed to verify whether the two leading drug candidates (pioglitazone and vitamin E) were any better than placebo for treating patients with NASH.

The researchers randomly assigned 247 adults with biopsy-confirmed NASH but without diabetes mellitus to one of three treatment groups: 30 mg per day of pioglitazone plus placebo, 800 IU of vitamin E per day plus placebo, or two placebo tablets daily. 90% of the participants had a repeat liver biopsy after 96 weeks of their assigned treatment. The primary outcome was a composite of an improvement in hepatocellular ballooning, no worsening of fibrosis, and improved activity scores for nonalcoholic fatty liver disease (NAFLD). Secondary outcomes included improvements in overall NAFLD activity and individual component scores, changes in liver enzyme levels, and health-related quality of life.

Twice as many patients treated with vitamin E achieved the primary outcome, compared with those who received placebo (43% versus 19%). Although more patients in the pioglitazone group than the placebo group fulfilled the primary outcome (34% versus 19%), the difference was not considered statistically significant, perhaps because the pioglitazone group contained a disproportionately large number of patients whose samples showed no hepatocellular ballooning at baseline. Treatment with either vitamin E or pioglitazone resulted in improvements in several secondary outcomes. However, "neither drug produced a mean improvement in fibrosis score and pioglitazone was associated with weight gain," explains Sanyal. He goes on to say that the findings "provide a rationale for the study of a combination of pioglitazone and vitamin E."

Sanyal cautions that a high proportion of patients treated with either vitamin E or pioglitazone did not respond to these treatments. The researchers are currently carrying out subgroup analyses to identify factors that might be associated with a response to these two drugs. Their findings also need to be validated in patients with NASH plus diabetes mellitus. Further studies, "will also be necessary to study the impact of vitamin E therapy on the cardiovascular risk profile [of patients] with NASH, [as] data in the literature suggest that high doses of vitamin E [might increase this risk]," says Sanyal.

Claire Greenhill

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