

Possible new treatment for nonalcoholic steatohepatitis

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Nonalcoholic steatohepatitis is characterized histologically by hepatic steatosis, lobular inflammation and hepatocellular ballooning. It is a common liver disease which can progress to cirrhosis in up to 15% of patients. The disease is closely associated with insulin resistance and features of metabolic syndrome. As key factors contributing to hepatic injury in these patients have been implicated the insulin resistance and the oxidative stress. There is no currently available therapy – of proven benefit –, but both insulin resistance and oxidative stress are attractive targets for therapy.

The Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial, was a phase 3, multicentric, randomized, placebo-controlled, double-blind clinical trial of pioglitazone or vitamin E for the treatment of adults without diabetes who had biopsy-confirmed nonalcoholic steatohepatitis. All subjects underwent a liver biopsy within 6 months before randomization. Steatohepatitis was categorized as absent, possible or definite. Disease activity was assessed with the use of the nonalcoholic fatty liver disease activity score, which is based on a standardized grading system for steatosis (on a scale of 0 to 3), lobular inflammation (on a scale of 0 to 3), and hepatocellular ballooning (on a scale of 0 to 2) with higher scores indicating increasing severity. The inclusion criteria were definite or possible steatohepatitis with an activity score of 5

or more, or definite steatohepatitis with an activity score of 4. A score of at least 1 for hepatocellular ballooning was required in all cases. Exclusion criteria were alcohol consumption of more than 20 g per day (women) and 30 g per day (men) for at least 3 consecutive months during the previous 5 years; cirrhosis, hepatitis C or other liver diseases, heart failure, or use of drugs known to cause steatohepatitis.

Between January 2005 and January 2007, 339 patients were assessed for eligibility, from which 247 were randomly assigned to one of the three groups for 96 weeks of study treatment: a group receiving pioglitazone 30 mg once daily and a vitamin E-like placebo once daily (80), a group receiving vitamin E 800 IU once daily and a pioglitazone-like placebo once daily (84), or a group receiving a pioglitazone-like placebo once daily and a vitamin E-like placebo once daily (83). The primary outcome was an improvement in histologic findings, which required an improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score and either a decrease in the activity score for nonalcoholic fatty liver disease to a score of 3 or less, or a decrease in the activity score of at least 2 points, with at least 1 point decrease in either the lobular inflammation or steatosis score. Secondary outcomes included changes in the overall activity score for nonalcoholic fatty liver disease as well as in individual component scores for steatosis, lobular inflammation, hepatocellular ballooning and fibrosis, and changes in serum aminotransferase levels, anthropo-

metric measures and insulin resistance and lipid profiles. An additional secondary outcome was the change in health-related quality of life from baseline to the end of treatment.

Vitamin E therapy, as compared with placebo, was associated with a significantly higher rate of improvement in nonalcoholic steatohepatitis (43% vs. 19%, $P=0.001$), but the difference in the rate of improvement with pioglitazone as compared with placebo was not significant (34% and 19%, respectively; $P=0.04$). Serum alanine and aspartate aminotransferase levels were reduced with vitamin E and with pioglitazone, as compared with placebo ($P<0.001$ for both comparisons), and both agents were associated with reductions in hepatic steatosis ($P=0.005$ for vitamin E and $P<0.001$ for pioglitazone) and lobular inflammation ($P=0.02$ for vitamin E and $P=0.004$ for pioglitazone) but not with improvement in fibrosis scores ($P=0.24$ for vitamin E and $P=0.12$ for pioglitazone). Subjects who received pioglitazone gained more weight than did those who received vitamin E or placebo; the rates of other side effects were similar among the three groups. Although pioglitazone did not meet the prespecified significance level for the primary outcome, it was associated with highly significant reductions in steatosis, inflammation, and hepatocellular ballooning, as well as with im-

provements in insulin resistance and liver-enzyme levels. It also led to the resolution of steatohepatitis in a significant proportion of subjects.

The authors consider that the enthusiasm for the potential benefits of pioglitazone and vitamin E must be tempered by the finding that there was an improvement in histologic features in only 34% of the subjects who received pioglitazone and 43% of those who received vitamin E, and steatohepatitis resolved in only 47% and 36% of the subjects in those two groups, respectively. Neither agent was associated with a significant improvement in the mean fibrosis score after 96 weeks of treatment. There was also no significant reduction in portal inflammation, which has been linked to advanced disease. Given the certainty of relapse after discontinuation of the drug, it is likely that whichever drug is prescribed for nonalcoholic steatohepatitis, it will need to be taken indefinitely. The weight gain among the subjects receiving pioglitazone — which did not resolve after discontinuation of the drug — also detracts from its long-term usefulness. The unknown long-term potential for adverse events with vitamin E and pioglitazone therapies must be factored into the decision about whether to use these agents. □



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Sanyal AJ, Chalasani N et al – Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. *N Engl J Med* 2010; 362:1675-85