TZD May Boost Fracture Risk for Men, Women

BY MIRIAM E. TUCKER

FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN DIABETES ASSOCIATION

ORLANDO — Hip and distal fractures were found to be elevated both in women and men who had taken thiazolidinediones in an analysis of all hospitalizations for fracture in Scotland during 2000-2008.

The current product labels for rosiglitazone and pioglitazone state that the fracture risk associated with the thiazolidinedione (TZD) class is predominantly for distal fractures in women. But the current study, which included an analysis using patients as their own controls to overcome treatment allocation bias, showed that the risk of hip fractures is substantially elevated in men and women. The findings suggest that the Food and Drug Administration should consider whether a change in drug label is indicated, Dr. Helen Colhoun, professor of public health at the University of Dundee, Scotland, said at the meeting. No difference in risk was noted between the two individual TZDs, she noted.

A clinical database identified all individuals in Scotland aged at least 40 with diagnosed type 2 diabetes, and linked those data with hospital admission records. The study comprised a total 82,027 person-years of TZD use in 35,606 users (68% rosiglitazone, 32% pioglitazone) and 6,209 fractures in 5,094 individuals.

There were 1,375 fractures among the 35,606 with diabetes who had used TZDs (3.9%) and 4,835 among the 112,100 (4.3%) who had never used TZDs. Patients who had used TZDs were significantly younger, had a higher body mass index, were less likely to have had a prior fracture, and less likely to have had recent cardiovascular disease.

After adjustment for diabetes duration, prior CVD, baseline and time-dependent exposure to other medications, and BMI, the rate of fracture per cumulative year of TZD exposure was significantly elevated for hip fracture in both men (hazard ratio, 1.14) and women (HR, 1.17) and for distal fracture in women (1.16).

In the self-controlled case series, the incidence rate ratio comparing the exposed and unexposed periods of time for each individual patient demonstrated a significantly increased risk of hip fractures during the period of TZD exposure for the group as a whole (incidence rate ratio, 1.98) and in both men (2.23) and women (1.9). The risk for distal fractures was significantly greater for the entire group (1.4) and for women (1.57) but was not significant among men.

The fracture rate per cumulative year of TZD exposure was significantly elevated for hip fracture in men (HR, 1.14) and women (HR, 1.17) and for distal fracture in women (HR,1.16).

The incidence rate ratio by duration of TZD exposure rose from 1.45 at less than 1 year to 3.59 after 6 years of exposure, Dr. Colhoun reported.

The overall relative risk in the self-controlled case series of approximately 2 and a current prevalence of exposure of about 20% implies that about 17% of fractures in patients with diabetes could be attributable to TZDs, she noted.

Of note, she added, this analysis assumes that the absence of TZDs would not result in more use of another agent that also increases fracture risk such as insulin. Studies are underway to assess that further and to build a predictive model of fracture in diabetes. Other studies are looking at whether reducing the TZD dose might lower the fracture risk, and whether the risk goes away when the drug is stopped. Preliminary data suggest that the risk remains high, she said.

Wellcome Trust Scottish Health Informatics Programme and the Chief Scientist's Office, Scotland, funded the study. Dr. Colhoun disclosed that she has received research support from Pfizer, Eli Lilly, Boehringer Ingelheim, AstraZeneca, and Roche. She serves on the speakers bureau for Pfizer, is a board/advisory panel member for Eli Lilly, and owns stocks/shares in Roche. ■