Thiazolidinedione use in patients with Type 2 diabetes may increase risk for diabetic macular edema

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Treatment with glucose-lowering thiazolidinedione drugs in patients with Type 2 diabetes appears to be associated with an increased risk of diabetic macular edema (a complication that may affect vision) at 1-year and 10-year follow-up evaluations, according to a report published Online First by *Archives of Internal Medicine*.

The risk-benefit ratio for thiazolidinediones, which are often used as a second- or third-line therapy in conjunction with oral agents or insulin, has been discussed after a series of metabolic and cardiovascular outcome studies. Several analyses have highlighted adverse effects, including increased incidence of bone fractures, fluid retention and a potentially increased risk of bladder cancer. Some small clinical studies have suggested an association between the medication and diabetic macular edema (swelling involving an area of the retina), which can affect up to 20 percent of patients with type 2 diabetes (T2D), according to the study background.

Iskandar Idris, M.D., F.R.C.P., F.R.C.P.(Edin), of the Sherwood Forest Hospitals Foundation Trust, Nottinghamshire, England, and colleagues conducted a retrospective study of 103,368 patients with T2D and no diabetic macular edema (DME) at baseline using The Health Improvement Network (THIN) database, which collects electronic data from a volunteer sample of United Kingdom general practices.

At one year, the incidence of DME was 1.3 percent (41 cases) among thiazolidinedione users (n=3,227 patients) and was 0.2 percent (227 cases) among nonusers of these drugs.

"This large retrospective cohort study analyzed the primary care electronic medical records of more than 100,000 patients with type 2 diabetes and showed that, even after adjustment for various confounding factors known to influence diabetic retinopathy, exposure to a thiazolidinedione is associated with an increased risk of developing DME. The association was evident with both pioglitazone and rosiglitazone," the authors comment.

The authors suggest that the patients at greatest risk of developing DME were those taking thiazolidinediones in combination with insulin.

"A larger and more detailed meta-analysis of randomized controlled trials (ideally in high-risk patients) will be needed to clearly establish the risk-benefit profile of thiazolidinediones in patients with, or at risk of, DME," the authors conclude. "Clinicians should be vigilant in the clinical screening for DME among those patients taking thiazolidinediones."

In a commentary, Sonal Singh, M.D., M.P.H., and Jodi B. Segal, M.D., M.P.H., of The Johns Hopkins University School of Medicine, Baltimore, write: "…several limitations preclude definitive conclusions. First, the authors did not have information on the duration of thiazolidinedione exposure or duration of diabetes in the THIN data."

"In contrast, other observational studies have reported no elevated risk," the authors continue. "In conclusion, we can neither be certain that thiazolidinediones cause macular edema nor be reassured that such a risk does not exist. Future studies using new-user incipient cohort designs with validated exposure and outcome definitions and appropriate

adjustment for diabetes severity may provide additional information on this potential association."

"What should clinicians do when faced with imperfect evidence? Despite the uncertainty regarding the risk of macular edema and thiazolidinediones, the occurrence of characteristic visual symptoms among patients taking thiazolidinediones or any other diabetic medication should prompt evaluation and ophthalmologic referral for DME evaluation, as noted in the current drug labels," they conclude.

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