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LETTERS TO THE EDITOR

Is the Tolerability of Long-Term Thiazolidinedione Therapy Overstated?

The study by Tang et al. (1) concluded that their retrospective chart review demonstrated the tolerability of long-term thiazolidinedione (TZD) therapy in a diabetic population with established chronic heart failure (HF). Although we applaud their efforts to study this important topic, we believe the data presented are not so clear, and that their conclusions that a large majority of chronic HF patients tolerate these agents are overstated.

First, we believe the definition of TZD-related fluid retention, as a 10-pound weight gain from baseline, in addition to signs or symptoms of volume overload, is far too exclusive of important levels of fluid retention. By using this cut-off, we can be sure that those patients had severe fluid retention. However, we do not know the number of other patients who had important levels of weight gain or edema and who were missed by the investigators' likely insensitive criteria. Heart failure guidelines recommend action when weight increases by 2 to 4 pounds depending on how quickly it occurs.

Second, we disagree that the reported incidence of fluid retention of 17.1% is an overestimate due to selection bias. In fact, it is probably an underestimate. Obtaining data from a chart review can only lead to under-reporting the true incidence of fluid retention and adverse events. Furthermore, the majority of patients had stable New York Heart Association functional class I or II heart failure where TZD therapy is not contraindicated. (The incidence of edema [with or without weight gain] in TZD randomized controlled trials ranged between 2% and 15% [2,3].)

Third, the intolerability of these agents in this population is further illustrated by the fact that 31% discontinued TZD therapy within one year of initiation (most due to fluid retention), whereas the rate of discontinuation was far <0.1% in randomized controlled trials (2,3). Also of concern is that 26% of patients who met the criteria for fluid retention were hospitalized. Finally, we are concerned that both the data and the discussion regarding the incidence of fluid retention and characteristics of the non-TZD control group were very limited. This data would likely provide more insight into the true tolerability of these medications in this population.

In summary, we agree that further studies are needed to examine the relationship between TZD-related fluid retention and patient cardiac status. We believe this study and its conclusions should be interpreted very carefully, as the true risks of adverse effects related to volume expansion are likely understated.

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REPLY

We appreciate the comments by Dr. Malone and his colleagues regarding our recent report on the characteristics of fluid retention after initiation of thiazolidinedione (TZD) therapy in diabetic patients with established chronic heart failure (HF). In our report, we fully acknowledged that fluid retention does occur with TZD use in patients with established HF, and until we have more experience with this drug class "there is little doubt that TZDs. . .should be avoided in highly symptomatic patients with HF who are already having difficulty maintaining a balanced volume status" (1). Although we recognize that the definition of fluid retention is arbitrary, there is currently no gold standard for "important levels of fluid retention." We chose the 10-pound limit to account for the long-term, nonedematous weight gain associated with TZD use that has been previously reported in the literature (2). It is noteworthy that 68% of patients received 12 months of TZD therapy without demonstrating significant fluid retention. Also, 20% of patients in our cohort had TZD discontinued owing to reasons other than edema. Until we have more objective measures to quantify the degree of fluid retention (such as sequential plasma volume analyses or surrogate markers like plasma B-type natriuretic peptide levels), observations of this nature can only rely on "insensitive" clinical criteria.

The selection bias in this retrospective observational study originated from the referral nature of the specialized HF clinic, where a large number of patients are seen specifically because of fluid retention following TZD initiation. Meanwhile, the non-TZD user "control" group in our study was used in a nested case-controlled manner to illustrate the discrepancy in clinical presentation between TZD-related fluid retention and what we commonly consider to be HF exacerbation independent of TZD use. As stated in our discussion, the incomplete nature of retrospective data collection precludes any statistical comparisons between groups (including drug tolerability) so as to avoid false inferences. Although we agree that any association between TZD-related fluid retention and patient's cardiac status should be interpreted with caution, we argue against the proscription of this drug class in patients with HF simply by equating fluid retention with HF exacerbation. What is more alarming to us is the paucity of published reports in this area (limited to sporadic case reports) over the past few years despite widespread recognition of the metabolic syndrome and the potential benefits of this class of drugs in such patients. The true incidence of TZD-related fluid retention and TZD tolerability in patients with HF can only be determined by well-designed prospective studies specifically addressing patients with HF.