Selling Safety—Lessons From Muraglitazar

James M. Brophy, MD, FRCPC, PhD

**Peroxisome proliferator–activated receptors (PPARs)** are nuclear cell transcription factors with isoform agonists that exhibit clinical benefit. The PPAR-γ agonists increase insulin sensitivity, explaining the antidiabetic action of the thiazolidinediones rosiglitazone and pioglitazone. PPAR-α agonists, including the fibrates, increase fatty acid oxidation, leading to a decrease in plasma triglycerides and a modest increase in high-density lipoprotein cholesterol. Muraglitazar is the first dual-PPAR agonist to be considered for general marketing both as monotherapy and combined therapy by the US Food and Drug Administration (FDA). Given the emerging epidemic of type 2 diabetes, it is easy to understand the enthusiasm for this new class of drugs. Tight glycemic control reduces diabetic microvascular complications, although both old and new studies have failed to convincingly show decreased macrovascular complications of stroke, cardiac disease, and peripheral vascular disease.

On September 9, 2005, an FDA advisory committee reviewed muraglitazar’s efficacy and safety data and recommended approval and on October 18, 2005, it was reported that the FDA issued an “approvable letter” for this drug. However, in this issue of *JAMA*, Nissen et al have reanalyzed these data and challenge the advisory board’s recommendation. Courtesy of a transparent FDA approval process that provides online submission information, Nissen et al were able to contrast the 2374 patients taking muraglitazar at 5 mg or less vs the combined 1351 patients exposed to either placebo or pioglitazone. Their analysis demonstrated a 2.23 (95% confidence interval, [CI], 1.07-4.06) increased risk in the composite outcome of death, myocardial infarction, or stroke and a 7.4 (95% CI, 0.97-56.8) relative risk of congestive heart failure (CHF).

The authors rightly mention that a potential limitation of their analysis was their use of simple proportion tests and not the more informative survival time analysis. Nevertheless they feel confident in recommending that approval of muraglitazar be delayed pending a dedicated cardiovascular trial. In contrast, the sponsor’s presentation to the advisory committee concluded that no significant excess risk of deaths or cardiovascular events occurred with muraglitazar treatment. While there may be disagreement over which analysis to believe, a consensus should exist that these differences indicate less than robust data.

Is it possible, at least partially, to reconcile these radically different interpretations of the same data? Unlike the report by Nissen et al, the sponsor presented the data as 3, not 2, distinct groups and calculated event rates per patient year of exposure (TABLE), thereby logically weighting by duration of exposure. However the 495 patients, representing 990 patient-years of exposure, with subtherapeutic doses of 2.5 mg or less were maintained in the denominator. Since FDA approval was not sought for these small doses of muraglitazar, the inclusion of these data in the safety analysis for the proposed marketed doses may be questioned. Because there were no associated cardiovascular events among these patients, the effect is a dilution of the clinically pertinent risk estimate. The recalculated event rate for the proposed marketed doses of muraglitazar is 97 events per 2447 patient-years, an excess of 20% compared with placebo alone and an excess of 67% compared with the combined placebo-pioglitazone control group. There is obvious variability in cardiovascular event rates across the 5 different trials, but this heterogeneity can only be properly explored with further studies.

Muraglitazar users also had a 2- to 4-k~g increase in weight, a 10% incidence of edema, and 13 adjudicated cases of CHF (compared with 1 case in the control group) despite the strict exclusion of all patients with moderate or severe baseline CHF. Although patients with mild CHF symptoms (New York Heart Association class I and II) were eligible, only 25 were recruited and since their CHF risk was increased 10-fold, the sponsor’s claim that safety has been demonstrated for this group rings hollow. Systematic baseline ejection fractions were not recorded but none of the patients had a value below 40%, implying that CHF risk prediction for future muraglitazar users will likely be problematic. These elevated CHF rates are possibly related to increased circulating volume and have been consistently observed with other PPAR-γ agonists. Moreover, the rates from these clinical

**See also p 2581.**

©2005 American Medical Association. All rights reserved.
trial data may be underestimates of the true population risk because unselected diabetic populations are likely to be older and have an increased possibility of occult CHF that may be more prone to drug-induced decompensation. Combining the CHF cases with the other cardiovascular events reveals that the total muraglitazar cardiovascular risk exceeds the placebo risk and the combined control group risk by 33% and by 89%, respectively (Table).

Although hepatotoxicity has not been observed with muraglitazar (unlike the first PPAR-γ troglitazone, withdrawn due to liver toxicity), carcinogenicity has been a concern in animal studies involving other dual-PPAR agonists. The sponsor’s presentation to the advisory committee concluded that cancer rates were not increased. However, 34 cancers were reported among 3125 patients (3471 patient-years of exposure) in the muraglitazar group for an incidence of 9.8 per 1000 patient-years (95% CI, 6.7-13.3), whereas 1 cancer was reported among 528 placebo patients (332 patient-years exposure), for an incidence rate of 3.0 per 1000 patient-years (95% CI, 0.1-21.3). Although the CIs overlap, this is a worrisome observation that requires immediate further study as a very large increase in cancer risk cannot be excluded with the limited available data. Animal work showing urinary bladder carcinomas in muraglitazar-treated rats within 6 to 15 months of follow-up at doses only 7 to 8 times of those given to humans may have a clinical correlate in the increased bladder cancer risk observed with pioglitazone.

Generically, there are specific methodological decisions in the sponsor’s FDA application that may foster an illusion of safety. The following are several, perhaps unintended but nevertheless disingenuous, methods observed in the application that may have contributed to an overestimate of the safety profile:

1. Selecting a study population unlikely to have adverse outcomes but nonrepresentative of potential future users (eg, exclusion of elderly patients, even though more than one third of type 2 diabetes occurs in this group)

2. Conducting underpowered studies increasing the failure rate to detect meaningful safety differences (ie, maximizing rather than minimizing type II errors)

3. In contrast to efficacy determinations, reporting individual rather than composite safety outcomes to decrease the likelihood of establishing statistical significance (eg, separate cardiovascular events from CHF)

4. Limiting preapproval peer-review publication of results so as to minimize scrutiny and debate of both methods and results (eg, of all submitted data only 1 study of 340 patients has been published)

5. Evoking biological implausibility of safety concerns by the use of surrogate measures (eg, treatment reduces C-reactive protein [CRP]) implying safety, despite no proof that CRP reduction is clinically correlated with improved safety)

6. Recording outcomes only in patients who are fully compliant with prescribed treatment because this self-selected group will likely have fewer adverse events (eg, unknown impact of the nonanalysis of the 15% discontinued cases)

7. Ignoring the totality of the evidence by excluding consideration of confirmatory safety signals seen in studies of similar molecules (eg, CHF and bladder cancer outcomes with pioglitazone)

8. Diverting attention to unproven but potential benefits by concentrating on reductions in surrogate laboratory values (eg, hemoglobin A1c) rather than in meaningful patient health outcomes.

Risk-benefit assessment is a dynamic process with few absolutes. A new drug for a uniformly fatal disease with no other treatment options is likely, even in the presence of some treatment risks, to be approved by regulators and accepted by patients. Conversely for muraglitazar, for which no meaningful outcome benefits have been demonstrated and other treatments exist, the safety standards should be proportionally higher and importantly less uncertainty should be tolerated about suspected risks.

What future studies are now required to allay these safety concerns? The sponsor has proposed a pharmacovigilance (observational) study of muraglitazar compared with conventional type 2 diabetes treatments in 15 000 patients with annual questionnaires during 5-year follow-up. While well-performed observational studies may provide useful information on drug safety, residual concerns will generally remain due to possible selection or channeling biases. A large premarketing safety trial as proposed by Nissen et al will provide more secure evidence and has an additional advantage of limiting risk only to study participants while safety concerns are being assessed.

In conclusion, although muraglitazar may yet prove to be a valuable addition to the clinical armamentarium, the meticulous examination of the current evidence by Nissen and colleagues should focus serious attention on the potential cardiovascular risks of this drug. Residual safety concerns surrounding carcinogenicity also have not been com-

---

**Table. Incidence of Cardiovascular Event Rates**

<table>
<thead>
<tr>
<th></th>
<th>Patient Exposure, y</th>
<th>No. of Patients With Event</th>
<th>Incidence per 1000 Patient Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>330</td>
<td>11</td>
<td>33.37</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>762</td>
<td>15</td>
<td>19.68</td>
</tr>
<tr>
<td>FDA submission muraglitazar</td>
<td>3437</td>
<td>97</td>
<td>28.22</td>
</tr>
<tr>
<td>Combined placebo/ pioglitazone control group</td>
<td>1092</td>
<td>26</td>
<td>28.22</td>
</tr>
<tr>
<td>Recalculated muraglitazar (without CHF)</td>
<td>2447</td>
<td>97</td>
<td>30.94</td>
</tr>
<tr>
<td>Recalculated muraglitazar (with CHF)</td>
<td>2447</td>
<td>110</td>
<td>44.95</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; FDA, US Food and Drug Administration.

*First 3 rows taken from the manufacturer’s FDA presentation (slide 71). Recalculated rates exclude the person-time that accumulated with patients exposed to <2.5 mg/d of muraglitazar.
Radiation has proven to be an indispensable tool in the curative management of malignant disease, especially for primary carcinomas of the pelvis including prostate, rectal, cervical, endometrial, and anal cancers. In this setting, radiotherapy is used either alone or in combination with systemic, hormonal, and/or surgical therapies. The ultimate goal of this radiation-based therapy is to provide long-term disease control or a “cure” with as little treatment-related morbidity as possible. Yet, the study of long-term toxicity associated with treatments that include radiation therapy has received little attention over the years.

Radiation toxicity can roughly be divided into early and late effects. Early or acute effects, such as nausea, skin reactions, diarrhea, and neutropenia, tend to be temporary and, for the most part, resolve shortly after the completion of therapy. Late effects, such as connective tissue fibrosis and secondary malignancies, can occur long after the completion of radiation therapy. The causes for late radiation injuries are not completely understood. The 2 main theories consist of damage to the cellular matrix and vascular injury. However, the etiology for long-term sequelae is probably much more complex and likely involves a cascade of cellular, vascular, and cytokine changes induced by radiation.

In this issue of JAMA, Baxter and colleagues provide compelling evidence for what many radiation oncologists have long believed, despite a paucity of literature about modern radiation delivery: that pelvic radiotherapy increases the risk of bone fractures. Of the 6428 women in the study, 556 were diagnosed with anal cancer, 1605 with cervical cancer, and 4267 with rectal cancer. Overall, 44.4% received radiation therapy and 55.6% did not. The cumulative incidence of pelvic fractures within the first 5 years of the study was increased for women in the irradiated group compared with women in the nonirradiated group: 14% vs 7.5% for women with anal cancer, 8.2% vs 5.9% for cervical cancer, and 11.2% vs 8.7% for rectal cancer. As Baxter et al show, an increase in the relative risk of pelvic fractures associated with the administration of pelvic radiotherapy is a significant public health issue that deserves attention.

However, there are several limitations to these findings. First, as noted by the authors, this work represents a retrospective cohort study that could lead to undetected bias. Despite controlling for age and race (as surrogates for the development of osteoporosis), there may be other potential confounding factors. Several medications including steroids, heparin, and thyroid hormone therapy have been known to contribute to the risk of osteoporosis and may have acted synergistically with radiation therapy. Additionally, women who had received pelvic irradiation for their cervical cancer may have undergone an earlier total abdominal hysterectomy and bilateral oophorectomy. Osteoporosis from estrogen deficiency may have already

See also p 2587.