ARBs Tied to Modest Increases in Cancer Risk

BY DIANA MAHONEY

FROM THE LANCET ONCOLOGY

Angiotensin-receptor II blockers are associated with a modestly increased risk of new cancer diagnoses according to a meta-analysis of randomized controlled trials.

The limited amount of new cancer data in the available literature, however, precludes the calculation of exact cancer risk associated with each individual agent in this class of drugs, wrote lead investigator Dr. Ilke Sipahi and colleagues at Case Western Reserve University in Cleveland.

Angiotensin receptor II blockers (ARBs) are commonly used for the treatment of hypertension, heart failure, and diabetic neuropathy. Because a number of large ARB trials have been completed since 2003, when "an unexpected finding" of significantly higher fatal cancers among patients taking the ARB candesartan was observed in a study assessing the efficacy of the drug in heart failure (Lancet 2003;362:759-66), Dr. Sipahi and his colleagues designed a meta-analysis of the published randomized controlled trials drugs in this class to examine their effect on the occurrence of new cancers. Secondary objectives included the determination of whether ARBs are associated with the occurrence of specific solid-organ cancers and cancer deaths, they wrote.

The meta-analysis included studies published before November 2009 in which an ARB was given in at least one group. Only those studies that enrolled least 100 patients and had a minimum 1 year follow-up were considered, according to the authors. Of the trials that fit these criteria and reported cancer data, five (61,590 patients) had new-cancer data available and were included for the evaluation of the primary outcome of new cancer occurrence. Additionally, for consideration of the secondary outcomes, five trials that reported data on common types of solid organ cancers (68,402 patients) and eight trials that reported data on cancer deaths (93,515) were evaluated, the authors wrote, noting that nine trials were included overall (Lancet Oncol. 2010 [doi:10.1016/S1470-2045(10)70142-6]).

For the primary outcome of cancer recurrence, patients who were randomized to ARB treatment had 7.2% risk of new cancer occurrence compared with a 6.0% risk among patients in the control groups, which is a statistically significant increase, the authors reported. An analysis of three of the trials in which cancer was a prespecified end point and cancer data was rigorously collected also showed a significant increase in risk of cancer with ARBs, they wrote.

Because the ARB telmisartan was used as the study drug in 86% of the patients randomized to an ARB, the investigators conducted a meta-analysis of three of the trials looking at this drug showed an increase in new cancer occurrence of borderline significance. Analyses looking specifically at patients on background ACE inhibitor therapy and looking at patients without concomitant ACE inhibitor treatment also showed significant increases in new cancer occurrences, they reported.

For the secondary outcome of the occurrence of specific solid organ cancers, the "meta-analysis showed an increase in relative risk for the occurrence of new lung cancer in patients randomized to an ARB compared with control," the authors wrote. "This effect was also seen in the subgroup of patients who received background ACE-inhibitor therapy." While there was an excess of prostate cancer in the ARB groups in all five trials, it was not significant in meta-analysis, they stated.

When evaluating for cancer deaths, the authors wrote "there was no significant difference in cancer deaths between patients randomized to ARBs and those randomized to control for the duration of the follow-up."

The clinical significance of the "modest but significant" increased risk of new cancer occurrence is unknown, the authors conceded. "The finding of a 1.2% increase in absolute risk of cancer over an average of 4 years needs to be interpreted in view of the estimated 41% lifetime cancer risk," they wrote.

Importantly, because new cancer data were available for only three of seven FDA-approved ARBs, and because most of the patients included in the meta-analysis received telmisartan, "it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug," the authors stated, nor is it known whether the remaining four ARBs are associated with an increased risk of new cancers.

The mechanism for the possible increase in new cancer occurrences associated with ARBs is uncertain, according the authors. Although experimental studies using cancer cell lines and mouse models have implicated the renin-angiotensin system in the regulation of cell proliferation, tumor growth, angiogenesis, and metastasis, and evidence shows that both angiotensin II type-1 blockade with ARB and direct stimulation of angiotensin II type-2 are capable of stimulating tumor angiogenesis in vivo, the authors wrote, "the relevance of these observations in human malignancy is largely unknown."

Although the findings of this study are limited by the fact that the pooled results come from trials not designed to explore cancer outcomes as the primary end point and by the lack of individual patient-level cancer data, "meta-analysis can be useful in providing insights into issues of safety and rare adverse events that might provide the hypothesis for a prospective trial," the authors wrote, noting that the findings "warrant further investigation." ■

MY TAKE

This Raises Crucial Safety Questions

The meta-analysis linking angiotensin receptor blockers with an increased risk of incident cancer raises crucial drug safety questions. "Are angiotensin-receptor blockers associated with increased risk of incident malignancies? Should we be concerned about all ARBs or a single drug, telmisartan? How can this uncertainty best be resolved? What actions should practitioners take while this concern undergoes further examination and analysis?"

While the meta-analysis has its strengths—particularly its size, the thoroughness of the literature search, and the application of appropriate filters to exclude potentially unreliable data, "there are also important weaknesses, which the investigators acknowledge—including the post hoc nature of this investigation and the fact that the trials were not designed to explore cancer outcomes," leading the investigators to be "appropriately cautious" in their interpretation of the data.

Until regulators review the possible association between ARB use and cancer and report their findings, "we should use ARBs, particularly telmisartan, with greater caution. These drugs are often overprescribed, as a result of aggressive marketing and in the absence of evidence that they are better than angiotensin-converting enzyme inhibitors. ARBs can be reserved for patients with intolerance to ACE inhibitors." Using ARBs more selectively will also save money, "since nearly all ARBs are proprietary while ACE inhibitors are generic."

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Deaths in Olmesartan Studies Prompt FDA Safety Review

BY ELIZABETH MECHCATIE

An increased rate of cardiovascular deaths in patients with type 2 diabetes treated with olmesartan, compared with placebo, in two studies is the focus of a safety review by the Food and Drug Administration, the agency announced last month.

The FDA plans to evaluate the data from the two clinical trials, which are examining whether treatment with olmesartan slows the progression of kidney disease in patients with type 2 diabetes. In both studies, there were more cardiovascular deaths—myocardial infarction, sudden death, or stroke—in those treated with olmesartan than in those on placebo. Olmesartan is an angiotensin II receptor blocker (ARB), marketed as Benicar by Daiichi Sankyo Inc. for hypertension.

"The review is ongoing and the agency has not concluded that Benicar increases the risk of death," the statement said. "FDA currently believes that the benefits of Benicar in patients with high blood pressure continue to outweigh its potential risks." The FDA is advising health care professionals to continue to follow the recommendations in the olmesartan label when prescribing the drug and to report adverse events in patients treated with the drug to the agency's MedWatch adverse event reporting program.

Both studies were completed in 2009. One, the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study, conducted in Germany, compared the time to first occurrence of microalbuminuria in 4,447 patients with type 2 diabetes and at least one additional cardiovascular risk factor and normoalbuminuria before being randomized to placebo or olmesartan.

The second study—Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT)—was conducted in China and Japan, and compared the first occurrence of the doubling of serum creatinine level, death, or end-stage renal disease over 5 years in 566 patients with type 2 diabetes and a clinical diagnosis of diabetic nephropathy.

Cardiovascular deaths were secondary end points in both trials. In ROADMAP, 15 cardiovascular deaths occurred in the olmesartan-treated patients, compared with 3 in the placebo patients; 7 of those 15 were sudden cardiac deaths. In ORIENT, 10 cardiovascular deaths occurred in the treated patients, while 3 occurred in the placebo group. ■

Pages 20a—20b