Agent Promises New Metabolic Syndrome Strategy

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SAN ANTONIO — The discovery that the angiotensin II receptor blocker telmisartan also acts as a partial agonist of peroxisome proliferator-activated receptor-γ makes it a uniquely promising candidate for the treatment of metabolic syndrome and prevention of type 2 diabetes and cardiovascular disease, Dr. Theodore W. Kurtz said at a meeting of the American Heart Association Council for High Blood Pressure Research.

Whether telmisartan fulfills this promise should be known sometime in 2008, when results are expected from two large ongoing clinical trials with a variety of cardiovascular and metabolic end points, added Dr. Kurtz, professor of laboratory medicine at the University of California, San Francisco.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) has randomized more than 25,000 patients at high cardiovascular risk to telmisartan, ramipril, or both. The Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) is comparing telmisartan to placebo in nearly 6,000 high-risk patients.

Dr. Kurtz was honored with the Novartis Award for Hypertension Research at the meeting, in part for groundbreaking work in which he identified several genes that play a key role in the development of components of the metabolic syndrome in rats. Subsequent work indicates these same genes figure importantly in human metabolic syndrome.

One of these genes is Cd36, also known as FAT (fatty acid translocase), an insulin-resistance gene causing defective fatty acid and glucose metabolism. Another is mitochondrial cytochrome C oxidase-1 (MTCO 1), a variant linked to increased plasma insulin and triglyceride levels, increased muscle triglyceride, and reduced muscle insulin sensitivity.

Metabolic syndrome is associated with a fivefold to ninefold increased risk of developing type 2 diabetes and twice to four times the risk of cardiovascular morbidity and mortality. The syndrome, which affects up to one-quarter of adults in industrialized nations, is characterized by the clustering of hypertension, dyslipidemia, and insulin resistance. The emerging consensus is that abnormal deposition of fat in tissues where it doesn't belong, such as visceral organs and muscle, lies at the syndrome's core.

Treatment of metabolic syndrome has been a thorny issue. β-blockers and diuretics are time-proven antihypertensive drugs but can worsen dyslipidemia and reduce insulin sensitivity.

Dr. Kurtz noted that PPAR-γ activators such as pioglitazone and rosiglitazone modulate Cd36 and MTCO 1 activity, enhance fatty acid metabolism, and stimulate mitochondrial function. They are also known to be useful for treatment of the metabolic syndrome and type 2 diabetes. Recently they've also been shown effective in preventing development of type 2 diabetes in high-risk individuals. However, they are not optimal agents for treatment of metabolic syndrome because they have only modest blood pressure–lowering effects and have the problematic side effects of fluid retention, weight gain, and increased risk of heart failure, he added.

When Dr. Kurtz and coworkers were enlisted in a program to search for PPAR-γ activators having stronger antihypertensive action without the side effects of conventional PPAR-γ agonists, they noted that telmisartan alone among the angiotensin II receptor blockers (ARBs) bore a structural similarity to the conventional PPAR-γ activators. In in vitro studies, telmisartan exhibited a PPAR-γ–activating effect at therapeutically relevant concentrations, while other ARBs did not.

In his studies of animals with diet-induced insulin resistance, Dr. Kurtz showed that telmisartan modulated the expression of Cd36 and MTCO 1, protected against visceral fat deposition, and improved lipid and glucose metabolism. A recent Japanese CT study showed it also protects against visceral fat accumulation in humans, while European studies showed that telmisartan improves insulin sensitivity and lipid profiles in patients with metabolic syndrome. Telmisartan's selective effect means it doesn't have the side effects seen with full agonists of PPAR-γ.

Dr. Kurtz has received research grants from Boehringer Ingelheim, which markets telmisartan, as well as numerous other pharmaceutical companies. ■