Novel Thyroid Mimetics May Play Expanded Role

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CHICAGO — A new generation of oral selective thyroid hormone receptor agonists shows promise for the treatment of dyslipidemia, obesity, and metabolic syndrome.

For one of these agents, 3,5-diiodothyropropionic acid (DITPA), it's a case of one door opening as another slams shut.

DITPA was developed for treatment of heart failure, an application for which it proved disappointing within the past year in an aborted phase II trial. But the same study intriguingly showed DITPA substantially reduced body weight, LDL cholesterol, and triglycerides, Dr. Paul W. Ladenson said at the annual meeting of the American Thyroid Association.

Thyromimetics may be an alternative for statin-intolerant patients, and an adjunct for greater LDL reductions.

DR. LADENSON

He also highlighted two other investigational thyromimetic compounds with potent lipid-lowering properties: eprotirome and MB07811.

In short-term studies, their lipid-lowering effects appear to be additive to those of statins, raising the prospect of enhanced LDL lowering through combination therapy.

DITPA improved left ventricular function and increased cardiac output in animal models of heart failure, providing the impetus for the phase II, placebo-controlled Veterans Affairs investigation. The planned 24-week trial was terminated early after enrollment of 86 patients with New York Heart Association class 2-4 heart failure—only about half of the planned number—because DITPA wasn't improving cardiac end points and was poorly tolerated, with a high dropout rate due to minor but annoying adrenergic side effects, explained Dr. Ladenson, professor of medicine, pathology, oncology, radiology, and international health, and director of the division of endocrinology and metabolism at Johns Hopkins University, Baltimore.

The metabolic outcomes, however, were attention grabbing.

At 16 weeks, the DITPA-treated group averaged a 15% loss in body weight and a commensurate reduction in body mass index, both reversible following treatment discontinuation.

The DITPA group also experienced a 25-mg/dL drop in serum triglycerides and a 20-mg/dL reduction in LDL cholesterol.

This was particularly noteworthy because all study participants were already on statin therapy, in accord with VA policy, observed Dr. Ladenson, who is editor in chief of the Journal of Endocrinology and Metabolism.

On the downside, the DITPA group experienced increased markers of bone degradation and an increase in osteocalcin level, suggesting a thyroid hormone–like acceleration of bone turnover. DITPA also reduced serum-free T_4 and T_3 concentrations, although without any symptoms of hypothyroidism or thyrotoxicosis.

"Whether this compound would have clinical application in a lower dose that avoids the minor adrenergic side effects remains to be seen," the endocrinologist commented.

Turning to eprotirome, Dr. Ladenson said that two phase II investigations of the synthetic thyromimetic agent have been completed.

The first, presented at last year's American Thyroid Association meeting, involved 98 hyperlipidemic patients randomized to 16 weeks of eprotirome at 100 or 200 mcg/day or placebo. Eprotirome resulted in reductions of about 25% in LDL and apolipoprotein B, along with decreases in lipoprotein(a) of 37% at 100 mcg and 45% at 200 mcg. Triglycerides fell by 25% in subjects with normal baseline levels, and by 40% in hypertriglyceridemic individuals.

No cardiac, bone, or muscle effects were noted with eprotirome, which has a sevenfold greater affinity for the beta isoform of the thyroid hormone receptor than does T_3. A mild transient elevation in liver enzymes was noted.

Serum-free thyroxine declined modestly while staying within normal range, with no significant change noted in thyroid stimulating hormone or T_3 levels, Dr. Landenson said.

A second phase II study involving 189 patients demonstrated that eprotirome, added to treatment with atorvastatin or simvastatin, achieved additional lipid reductions comparable in magnitude to eprotirome monotherapy, according to a recent announcement by eprotirome's developer, the Swedish company Karo Bio. This study has not yet been formally presented or published.

The small-molecule thyroid receptor beta-selective agent MB07811 is earlier in development.

La Jolla, Calif.–based Metabasis has completed a phase IB randomized, double-blind, placebo-controlled 2-week trial involving 56 hyperlipidemic subjects in which MB07811 demonstrated dose-dependent reductions in LDL of up to 41% accompanied by a 30% drop in triglycerides.

Mild transient elevations in liver enzymes and shifts in thyroid hormone levels were documented, but no cardiac or blood pressure effects occurred. In animal studies, adding MB07811 to atorvastatin resulted in LDL lowering equivalent to and additive with the statin.

Thus, in the future it's possible that beta-selective thyromimetics will have dual roles: as an LDL-lowering alternative to statins in statin-intolerant patients, and as an adjunct to statins to achieve greater LDL reductions than obtainable with monotherapy. Large randomized controlled trials will clearly needed first, Dr. Ladenson said.

In an editorial accompanying publication of an eprotirome pilot investigation earlier this year, Dr. Scott M. Grundy cautioned that these trials will need to be particularly long, large, and definitive.

That's because thyroid hormone receptor-beta, while present mainly in the liver, is also widely distributed elsewhere in the body, including the pituitary, raising the possibility of systemic side effects even with selective thyromimetic agonist therapy, according to Dr. Grundy (Proc. Natl. Acad. Sci. USA 2008;105:409-10), who is chairman of the department of clinical nutrition at University of Texas Southwestern Medical Center, Dallas, and cochair of the National Heart, Lung, and Blood Institute's Adult Treatment Panel IV.

Dr. Ladenson disclosed that he has no financial ties to any commercial interests. ■