GHRH Analogue Trims Visceral Fat in HIV Study

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LOS ANGELES — Visceral adipose tissue declined by 15% in HIV patients treated for 26 weeks with a growth hormone–releasing hormone (GHRH) factor analogue, while visceral fat in patients assigned to placebo increased 5%, Dr. Steven Grinspoon reported at the 14th Conference on Retroviruses and Opportunistic Infections.

"This was a very potent effect, a net change of 20% versus placebo in 6 months," said Dr. Grinspoon, director of the Massachusetts General Hospital Program in Nutritional Metabolism in Boston.

An "emerging consensus" of data suggests that cardiovascular risk is substantially elevated in patients with HIV, underscoring the clinical importance of a shift seen in the ratio of subcutaneous and visceral fat in patients undergoing antiretroviral treatment, he said. These patients often have a reduction in subcutaneous fat, but a substantial increase in visceral fat, which is a significant independent predictor of cardiovascular risk.

In previous studies, growth hormone has been shown to be efficacious in reducing visceral fat, but its superphysiologic impact on glucose parameters and other side effects limit its clinical usefulness.

By contast, the agent used in this trial, TH9507, is an analogue of a precursor hormone to growth hormone that accomplishes visceral fat reduction "in a more gentle physiological way," Dr. Grinspoon said.

The phase III, multicenter, double-blind trial randomized 412 HIV patients on stable triple therapy to receive one daily subcutaneous injection of 2 mg TH9507 (275 patients) or placebo (137 patients) for 6 months. Approximately 19% of the study participants had type II diabetes or glucose intolerance at baseline. Lipid-lowering agents were permitted.

Not unexpectedly, roughly 20% of study subjects failed to complete the trial, but the numbers of dropouts were comparable between treatment arms and the results were calculated using an intent-to-treat analysis.

The patients' percentage of visceral abdominal tissue was measured by computed tomography at the L4-L5 level. Secondary and safety end points included measurements of participants' lipid profiles, insulin-like growth factor 1 (IGF-1), and glucose and insulin metabolism.

The absolute 15% reduction in visceral fat was equivalent to a 3-cm reduction in waist size—"a pants size," Dr. Grinspoon said, in spite of the fact that patients did not lose weight.

In addition to the improvement in visceral fat, trunk fat as measured by dual-energy x-ray absorptiometry also improved significantly in patients receiving TH9507, compared with patients receiving placebo (–1.0% change vs. 1.6% change, respectively; *P* less than 0.001).

Lipid levels were measured as well. "We saw positive effects across all lipid categories," he said, noting a particularly robust mean 18% change in triglycerides.

Mean IGF-1 levels increased by 81% among patients receiving the growth hormone precursor analogue and decreased by 5% among patients receiving placebo.

In sharp contrast to the effect of growth hormone, TH9507 did not precipitate changes in fasting glucose, 2-hour postprandial glucose, or insulin.

"It is much more tolerated, yet you get the same bang for the buck, a 15%-20% reduction in visceral fat, and improvements across lipids," he said at the meeting, also sponsored by the Foundation of Retrovirology and Human Health.

The two most common side effects—headache and arthralgias—were seen equally in treatment and placebo patients. However, more patients receiving TH9507 discontinued treatment because of adverse effects. Notably, six patients in the active treatment arm developed a rash, most often after 4 months of treatment, and one developed associated sweating, tachycardia, and shortness of breath.

These patients were "treated with Benadryl and did fine," but were released from the study as a precaution, Dr. Grinspoon said. A confirmatory study currently underway in Europe will also explore the durability of effects following discontinuation of the drug, which has not received FDA approval.

Dr. Grinspoon disclosed that he is an independent investigator and consultant to Theratechnologies Inc., of Montreal, manufacturer of TH9507. ■