Human Recombinant Leptin for Treatment of Hypothalamic Amenorrhea

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Hypothalamic amenorrhea due to strenuous exercise or chronic energy deficiency is associated with the dysfunction of the hypothalamic-pituitary-peripheral axes, resulting in infertility, bone loss, and stress fractures. The findings of a pilot randomized controlled trial showed that long-term treatment with human recombinant leptin (metreleptin) improved neuroendocrine and reproductive function in women with exercise-induced hypothalamic amenorrhea and low levels of circulating leptin. The treatment also increased bone mineral density (BMD) and bone mineral content, as measured in the lumbar spine.

In reporting the findings of the trial, Konstantinos N. Aronis, MD, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA, first noted that the study's hypothesis was based on the findings of a single-arm, proof-of-concept study that demonstrated an association between hypothalamic amenorrhea and hypoleptinemia, and showed that exogenous recombinant leptin replacement restored neuroendocrine and reproductive function and changed the levels of circulating bone markers in the short term (up to 2 to 3 months of treatment) [Welt CK et al. *N Engl J Med* 2004]. The current trial was designed to evaluate whether leptin replacement therapy is an efficient treatment for hypothalamic amenorrhea.

The trial began with 20 women (aged 18 to 35 years) who had exercise-induced hypothalamic amenorrhea and a low level of circulating leptin (<5 ng/mL). The women were randomly assigned to receive either metreleptin (n=11) or placebo (n=9) for 36 weeks. Three women in the metreleptin group were withdrawn from the study (two of them after 24 weeks), and three women in the placebo-treated group withdrew from the study.

The initial dose of metreleptin was 0.08 mg/kg/day, administered subcutaneously, and the dose was adjusted according to measured leptin levels. After a 3-month washout period, six women received open-label metreleptin for an additional 12 months. BMD and bone mineral content were assessed using dual-energy x-ray absorptiometry (DEXA) at baseline and every 3 months for the first year and then at 18 and 24 months. Metabolic, hormone, and bone parameters were measured in blood and urine at those time points.

Metreleptin restored menstruation in seven of 10 women who received metreleptin, compared with two of the nine women who received placebo (p=0.005). Four of seven metreleptin-treated women were determined to be ovulatory, as defined by serum progesterone level, measured on Day 21 of their cycles.

The percentage change in BMD (measured in the lumbar spine) from baseline was improved in the metreleptin treatment group during the treatment period, although the difference was not significant compared with the placebo (p=0.069). However, the increase from baseline was significant at 24 months (p=0.024). The bone mineral content (in the lumbar spine) was significantly higher in the metreleptin group than in the placebo group, beginning at 6 months (p=0.034), and the increase continued to be significant at 24 months (p=0.049).

Treatment with metreleptin also restored other neuroendocrine axes (adrenal, growth hormone, and thyroid). Levels of estradiol and insulin growth factor 1:insulin growth factor BP3 were significantly higher in the metreleptin treatment group than the placebo group during the treatment period (p=0.01 and p=0.04, respectively). Cortisol levels were significantly lower in the metreleptin group (p=0.020).

Dr. Aronis acknowledged several limitations of the study, including the small sample size and the lack of a control group (by design) in the second part of the trial. He added that the pilot study should be extended by larger clinical trials in which bone microarchitecture and fracture risk are also evaluated.

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