Treatment with GH May Be Associated with Increased Mortality

Written by Lori Alexander

Preliminary data suggest that all-cause mortality is increased among individuals who are treated with growth hormone (GH) for childhood short stature. However, causality can not be determined due to the preliminary nature of the results, as well as a low event rate, limited power, and potentially undefined confounders. The findings were reported by Jean-Claude Carel, Université Paris 7 Denis Diderot and Hôpital Robert Debré, Paris, France.

The data that were reported were from the Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE) trial, a large study that was undertaken to evaluate the long-term health of individuals who were treated with recombinant GH in childhood in eight European countries. The study in France began 2 years before studies in other countries, and Prof. Carel reported only the preliminary mortality data from the French population-based register of children who were treated with GH.

The register included 11,035 children who were treated exclusively with recombinant GH, with treatment starting between 1985 and 1996. Of them, 6928 children and were considered to have a low mortality risk (isolated idiopathic GH deficiency, short stature in children born short for gestational age, and idiopathic short stature). The children had a mean age of 15.1 years at the end of treatment, and the mean duration of treatment was 3.9 years.

Follow-up data on vital status were available for 95% of the patients. Prof. Carel and his coinvestigators measured all-cause and cause-specific mortality and calculated standardized mortality ratios (SMRs). All-cause mortality was higher for individuals who were treated in childhood than expected in the general population (SMR, 1.33; Table 1).

Table 1. All-Cause and Cause-Specific Mortality Associated with GH Treatment.

	Standardized Mortality Ratio (95% CI)
All-cause mortality	1.33 (1.08–1.64)
Malignant neoplasms of bone and articular cartilage	5.00 (1.01–14.61)
Diseases of circulatory system	3.07 (1.40–5.83)
Cerebrovascular diseases (subarachnoid or intracerebral hemorrhage)	6.66 (1.79–17.05)

In the multivariate analysis, adjusted for height at the start of treatment, the use of a high dose (>50 µg/kg/day) was associated with a mortality rate nearly 3 times that for a low dose (<20 µg/kg/day; SMR, 2.94; 95% CI, 1.22 to 7.07).

Analysis of cause-specific mortality among individuals who were treated in childhood demonstrated increased SMRs for malignant neoplasms of bone and articular cartilage (SMR, 5.00) and diseases of the circulatory system (SMR, 3.07; Table 1). Within diseases of the circulatory system, the mortality rate for cerebrovascular diseases (subarachnoid or intracerebral hemorrhage) was more than 6 times higher than the expected rate (SMR 6.66).

In closing, Prof. Carel emphasized that the results should be interpreted with caution because of the low event rate, the statistical limitations, the lack of mortality data from the other European studies that participated in SAGhE, and the lack of morbidity data from the French SAGhE study. He added that the results highlight the need for additional studies of long-term mortality and morbidity after GH treatment in childhood.

Transitioning to Denosumab from Continuous Alendronate Therapy Further Improves BMD in Postmenopausal Women with Osteoporosis

Written by Rita Buckley

Henry G. Bone, MD, Michigan Bone and Mineral Clinic, Grosse Pointe, Michigan, USA, presented findings on the efficacy and safety of a shift from alendronate (ALN) to denosumab (DMAb) in a subset of women from the 1-year Study of Transitioning from Alendronate to Denosumab (STAND; NCT00377819) trial who transitioned to DMAb after 5 or more years of continuous ALN therapy.

STAND was a multicenter, international, randomized, double-blind, double-dummy study in 504 postmenopausal women aged ≥55 years with a bone mineral density (BMD) score of ≤–2.0 and ≥–4.0 or more who had been receiving ALN therapy for at least 6 months. Subjects were randomly assigned to either continued weekly ALN treatment or subcutaneous denosumab 60 mg every 6 months and were followed for 12 months. The primary endpoint was noninferiority of DMAb compared with ALN [Kendler DL. *J Bone Min Res* 2010].

At Month 12, total hip BMD increased by 1.9% in the DMAb group versus 1.05% in the ALN group (p<0.0001).

DMAb subjects also showed significantly greater BMD gains compared with ALN at the lumbar spine, femoral neck, and 1/3 radius (all p<0.0125). Median serum c-telopeptide levels were significantly decreased in the DMAb group compared with the ALN group (p<0.0001) at all time points. Adverse events (AEs) and serious AEs were balanced between groups. No clinical hypocalcemic AEs were reported [Kendler DL. *J Bone Min Res* 2010].

In STAND, 149 women aged 70.0 ± 7.6 years had received ALN for ≥5 years. These women were slightly older and had worse hip but not spine BMD than those who were treated with ALN for <5 years. A total of 70 women transitioned to DMAb, and 79 women remained on ALN. Transitioning to DMAb for 12 months led to further significant increases in BMD of 2.95% (lumbar spine), 1.66% (total hip), and 1.02% (femoral neck). Those who remained on ALN had smaller changes in BMD of 1.55% (lumbar spine), 0.97% (total hip), and 0.25% (femoral neck). An interaction-by-subgroup analysis showed that the greater gains in BMD in the transition-to-DMAb subgroup that was exposed to ALN for ≥5 years were consistent with overall population results. Of the women who received ALN for ≥5 years, a similar number of AEs were reported in those who transitioned to DMAb and those who continued to receive ALN (81.4% and 84.8%, respectively). The most frequently reported AEs for both groups combined were nasopharyngitis (16.1%), back pain (11.4%), nausea (7.4%), bronchitis (7.4%), pain in the extremities (7.4%), and arthralgia (7.4%). There were no cases of osteonecrosis of the jaw, delayed fracture healing, or atypical femoral fractures.

According to Dr. Bone, results from the STAND follow-up study are consistent with those from the overall STAND study—ie, that the transition to DMAb after ≥5 years of continuous ALN treatment led to further significant gains in BMD at the lumbar spine, total hip, and femoral neck—and demonstrated a similar safety profile compared with patients who continued on ALN.

Results from the First Two Years of the FREEDOM Trial Extension

Written by Rita Buckley

Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM; NCT00089791) was a randomized, placebo-controlled, Phase 3 trial designed to test the effect of denosumab on risk of fracture in postmenopausal women during a 3-year follow-up period [Cummings SR et al. *N Engl J Med* 2009]. Henry G. Bone, MD, Michigan Bone and Mineral Center, Grosse Pointe, Michigan, USA, presented findings from the first 2 years of the FREEDOM trial extension.

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density.

A total of 7808 women aged between 60 and 90 years with osteoporosis were enrolled at 213 study sites worldwide. Subjects were randomly assigned to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. The primary endpoint was new verterbral fractures. Secondary endpoints included nonvertebral and hip fractures.

The cumulative incidence of new radiographic vertebral fractures in the denosumab group was 2.3% versus 7.2% in the placebo group (p<0.001). The cumulative incidence of hip fractures was 0.7% in the denosumab group versus 1.3% in the placebo group (p=0.04). The relative decrease in nonvertebral fractures in the treatment group was 20% (p=0.01), with no increase in the risk of adverse events

The extension study monitored crossover and safety data for up to 10 years in 4550 subjects who completed the FREEDOM trial; 2207 crossover and 2343 long-term subjects received 60 mg of denosumab every 6 months. The placebo group data reflect up to 4 doses of denosumab (2 years; crossover). The treatment group data reflect up to 10 doses over 5 years (long-term group).

During the first 2 years of treatment, the crossover group showed significant gains of 7.9% in lumbar spine BMD and 4.1% in total hip BMD (p<0.0001). The long-term group had further significant BMD increases of 13.7% in the lumbar spine and 7.0% in the total hip over the cumulative 5-year period (p<0.0001). Serum c-telopeptide of type 1 collagen was rapidly and similarly reduced after the first (crossover) or seventh (long-term) administration of denosumab.

The crossover group had lower yearly incidences of new vertebral and nonvertebral fractures than the control group. The rate of fractures in the long-term group remained low. Adverse events (AEs) and serious AEs (SAEs) in the crossover group were similar to or lower than in the placebo and denosumab FREEDOM groups. Neither AEs nor SAEs increased over time with long-term administration of denosumab.