GH for Short Stature May Increase Mortality Risk

BY AMY ROTHMAN SCHONFELD

FROM THE ANNUAL MEETING OF THE ENDOCRINE SOCIETY

BOSTON – After more than 2 decades of follow-up, mortality rates were significantly higher in patients who had been treated with recombinant growth hormone for short stature as children, especially those who received the highest doses.

Notable increases in mortality were observed related to bone tumors and diseases of the circulatory system such a subarachnoid or intracerebral hemorrhage, according to Dr. Jean-Claude Carel of the Hôpital Robert Debré and Université Denis Diderot in Paris, who presented the results at the meeting.

According to Dr. Carel, although there has been a considerable amount of data linking recombinant growth hormone (GH) and health, few studies have provided long-term follow-up. The data released were French data from the SAGHE (Safety and Appropriateness of Growth Hormone Treatments in Europe) trial, a large study from eight European countries evaluating the health of individuals treated in childhood for idiopathic growth hormone deficiency (75% of the group), idiopathic short stature, and body length at birth that was short for gestational age. The study was initiated first in France (2 years before the rest of Europe), and thus the longest follow-up is available for this cohort.

VITALS

Major Finding: During more than 2 decades of follow-up, 93 deaths were seen in 6,928 people who were treated as children with recombinant growth hormone for short stature, compared to an expected rate of 69. 7.

Data Source: A population based cohort study of 6,928 short children who were followed for 116,403 person years.

Disclosures: Dr. Carel reported ties to Lilly USA and Pfizer Global Research and Development.

The group consisted of 6,928 children who were treated during 1985-1996. Follow-up data on vital status were available in September 2009 for almost 95% of the patients, providing 116,403 person-years of observation. The mean age at the end of treatment was 15 years and the mean duration of treatment was almost 9 years.

During the follow-up, 93 deaths were observed, compared with 69.6 expected deaths, yielding a higher standardized mortality ratio (SMR) of 1.33, which Dr. Carel said was significant but moderate.

Although the mean dose was 24.6 mcg/kg per day – lower than doses currently recommended today – there was a significant trend of increasing mortality and GH dose. In multivariate analysis adjusted for height at the start of treatment, mortality rates in the 285 who received high doses (greater than 50 mcg/kg per day) was almost three times that of the low-dose group (adjusted SMR, 2.94). No significant effects were seen for treatment duration or overall GH exposure. Mortality was elevated in children with the shortest stature at treatment initiation (SMR, 1.57).

Further analysis about cause of death found that although overall cancer-related mortality was not higher than that of the general population, deaths resulting from bone tumors were five times higher than expected (SMR, 5.00), and deaths resulting from diseases of the circulatory system were threefold higher (SMR, 3.07). Particularly concerning were findings of more than a sixfold increase in deaths resulting from subarachnoid or intracerebral hemorrhage (SMR, 6.66) and a sevenfold increase in other heart diseases (cardiomyopathy and cardiomegaly, SMR, 7.11).

"These preliminary results should be taken with caution due to the low event rate, limited power, and potentially undetected confounders. Causality cannot be determined," said Dr. Carel. ■

Androgenetic Alopecia Not Uncommon in Children, Teens

BY SHARON WORCESTER

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE FLORIDA SOCIETY OF DERMATOLOGY AND DERMATOLOGIC SURGERY

BOCA RATON, FLA. – Androgenetic alopecia is fairly common in the pediatric population, and in adolescent girls it should prompt an evaluation for hyperandrogenism, according to Dr. Seth J. Orlow.

Androgenetic alopecia is a presenting symptom of polycystic ovary syndrome (PCOS) in a considerable number of cases, he said at the meeting."I think this is a place where we can really make a difference," said Dr. Orlow, chair of dermatology and professor of pediatric dermatology, cell biology, and pediatrics at New York University.

One of the most useful lab tests in adolescent girls presenting with early androgenetic alopecia is free and total testosterone, which at elevated levels can serve as a marker for PCOS.

"In a girl who presents with early-onset androgenetic alopecia, think about early presentation of PCOS. It's definitely worth it to test them," he said.

A chart review of 438 consecutive pediatric patients with alopecia seen by Dr. Orlow and his colleagues over a 12-year period underscored the importance of looking for this diagnosis, and illustrated other characteristics of androgenetic alopecia in both girls and boys.

The study showed that androgenetic alopecia was the second most common type of alopecia (after alopecia areata, which accounted for 55% of cases), involving 13% of the cases overall.

Among the 123 adolescent patients, however, 42% (52 patients: 36 boys and 16 girls) had androgenetic alopecia, for a total of 38 boys and 19 girls with androgenetic alopecia among the 438 studied.

Female Findings

Of the 19 girls, 9 had hyperandrogenism. Three had clinical signs and six had biochemical signs of hyperandrogenism. Of the six with biochemical signs, three had elevated free and total testosterone levels, one had elevated free and total testosterone and elevated dihydroepiandrosterone sulfate, one had an elevated free testosterone level only, and one had an elevated total testosterone level only. Seven of the girls were oligomenorrheic, and two were premenarchal. Clinical signs other than the androgenetic alopecia included hirsutism in four girls, acne in six, and seborrheic dermatitis in two.

Other laboratory findings in the 19 girls with androgenetic alopecia included antithyroid antibodies in 1of 5 tested and low serum iron in 3 of 14 tested. None of the girls tested had abnormal thyroid function, iron deficiency anemia, or low testosterone levels, Dr. Orlow said.

The most common presentations in girls were diffuse scalp thinning and thinning at the crown, each occurring in 8 of the 19 patients. The remaining three girls presented with frontal thinning only.

Male Findings

Findings in the boys presenting with androgenetic alopecia included antithyroid antibodies in 1 of 7 tested, hyperandrogenemia in 2 of 14 tested, and low testosterone levels in 3 of 14 tested. None of the boys had abnormal thyroid function, low serum iron, or iron deficiency anemia.

Androgenetic alopecia is a presenting symptom of PCOS in a considerable number of cases.

DR. ORLOW

A disproportionate number of boys (13 of the 38) presented with classic female pattern androgenetic alopecia with diffuse thinning of the crown. The remaining boys presented with bitemporal vertex thinning (18 boys), vertex only thinning (4 boys), or frontal and vertex thinning (3 boys), Dr. Orlow said.

Concomitant findings included acne in 32% of the girls and 50% of the boys, and seborrheic dermatitis in 37% of the girls and 16% of the boys. A family history of androgenetic alopecia was present in both, with 82% of the boys and 87% of the girls having an affected first- or second-degree relative.

Differential Diagnoses

It is important to consider possible differential diagnoses in patients presenting with what appears to be androgenetic alopecia. These include acute telogen effluvium, chronic telogen effluvium (particularly in girls), and diffuse alopecia areata, he said.

If the clinical diagnosis is unclear – in boys with female pattern hair loss, in girls with very young onset, or if the patient or parents have a great deal of anxiety about the diagnosis – a biopsy may be helpful, he said.

Of the 57 patients with androgenetic alopecia included in his chart review, 14 (5 girls and 9 boys) underwent biopsy; all of the biopsies showed typical features of androgenetic alopecia, including increased vellus/telogen hairs and connective tissue streamers/follicular stelae below small vellus follicles.

Eight of the 14 also had varying degrees of peri-infundibular lymphocytic inflammatory infiltrate and fibrosis.

Treatment

Treatment options for patients with androgenetic alopecia include minoxidil, finasteride (in boys), and spironolactone.

Minoxidil was used in 16 of the 19 girls; 4 of 6 with greater than 6 months of follow-up had stabilized at 1 year. One developed increased facial hair on treatment, which resolved with a switch from a 5% to a 2% formulation, Dr. Orlow said. Two patients discontinued treatment because of a lack of efficacy and/or headache and nausea.

In the boys, 36 of the 38 were treated with minoxidil, and 18 of 23 with at least 6 months of follow-up were stabilized. Two never started treatment and two discontinued for lack of efficacy and acne.

Finasteride was used in nine boys, including seven who also received minoxidil. In six boys, with at least 6 months of follow-up, all had better hair density (including four on concomitant minoxidil). One experienced sexual dysfunction, which resolved spontaneously, Dr. Orlow said.

"I did not treat – and would not treat girls [with finasteride], nor did I find any case reports of finasteride use in girls," he said. There are a few case reports, however, of spironolactone being used in girls with some success.

The findings of the chart review (Br. J. Dermatol. 2010; 163:378-85) underscore the importance of understanding that alopecia is a common complaint in the pediatric population, that androgenetic alopecia is the most common form of hair loss in adolescents, and that it can be a presenting sign of an underlying endocrine disorder, said Dr. Orlow, who reported having no relevant financial disclosures. ■