GH Deficiency Research Highlights

I am Paul Saenger. I'm a pediatric endocrinologist, professor of pediatrics at New York University in New York, and I have been doing pediatric endocrinology for several decades. I'm going to talk to you today in a CME on highlights of the last Endocrine Society meeting in Atlanta, Georgia. We'll focus on particularly research highlights of that conference that dealt with growth hormone deficiency and short stature and treatment modalities with growth hormone that we have now at our disposal.

Here are my disclosures.

Firstly, what is growth hormone deficiency? It's characterized by inadequate secretion of growth hormone from the anterior pituitary gland. Symptoms are varied and can include reduced energy levels, altered body composition, osteoporosis, reduced muscle strengths, lipid abnormalities, insulin resistance, and impaired cardiac function. It can be congenital or acquired.

There are a number of FDA-approved human growth hormones that are available for treatment in the United States and Canada. They include Genotropin, Humatrope, Norditropin, Nutropin, and Saizen. They're all, obviously, somatropin, so growth hormone. Weekly formulations of human growth hormone have also been recently approved including lonapegsomatropin and somapacitan.

Other non-growth hormone treatments are also being investigated.

Growth hormone deficiency is a rare condition. It's 1 in 4,000 children. The data represented at large medical conferences, like the Endocrine Society meeting may get easily overlooked, as a result.

In the next minutes, I will present updates on recently presented clinical trials with long-acting growth hormone and other growth promoting hormones. First, here is a slide that shows once-weekly Somatrogon in comparison to daily Genotropin in pediatric growth hormone deficiency patients. So these were all prepubertal patients. And you can see that in most of the studies, we always have more boys than girls, because more short stature boys come to our attention and are being evaluated than girls.

For these investigational trials that have been going on for three to four years, the data were pooled and analyzed and then compared with growth data from matched subsets of growth hormone treated patients by Ranke and Lindberg. We found that the cohort of these patients treated with a long-acting growth hormone showed just the same kind of growth hormone in centimeters per year, we would see with the daily.

This is very reassuring that we can get, with a long-acting growth hormone given once a week by a subcutaneous injection, good somatic growth compared to children with daily growth hormone. I think that is a significant advance, because it may indeed increase compliance or adherence to a hormonal treatment and lead to better outcomes for children and their families.

Next slide shows safety and efficacy of another long-acting growth hormone recently approved by the FDA, and that is Lonapegsomatropin. These are the results from a study that lasted 130 weeks and was an open-label study and an extension of clinical trials that had preceded it.

As you can see, the children and teenagers treated with the long-acting growth hormone showed continued improvement of height SDS through their third year. They were already for three years on the long-acting growth hormone. Their third year of therapy.

This form of long-acting growth hormone called Lonapegsomatropin continued to demonstrate a safety profile particularly addressing issues with carbohydrate metabolism, a somatropin therapy. So this is very good news, showing a growth rate that was similar or slightly better than the daily growth hormone amounting to 9.3 centimeters. And again, this study was carried out over 130 weeks in this trial.

Next slide shows another long-acting growth hormone. The drug is called somapacitan. This is a safety extension of an ongoing trial. It went from phase 2 to phase 3, and the initial trial was showing an ongoing exciting improvement in growth rates expressed as an annual growth rate.

And this now shows data from a four-year study. And it shows quite impressive support of the efficacy and the safety result of this form of long-acting growth hormone, somapacitan, observed in these trials. It was well tolerated and no safety signals were identified.

I have to stress that the patients did not form antibodies, neutralizing or blocking antibodies. And they were also considered safe immunological basis.

And in this next slide shows this form of long-acting growth hormone, Norditropin, in this trial called REAL 4. It's an ongoing phase 3 trial, testing the efficacy and safety of the weekly subcutaneous long-acting growth hormone compared to daily. You can see at near time point, mean IGF-1 levels, that's something we always measure in patients receiving growth hormone, were similar between the long-acting and the daily interval. Quite impressively within the normal range from minus two to plus two SD. This compound, somapacitan, was well tolerated with no safety or local tolerability issues.

In conclusion, the once-weekly growth hormone in this version or this company's product has similar efficacy and safety compared to daily. This is particularly impressive in treatment-naive patients, but also in patients who were then switched from daily long-acting, which will probably be scenario for most patients who are being treated with long-acting growth hormone, that they have been on daily growth hormone before.

Another study, by Dr. Welch and colleagues, was the effect of recombinant growth hormone on measures of strength, endurance, and physical mobility. These data show that the measures for isokinetic strength, endurance, agility, and power improve after 12 months of growth hormone therapy. This is important because a growth hormone is just not only affecting growth, but also, as you can see here, measures of strength, endurance, and physical performance. That is very important because particularly in adult growth hormone deficiency, these measures or these parameters are often adversely affected.

The next slide is an important slide because it is a non-growth hormone agent that is used here in short stature caused by various genetic mutations. So the previous slides were always for growth hormone deficiency. This here is a completely different compound. It's a C-type natriuretic peptide analog which binds to the receptor on chondrocytes, leading then to increased chondrocyte proliferation and differentiation, and that may also engender skeletal growth.

The compound has been approved last year by the FDA for the treatment of achondroplasia. Here in this study, this compound, vosoritide, was used in Ras-dependent extracellular signal-regulated kinase and mitogen-activated protein pathway deficiencies.

What are RASopathies, as the term is called? RASopathies are rare diseases, often associated with short stature. One of the most well studied is Noonan syndrome and it is associated with short stature and cardiac lesions, but also neurofibromatosis and other conditions that are particularly manifesting itself in cutaneous lentiginous type syndromes. So these RASopathies are a wide group of patients that have short stature.

So in this phase 2 study. This compound, which is not a growth hormone, was assessed in improving growth in six categories: hypochondroplasia, which is quite different from achondroplasia, RASopathies, as I just explained to you, aggrecan deficiency, which is another form of short stature caused by hormonal deficiency, and heterozygous NPR2 mutations, and SHOX deficiency. So these are conditions that are known to the clinician is causing considerable or severe short stature.

In conclusion, we showed that in children with these genetic forms of short stature, vosoritide treatment may work as a precision therapy to improve growth in multiple genetic conditions which interact with the ERK1/2-MAP kinase pathway. So this is a significant departure, as it opens up new treatment modalities for patients with short stature which are not characterized by growth hormone deficiency. And obviously, these preliminary data are exciting and need to be confirmed in longer phase 3 studies.

Now we have to talk about the real world studies and registries that have been a hallmark of the growth hormone field. And particularly, we see in the next slide, the economic burden of growth hormone deficiency. Here, adult studies, adult patients with growth hormone deficiency, it was shown that they experience a substantial comorbidity and economic burden compared to non-growth hormone deficiency patients.

Adult growth hormone deficiency patients remain primarily untreated and present a significant healthcare burden because the adherence to growth hormone therapy is often poor and adults stop treatment. That may be because they don't like daily injections, and therefore, in this particular arena, long-acting growth hormone may provide a new avenue to increase healthcare for patients with adult growth hormone deficiency.

A study from Harvard, efficacy in older growth hormone deficiency patients was analyzed. These data suggest similar clinical outcome with growth hormone replacement therapy in patients with adult deficiency aged over 60, compared to adults between 35 and 60, without additional risk of adverse drug reactions in the older patients. The visual effects of growth hormone are also well preserved in older patients.

This next investigation shown on this slide was to determine predictors of response to daily growth hormone for height outcomes using longitudinal analysis across five years of real-world data from pediatric patients with growth hormone deficiency, Noonan syndrome, and Prader-Willi syndrome, and Turner syndrome. The last two syndromes that I mentioned are not characterized by growth hormone deficiency. These patients make normal growth hormone, but growth hormone as an additive improves their height and stature outcome quite impressively.

So the data were combined in long, large studies. Again, 3,700 females, and as we expect, many more males, nearly 9,000 with these three conditions. On average, growth hormone treatment resulted in improvement in their final height over baseline across all indications. Patients with growth hormone deficiency, not unexpectedly, had the highest improvement, while patients with Turner syndrome had the lowest improvement, but also improved their height. And we as physicians are always very pleased when we reach a final height in Turner patients of five feet or better, which is, I think, a very realistic therapeutic goal. Whereas untreated, their height may rest at 4' 6" or 4' 7".

So we show that these treatment responses lead to better outcome in adult height. Increasing the dose of growth hormone also led to a better outcome. And therefore, we have to welcome this large survey of almost 15,000 patients as far as official outcomes of growth hormone therapy are concerned.

Now, of course growth hormone may have effects on the metabolic system. Here on this slide, long-term effects of growth hormone replacement therapy on glucose tolerance and in adults with growth hormone deficiency is analyzed. And one can say conclusively, overall, growth hormone replacement therapy was safely used in regard with impaired glucose tolerance in adults with growth hormone deficiency. In these 53 patients, I think we did not see any adverse effects on hemoglobin A1C, as shown here on the slide, or on the BMI, as also shown here. And therefore, this is, I think, a beneficial outcome of these studies addressing another important aspect of adult growth hormone deficiency.

Here are the clinical pearls. We have seen a number of studies with long-acting growth among which will probably very rapidly be developing into the mainstay as the form of growth hormone therapy in pediatric patients and adult patients leading to better compliance, better adherence, and maybe even better outcome. But certainly, much more congenial and much better tolerated by patients and parents, as the injection is not daily, but only once a week.

Children treated with once-weekly growth hormone showed good growth, very comparable, sometimes even better, than children treated with daily growth hormone. Children and adolescents treated with the long-acting growth hormone over three to four years showed impressive safety data and very good response.

And once-weekly growth hormone shows a similar safety profile, and also similar mean IGF-1 levels in treatment-naive children with growth hormone deficiency. And the safety profile was confirmed in an extension trial that I also presented, leading up to the three to four year that we have reviewed here.

Adult patients with growth hormone deficiency experienced a substantial comorbidity and economic burden compared to non-growth hormone deficiency controls. Treatment for these patients is important. And with long-acting growth hormone formulations becoming available for this age group, it also should lead to a significant reduction of the healthcare burden for this patient.

Older patients with growth hormone deficiency had similar outcomes, and therefore, should also be offered this treatment. And the outcome was similar to middle-aged controls or middle-aged patients who were enrolled.

Growth hormone treatment resulted in height improvements over baseline in a number of indications. The best results were seen in patients, children with growth hormone deficiency, but they still had open growth plates.

Earlier treatment with growth hormone leads also to better outcomes. That is important because the average pediatric patient enrolled in growth hormone treatment program is still, unfortunately, advanced in age, 12 years, the average data. Whereas we would like to get these patients on treatment as early as four to six years of age, which leads to better height outcome in the end. Increasing the dose of growth hormone also led to better outcomes in adult height.

Growth hormone replacement therapy was safely used in regard with impaired glucose tolerance in adults with growth hormone deficiency.