

fect” that extends protection against cardiovascular disease beyond the initial period of intensive glycemic control.

The group with early-onset diabetes in the present study clearly had higher average glucose levels for a relatively longer duration than did the later-onset group. In addition, the early-onset group may have had a higher incidence of neuropathy – including damage to the autonomic nerves, which is itself a risk for cardiovascular events – and cerebral and peripheral arterial disease as well, each factor increasing the relative risk for such an event.

Therefore, it is hardly surprising that those patients exposed to a longer duration of diabetes are at higher risk for cardiovascular disease. In fact, VA-HIT (Veterans Affairs High-Density Lipoprotein Intervention Trial) showed that after 16 years duration of diabetes, the positive impact of intensive insulin therapy was outweighed by the risk of adverse outcomes, another indication of the importance of considering duration of diabetes as a risk factor for complications, and a limitation on our ability to achieve the best outcomes for that patient.

Clearly more studies are needed to

explore the point raised again by Dr. Wannamethee and colleagues.

Although such observational studies as theirs have many methodological flaws that limit our ability to generalize the findings, I think that his findings are credible, and fit well with what has been previously published. ■

DR. HELLMAN is clinical professor of medicine at the University of Missouri, Kansas City, and past president of the American Association of Clinical Endocrinologists. He has no relevant disclosures.

Syndrome: Norditropin® was studied in a two-year prospective, randomized, parallel dose group trial in 21 children, 3–14 years old, with Noonan syndrome. Doses were 0.033 and 0.066 mg/kg/day. After the initial two-year randomized trial, children continued Norditropin® treatment until final height was achieved; randomized dose groups were not maintained. Final height and adverse event data were later collected retrospectively from 18 children; total follow-up was 11 years. An additional 6 children were not randomized, but followed the protocol and are included in this assessment of adverse events. Based on the mean dose per treatment group, no significant difference in the incidence of adverse events was seen between the two groups. The most frequent adverse events were the common infections of childhood, including upper respiratory infection, gastroenteritis, ear infection, and influenza. Cardiac disorders was the system organ class with the second most adverse events reported. However, congenital heart disease is an inherent component of Noonan syndrome, and there was no evidence of somatropin-induced ventricular hypertrophy or exacerbation of preexisting ventricular hypertrophy (as judged by echocardiography) during this study. Children who had baseline cardiac disease judged to be significant enough to potentially affect growth were excluded from the study; therefore the safety of Norditropin® in children with Noonan syndrome and significant cardiac disease is not known. Among children who received 0.033 mg/kg/day, there was one adverse event of scoliosis; among children who received 0.066 mg/kg/day, there were four adverse events of scoliosis [see *Warnings and Precautions*]. Mean serum IGF-I standard deviation score (SDS) levels did not exceed +1 in response to somatropin treatment. The mean serum IGF-I level was low at baseline and normalized during treatment. **Clinical Trials in Children with Turner Syndrome:** In two clinical studies wherein children with Turner syndrome were treated until final height with various doses of Norditropin®, the most frequently reported adverse events were common childhood diseases including influenza-like illness, otitis media, upper respiratory tract infection, otitis externa, gastroenteritis and eczema. Otitis media adverse events in Study 1 were most frequent in the highest dose groups (86.4% in the 0.045–0.067–0.089 mg/kg/day group vs. 78.3% in the 0.045–0.067 mg/kg/day group vs. 69.6% in the 0.045 mg/kg/day group) suggesting a possible dose-response relationship. Of note, approximately 40–50% of these otitis media adverse events were designated as “serious” [see *Warnings and Precautions*]. No patients in either study developed clearcut overt diabetes mellitus; however, in Study 1, impaired fasting glucose at Month 48 was more frequent in patients in the 0.045–0.067 mg/kg/day group (n=4/18) compared with the 0.045 mg/kg/day group (n=1/20). Transient episodes of fasting blood sugars between 100 and 126 mg/dL, and, on occasion, exceeding 126 mg/dL also occurred more often with larger doses of Norditropin® in both studies [see *Warnings and Precautions* and *Adverse Reactions*]. Three patients withdrew from the 2 high dose groups in Study 1 because of concern about excessive growth of hands or feet. In addition, in Study 1, exacerbation of preexisting scoliosis was designated a serious adverse reaction in two patients in the 0.045 mg/kg/day group [see *Warnings and Precautions*]. **Clinical Trials in Children Born Small for Gestational Age (SGA) with No Catch-up Growth by Age 2–4 Years: Study 1 (Long-Term):** In a multi-center, randomized, double-blind study, 53 non-GHD children with short stature born SGA with failure to catch-up were treated with 2 doses of Norditropin® (0.033 or 0.067 mg/kg/day) to final height for up to 13 years (mean duration of treatment 7.9 and 9.5 years for girls and boys, respectively). The most frequently reported adverse events were common childhood diseases including influenza-like illness, upper respiratory tract infection, bronchitis, gastroenteritis, abdominal pain, otitis media, pharyngitis, arthralgia, and headache. Adverse events possibly/probably related to Norditropin® were otitis media, arthralgia, headaches (no confirmed diagnoses of benign intracranial hypertension), gynecomastia, and increased sweating. One child treated with 0.067 mg/kg/day for 4 years was reported with disproportionate growth of the lower jaw, and another child treated with 0.067 mg/kg/day developed a melanocytic nevus [see *Warnings and Precautions*]. There were no clear cut reports of exacerbation of preexisting scoliosis or slipped capital femoral epiphysis. No apparent differences between the treatment groups were observed. In addition, the timing of puberty was age-appropriate in boys and girls in both treatment groups. Therefore, it can be concluded that no novel adverse events potentially related to treatment with Norditropin® were reported in long-term Study 1. **Study 2 (Short-Term):** In a multi-center, randomized, double-blind, parallel-group study, 98 Japanese non-GHD children with short stature born SGA with failure to catch-up were treated with 2 doses of Norditropin® (0.033 or 0.067 mg/kg/day) for 2 years or were untreated for 1 year. The most frequently reported adverse events were common childhood diseases almost identical to those reported above for Study 1. Adverse events possibly/probably related to Norditropin® were otitis media, arthralgia and impaired glucose tolerance. No apparent differences between the treatment groups were observed. However, arthralgia and transiently impaired glucose tolerance were only reported in the 0.067 mg/kg/day treatment group. Therefore, it can also be concluded that no novel adverse events potentially related to treatment with rhGH were reported in short-term Study 2. As with all protein drugs, some patients may develop antibodies to the protein. Eighteen of the 76 children (~24%) treated with Norditropin® developed anti-rhGH antibodies. However, these antibodies did not appear to be neutralizing in that the change from baseline in height SDS at Year 2 was similar in antibody positive and antibody negative children by treatment group. In both Study 1 and Study 2, there were no clear cut cases of new onset diabetes mellitus, no children treated for hyperglycemia, and no adverse event withdrawals due to abnormalities in glucose tolerance. In Study 2, after treatment with either dose of Norditropin® for 2 years, there were no children with consecutive fasting blood glucose levels between 100 and 126 mg/dL, or with fasting blood glucose levels > 126 mg/dL. Furthermore, mean hemoglobin A_{1c} levels tended to decrease during long-term treatment in Study 1, and remained normal in Study 2. However, in Study 1, 4 children treated with 0.067 mg/kg/day of Norditropin® and 2 children treated with 0.033 mg/kg/day of Norditropin® shifted from normal fasting blood glucose levels at baseline to increased levels after 1 year of treatment (100 to 126 mg/dL or > 126 mg/dL). In addition, small increases in mean fasting blood glucose and insulin levels (within the normal reference range) after 1 and 2 years of Norditropin® treatment appeared to be dose-dependent [see *Warnings and Precautions* and *Adverse Reactions*]. In both Study 1 and Study 2, there was no acceleration of bone maturation. A dose-dependent increase in mean serum IGF-1 SDS levels within the reference

range (but including a substantial number of children with serum IGF-1 SDS > +2) was observed after both long-term (Study 1) and short-term (Study 2) Norditropin® treatment. **Clinical Trials in Adult GHD Patients:** Adverse events with an incidence of ≥5% occurring in patients with AO GHD during the 6 month placebo-controlled portion of the largest of the six adult GHD Norditropin® trials are presented in Table 1. Peripheral edema, other types of edema, arthralgia, myalgia, and paraesthesia were common in the Norditropin-treated patients, and reported much more frequently than in the placebo group. These types of adverse events are thought to be related to the fluid accumulating effects of somatropin. In general, these adverse events were mild and transient in nature. During the placebo-controlled portion of this study, approximately 5% of patients without preexisting diabetes mellitus treated with Norditropin® were diagnosed with overt type 2 diabetes mellitus compared with none in the placebo group [see *Warnings and Precautions* and *Adverse Reactions*]. Anti-GH antibodies were not detected. Of note, the doses of Norditropin® employed during this study (completed in the mid 1990s) were substantially larger than those currently recommended by the Growth Hormone Research Society, and, more than likely, resulted in a greater than expected incidence of fluid retention- and glucose intolerance-related adverse events. A similar incidence and pattern of adverse events were observed during the other three placebo-controlled AO GHD trials and during the two placebo-controlled CO GHD trials.

Table 1 – Adverse Reactions with ≥5% Overall Incidence in Adult Onset Growth Hormone Deficient Patients Treated with Norditropin® During a Six Month Placebo-Controlled Clinical Trial

Adverse Reactions	Norditropin® (N=53)		Placebo (N=52)	
	n	%	n	%
Peripheral Edema	22	42	4	8
Edema	13	25	0	0
Arthralgia	10	19	8	15
Leg Edema	8	15	2	4
Myalgia	8	15	4	8
Infection (non-viral)	7	13	4	8
Paraesthesia	6	11	3	6
Skeletal Pain	6	11	1	2
Headache	5	9	3	6
Bronchitis	5	9	0	0
Flu-like symptoms	4	8	2	4
Hypertension	4	8	1	2
Gastroenteritis	4	8	4	8
Other Non-Classifiable Disorders (excludes accidental injury)	4	8	3	6
Increased sweating	4	8	1	2
Glucose tolerance abnormal	3	6	1	2
Laryngitis	3	6	3	6

The adverse event pattern observed during the open label phase of the study was similar to the one presented above. **Post-Marketing Experience** Because these adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The adverse events reported during post-marketing surveillance do not differ from those listed/discussed above in children and adults. Leukemia has been reported in a small number of GH deficient children treated with somatropin, somatrem (methionylated rhGH) and GH of pituitary origin. It is uncertain whether these cases of leukemia are related to GH therapy, the pathology of GHD itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not been able to conclude that GH therapy *per se* was responsible for these cases of leukemia. The risk for children with GHD, if any, remains to be established [see *Contraindications and Warnings and Precautions*]. Pancreatitis: cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops abdominal pain [see *Warnings and Precautions*]. The following additional adverse reactions have been observed during the appropriate use of somatropin: headaches (children and adults), gynecomastia (children), and pancreatitis (children).

OVERDOSAGE: Short-Term: Short-term overdose could lead initially to hypoglycemia and subsequently to hyperglycemia. Furthermore, overdose with somatropin is likely to cause fluid retention. **Long-Term:** Long-term overdose could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess growth hormone.

More detailed information is available upon request.

For information contact: Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540, USA, 1-888-NOVO-444 (1-888-668-6444)

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Novel Long-Acting Insulin Effective

BY MIRIAM E. TUCKER

FROM THE LANCET

Using the ultra-long-acting basal insulin degludec three times a week produced glycemic control comparable with that of daily insulin glargine in patients with inadequately controlled type 2 diabetes, in a phase II study.

“A three times a week, weekend-off, dosing regimen might appeal to some people with type 2 diabetes who are inadequately controlled on oral antidiabetic drug treatments, potentially helping with acceptance and early initiation of insulin therapy,” explained Dr. Bernard Zinman of the University of Toronto and his associates (Lancet 2011[doi:10.1016/S0140-6736(10)62305-7]).

Novo Nordisk’s insulin degludec is formulated in such a way that dosing could be reduced to just three times a week in previously insulin-naïve patients with type 2 diabetes – thereby reducing the risk for hypoglycemia and potentially improving adherence to insulin treatment, the authors wrote.

The trial results were first reported at the annual scientific sessions of the American Diabetes Association (CLINICAL ENDOCRINOLOGY NEWS, August 2010, p. 19)

The 16-week, randomized, parallel-group trial of 245 patients was done at 28 clinics in four countries. All patients had type 2 diabetes, were insulin naïve, and had been treated with one or two oral antidiabetic agents for more than 2 months.

The subjects were randomized to one of four groups: insulin degludec either three times a week (900 nmol/mL formulation, once daily (600 nmol/mL), or once daily (900 nmol/mL); or insulin glargine once daily (600 nmol/mL formulation). All four drug regimens were given in combination with metformin.

Mean hemoglobin A_{1c} and fasting plasma glucose concentrations were similar between the treatment groups. Reductions in HbA_{1c} from baseline were between 1.3% and 1.5% (to 7.2%–7.5%) and did not differ significantly between the groups. Fasting plasma glucose concentrations dropped 3.4–4.2 mmol/L from baseline and also did not differ between treatment groups.

The rates of hypoglycemia were low in all of the treatment groups, with 77%–92% reporting no episodes. However, the proportion of patients who had hypoglycemia in the once-daily 600-nmol/mL insulin degludec group was lower than was the proportion in the insulin glargine group and the insulin degludec three times a week group, with odds ratios of 0.26 and 0.31, respectively.

Adverse events were mild or moderate in severity, with no apparent treatment-specific pattern. Dr. Zinman has been a consultant to, an adviser for, and received grant support from Novo Nordisk, GlaxoSmithKline, Merck, Eli Lilly, Amylin, and Boehringer Ingelheim. ■



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somatropin (rDNA origin) injection