Management of children with idiopathic short stature
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Abstract
The Food and Drug Administration (FDA) approved the use of biosynthetic GH for the treatment of children with idiopathic short stature (ISS) in the US in 2003. Primarily, the decision was based on two studies: a randomized placebo-controlled study and a dose–response study, both demonstrating an increase in adult height over the predicted height at baseline and over placebo-treated controls by an average of 4–7 cm. Despite these data and FDA approval of GH treatment for ISS, there is still a significant controversy among paediatric endocrinologists about how, and to what extent, GH should be used in this indication. GH is clearly efficacious in several growth disorders and has the potential to alleviate debilitating short stature. However, it has been questioned whether ISS should be considered a condition warranting pharmacological treatment, whether the degree of morbidity of untreated ISS is clinically significant, and whether improved psychosocial status or well-being is achieved through GH treatment and height gain. The benefits must outweigh treatment costs and risks to justify GH treatment in ISS. The safety of GH treatment in ISS has been the main subject in two recent articles from pharmaceutical companies that conducted the pioneering studies mentioned earlier. No new safety concerns were observed in the ISS populations, but there were some limitations in study designs that prevent clinicians, their patients and families from ‘resting assured’. Studies addressing these controversial issues are needed before the widespread use of GH treatment in ISS is warranted.

European Journal of Endocrinology
155 S35–S38

Introduction
The specific aetiology for short stature in children is sometimes difficult to identify. If a healthy but small child has normal growth hormone (GH) responses to provocation tests, the condition may be termed idiopathic short stature (ISS) or non-GH-deficient short stature (1, 2). In a survey by the Lawson Wilkins Pediatric Endocrine Society, 94% of paediatric endocrinologists recommended GH therapy for some children with ISS, despite normal GH secretion (3). By now, thousands of children with ISS have received GH therapy (4, 5).

Efficacy of GH treatment in ISS
Several randomized trials have demonstrated that GH administration accelerates growth in the short term (6–8). Furthermore, most, but not all, non-randomized long-term studies suggest that GH increases adult height of children with idiopathic short stature (9–18). Thus, in the past, many children with idiopathic short stature received GH treatment despite a lack of definitive evidence for its efficacy. A meta-analysis (19), which included one small randomized trial (20) and three studies with non-randomized, untreated controls, reported a 5–6 cm difference in adult height between treatment (mean GH dose, 0.31 mg/kg per week) and control groups.

Two recent studies, a randomized placebo-controlled study (21) and a dose–response study (22) have provided firm, if not conclusive, evidence for the efficacy of GH treatment in ISS. In the randomized placebo-controlled study (21), adult height measurements were available for 33 of 68 subjects who received either GH with a dose of 0.22 mg/kg per week (mean) or placebo. The efficacy analysis demonstrated that the GH group achieved a significantly greater adult height than the placebo group (−1.81 vs −2.32 SDS respectively) by 0.51 SDS (3.7 cm; P=0.02; 95% confidence interval (CI)=0.10–0.92 SDS). Many subjects lacked adult height measurements, but two modified intent-to-treat analyses showed that height SDS gave a GH treatment effect similar to the primary efficacy analysis (0.52 SDS; 3.8 cm).

This paper was presented at the 4th Ferring Pharmaceuticals International Paediatric Endocrinology Symposium, Paris (2006). Ferring Pharmaceuticals has supported the publication of these proceedings.

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DOI: 10.1530/eje.1.02244
Online version via www.eje-online.org
At adult height measurement, or at last observation for analyses that included patients without adult height measurements, there were no statistically significant differences between treatment groups in treatment duration, chronological age or bone age. Mean height velocity was significantly greater in the GH group compared with the placebo group during the first 2 years of therapy, and consequently, height SDS increased in GH-treated patients compared with controls, whereas bone age progression was similar.

In the dose–response study (22), subjects were treated with GH at 0.24 mg/kg per week, 0.24 mg/kg per week for the first year and 0.37 mg/kg per week thereafter (0.24/0.37), or 0.37 mg/kg per week. Final height measurements were available for 50 patients at study completion (mean treatment duration, 6.5 years). For these 50 subjects, mean height SDS increased by 1.55, 1.52 and 1.85 for the dose groups of 0.24, 0.24/0.37 and 0.37 mg/kg per week respectively. For the primary comparison between 0.37 mg/kg per week and 0.24 mg/kg per week dose groups, the mean treatment difference (adjusted for differences in baseline-predicted height SDS) was 0.37 SDS (3.6 cm; \( P = 0.025 \)). Mean overall height gains (final height minus baseline-predicted height) were 7.2 and 5.4 cm for 0.37 and 0.24 mg/kg per week dose groups respectively.

Derived from the placebo-controlled and the dose–response study, Fig. 1 provides an approach to estimate the overall efficacy of a 0.37 mg/kg per week dose in ISS. The incremental effect of 0.37 compared to 0.24 mg/kg per week, estimated from the dose–response study was 3.6 cm (22). The overall effect of the 0.24 mg/kg per week dosage can be estimated roughly to be 3.7 cm from the results of the slightly lower dosage of the placebo-controlled study (21). These data together suggest that the overall treatment effect of 0.37 mg/kg per week is approximately 3.6 ± 3.7 = 7.3 cm.

The Food and Drug Administration (FDA) approved the use of biosynthetic GH for the treatment of children with idiopathic short stature (ISS) in the US in 2003, based primarily on these two studies (21, 22) demonstrating an increase in adult height over the predicted height at baseline and over placebo-treated controls by an average of 4–7 cm.

**Safety of GH treatment in ISS**

Most of the published data on the safety of GH treatment in ISS derive from large post-marketing research programmes. These observational studies have reported safety data for approximately 9000 patients with ISS, representing approximately 27,000 patient-years of GH exposure. Overall, adverse event (AE) rates for these patients with ISS have been similar to, or in some cases, lower than AE rates for patients with other GH-treated conditions (23, 24). For example, patients with ISS comprised 17.1% of the total National Cooperative Growth Study population, but accounted for only 4.6% of all serious AEs and 3.4% of deaths, the fewest of any of the patient populations (23). Similarly, patients with ISS had the lowest overall AE rate of all patient groups examined in the Kabi International Growth Study (5).

One report provides safety data from the two randomized registration studies in patients with ISS that formed the basis of the FDA approval for GH treatment of this form of short stature (25). In this report, a perspective of GH safety is provided in ISS relative to other patient groups for whom GH treatment is well established. The ISS AE data were compared with the AE data derived from registration studies of GH deficiency (GHD) and Turner syndrome (TS). In the ISS studies (21, 22), serious AEs (mainly hospitalizations for accidental injury or acute illness unrelated to GH exposure) were reported for 13–14% of GH-treated patients. Overall, AE rates (serious and non-serious) as well as rates of potentially GH-related...
AEs were combined in the GHD, TS and ISS studies (for ISS studies combined: otitis media 8%; scoliosis 3%; hypothyroidism, 0.7%; changes in carbohydrate metabolism 0.7% and hypertension 0.4%). Measures of carbohydrate metabolism were not affected by GH treatment in patients with ISS. There was no significant GH effect on fasting blood glucose in either study (GH dose range, 0.22–0.37 mg/kg per week) or insulin sensitivity (placebo-controlled study only).

Overall, the data on the dearth of severe adverse events found in all safety studies are important and reassuring. However, there are some limitations in the approaches used in these studies (24). The approach of assessing GH safety in ISS by comparing this population (which, by definition, does not have co-morbid conditions) with children, who have disorders with intrinsic heightened health risks (Turner syndrome; classical GH deficiency) is potentially problematic. The drug exposure was approximately 4 years on average in one study (21) and, in the other, a maximum of 7 years exposure was reported in cohorts assessed for efficacy (the average drug exposure in the full cohort was not specified) (22). Some patients included in the safety analyses had only one GH injection and others ceased study participation before receiving any GH. Limited drug exposure potentially underestimates risk assessment. Furthermore, in a situation of relatively short drug exposure for many subjects, expression of data in terms of patient-years of exposure can be confusing and misinterpreted. In both studies (21, 22), there was considerable subject attrition, potentially further limiting the ability to assess the frequency of adverse events. Both studies included many patients, who received GH in lower doses than those approved by the FDA, now raising questions about data applicability to future safety. Thus, it is unclear whether either study has the statistical power to detect increased risks. The power to detect small increases in risk with drug use depends on the size of the cohort, “with large cohorts needed to reliably demonstrate increased risks of even two- to three-fold” (25). With these reservations, GH appears safe in ISS, but the studies have not been powered to assess the frequency of rare GH-related events and long-term follow-up studies of GH-treated patients with ISS are warranted.

Conclusions

Safety of any treatment is not an absolute concept, but should be considered in relation to the morbidity of the untreated state, the benefit to be gained from treatment and alternative management approaches (25). We often accept unknown risks for the treatment of serious and/or life threatening diseases. However, ISS may not be considered a life-threatening condition. Furthermore, evidence of morbidity caused by ISS is scant. Therefore, interpretation of available safety data for GH must be done in relation to treatment effectiveness in meeting the therapeutic goals. If the goal is any gain in height for children with ISS, GH can generally be considered effective. Although there are exceptions; data suggest that several years of GH treatment for children with ISS can increase their adult height by, on average, 4–7 cm. If, however, the goal is improvement in psychosocial status or well-being through height gain, the data are less clear. Recent data suggest that few children with ISS have significant psychosocial morbidity (26). Without demonstration of an evident baseline morbidity, as is the case for ISS to date (27), it is difficult to demonstrate that a treatment improves well-being. The key issue is whether the available data on GH safety in ISS combined with available data on its efficacy, are sufficient to warrant widespread GH use today? There is currently no clear answer to this question.

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Received 20 April 2006
Accepted 4 July 2006