

Editorial: Safety and Efficacy of Growth Hormone Treatment for Idiopathic Short Stature

The issue of GH use for children with idiopathic short stature (ISS) is a major topic for pediatric endocrinologists and the child health community in general. In 2003, the Food and Drug Administration (FDA) approved biosynthetic GH for the treatment of children with ISS (short stature of unknown etiology, sometimes known as “short, otherwise normal”) whose heights are more than 2.25 sds below the mean and who are considered unlikely to reach a normal adult height (1, 2). This decision was based primarily on a randomized controlled trial (3) and a dose-response study (4) and also reflected other studies [including a meta-analysis (5) and a cohort trial (6)], which demonstrated an increase not only in short-term growth velocity but also in adult height over that predicted at baseline (4–6) or over placebo-treated controls (3).

Beyond FDA approval of GH for ISS in principle, there continues to be controversy about how and to what extent GH should be used for such children in practice. On the one hand, GH has the potential to alleviate debilitating short stature, and it is considered inappropriate to deny efficacious treatment to children with debilitating growth impairment—particularly given the inherent limitations in existing diagnostic tests and the recognition that children with similar degrees of short stature due to recognizable diseases (*e.g.* Turner syndrome, GH deficiency) could receive GH fairly readily. On the other hand, concern, expressed in articles and editorials, focuses on whether ISS should be considered a disease or condition warranting treatment (7); whether the degree of morbidity associated with untreated ISS is generally significant (8); whether the impact of GH on the child’s overall well-being is substantial (9); whether the large number of potential ISS recipients of GH (~1 of every 100 U.S. children) will increase heightism, require inordinate costs, and encourage expansion of drug use to more marginal populations (7, 10, 11); and whether treatment benefits outweigh treatment costs and risks.

To address the latter question, assessment is needed of the safety as well as the efficacy of GH treatment in ISS. In studies of GH treatment in non-ISS populations, several risks have been reported including pseudotumor cerebri, fluid retention, insulin resistance, increase in nevi, gynecomastia, and pancreatitis (12, 13). Some suggest that GH treatment of children with previous malignancies can increase the risk of secondary neoplasms (14). Each adverse effect has been considered relatively uncommon (12, 13). The premarketing studies of GH efficacy in ISS did not identify many adverse effects; however, interpretation of risk was difficult because

of relatively small numbers of subjects and absence of long-term follow-up.

The safety of GH treatment in ISS is the main subject of two articles in this month’s issue of the JCEM (15, 16). The articles are from two pharmaceutical companies that conducted pioneering studies of this condition. Both now reassess existing databases to address safety. They use different approaches: comparison of premarketing clinical trials in ISS with those for other disorders (Turner syndrome and GH deficiency) (15) and assessment of a postmarketing surveillance database (16). One also reexamines the question of GH effectiveness in promoting growth in ISS (16).

Regarding efficacy, analysis of the large postmarketing database (16) confirms findings of several previous clinical trials that GH can, on average, increase growth velocity and height sd scores of children with ISS. Such an observational study has clear inherent limitations, including entry criteria open to inconsistency due to variation in interpretation by individual physicians, potential heterogeneity of subject population, nonfeasibility of rigorous quality control of data, potential for nonrepresentative samples due to self-selection of participating physicians, estimation of some outcome parameters by interpolation between timed measures, and large drop-out rates for unspecified reasons. Yet, analyses of specific subsets from that database are remarkably consistent with previous studies and support the potential for GH to increase growth in children with ISS. Data on the effectiveness of GH for the remaining children in this ISS database were not provided. In this particular analysis, it is important to note (as the authors do) that comparisons of height sd scores after GH therapy with height sd scores at baseline tend to overinflate the degree of height gain that can be attributed to GH, as even untreated children with ISS show spontaneous increase in height sd scores with age. Unfortunately, the study was unable to assess predicted adult height in relation to achieved heights to address this issue, as bone age determinations were not required and final height measurements were not routinely obtained.

An important related question in studies of GH efficacy in ISS is the degree to which the study population includes children with constitutional delay in growth and development, as these children might be expected to show particularly robust spontaneous growth without any treatment. The investigators (16) addressed this question by comparing growth for children with bone ages more than 2.5 yr delayed with those whose bone ages were within 2.5 yr of chronological age, and they found no difference between the groups. Although the findings are consistent with the interpretation that constitutional delay is not a likely contributor to the apparent growth-promoting effect of GH, we do not know whether the results would be influenced by either alternative definitions of delayed bone age (*e.g.* delay by 1 or

Abbreviation: ISS, Idiopathic short stature.

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2 SD scores) or required performance and centralized readings of bone age (bone age readings were optional and read locally in the study). Indeed, the results differ strikingly from those of the randomized controlled trial (3) in which baseline bone age was the single strongest correlate of height gain during GH treatment of ISS.

Regarding safety, premarketing trials are often limited in their statistical power to reliably detect important adverse drug reactions and are further limited by inadequate follow-up necessary to detect adverse events widely separated in time from drug exposure (17). Therefore, as discussed by Brewer and Colditz (17), “FDA approval of a new drug does not exclude the possibility of rare but serious adverse drug reactions or common, delayed adverse drug reactions.” Instead, continuous assessment of safety is necessary throughout the life cycle of a new drug (18).

The two papers in this month’s issue of the journal use different approaches to examine the safety of GH treatment for children with ISS. Neither study finds evidence of major adverse events that can be clearly tied to GH therapy. Some sentinel events reported in the articles are addressed and appear unrelated to GH therapy, but continuous monitoring to more fully assess their risks is clearly needed. Overall, the dearth of severe adverse events found in these studies is important and reassuring. However, there are limitations to both approaches used in these studies that prevent practitioners and families from “resting assured.”

First, the drug exposure was approximately 4 yr on average in one study (15) and, in the other, a maximum of 7 yr exposure was reported in cohorts assessed for efficacy (the average drug exposure in the full cohort was not specified) (16). 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 by many subjects, expression of data in terms of patient-years of exposure can be confusing and misinterpreted. Second, in both studies, there was considerable subject attrition, potentially further limiting the ability to assess the frequency of adverse events. Third, both studies include many patients who received GH in lower doses than those now approved by the FDA, raising questions about data applicability to future safety. Fourth, 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 2- to 3-fold” (17). It has been suggested that investigators and practitioners consider the maximum risk with which data are compatible (19) by examination of the confidence limits surrounding indices of risk. For example, if the study’s data suggest that the risk of new malignancies associated with GH treatment of ISS is 0.45–3.24 (expressed, for example, as standardized incidence ratio) (16), the risk of such malignancies can be as low as 0.45 times but also as high as 3.24 times the background rate for the general population. Furthermore, the relative importance of risk depends on the nature of the adverse event under study; for example, a 3-fold increased risk of a relatively easy-to-treat adverse event (*e.g.* otitis media) may be acceptable, whereas a lower 2-fold in-

creased risk of a life-threatening adverse event (*e.g.* malignancy) may be unacceptable. If all U.S. children meeting FDA criteria for GH therapy (shortest 1.2% of children) were treated with GH, this would involve the treatment of approximately 400,000 children per year; even a small increase in serious adverse events in such a population would have major ramifications.

In addition to these overall issues, the approach of each study has inherent strengths and weaknesses. One involves rigorous clinical trials with systematic collection of data (15). However, the approach of assessing GH safety in ISS by comparing data for this population (which, by definition, does not have comorbid conditions) with data for children who have disorders involving intrinsic heightened health risks (Turner syndrome; classical GH deficiency including some with preexisting tumors) is potentially problematic.

The other study draws on a large postmarketing surveillance database (16). Postmarketing studies are important tools for cohort surveillance. Yet, underreporting of adverse events is a common problem. Previous studies for other drugs have shown that the more likely a physician is to prescribe a drug, the less likely s/he is to report an adverse event (17, 20). Because participating physicians in this study were instructed to report adverse reactions when there was a suspicion that treatment with GH may have been related to the event, prejudgment regarding causality could further limit reporting. Moreover, “postmarketing cohort studies to detect unknown ADRs [adverse drug reactions] has been considered disappointing” (17).

Finally, given the potentially long life span of children, the pediatric community (and parents) are particularly concerned about adverse drug effects widely separated in time from the original use of GH. Examples of surprising late sequelae for other drugs are well known (*e.g.* diethylstilbestrol, the appetite suppressants phenteramine and fenfluramine, cadaveric GH). Neither study in this month’s issue of the journal has long-term data (despite the number of patient-years’ exposure), and therefore neither can assess this issue.

How do the studies inform practice and policy? Drug safety is not an absolute concept, but instead must be considered in relation to the morbidity of the untreated state, alternative management approaches, and the benefit to be gained from treatment (17). We often accept unknown risks for the treatment of serious and/or life threatening diseases. However, ISS is not a life-threatening condition, and evidence of morbidity is scant. Therefore, interpretation of available safety data for GH must be done in relation to treatment effectiveness in meeting 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 (1.57–2.76 inches) (3–6). If, however, the goal is improvement in psychosocial status or in well-being through height gain, the data are less clear; recent data suggest that few children with ISS have significant psychosocial morbidity (8). Without clear baseline morbidity, it is difficult to demonstrate that a treatment improves well-being, and none has been demonstrated to date (9). In interpreting effectiveness, both safety

and cost must be considered. The cost of GH treatment for ISS is very high, at approximately \$5,000–40,000 per year or approximately \$35,000 per inch of height gained (5, 7).

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. It is tempting to consider available data suggesting few major risks of GH treatment in ISS, together with evidence that GH can increase height in ISS, as reason to significantly expand overall GH use in this condition. However, the uncertainties about whether treatment benefits well-being and whether the degree of height gain is appropriate for the duration and costs of treatment—combined with the limitations of available data on safety—may well dampen enthusiasm.

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