rhGH treatment for short stature: panacea or Pandora's box?

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Idiopathic short stature (ISS) describes patients with poor growth velocity and severe short stature in the absence of demonstrable hormone deficiencies or systemic illness. Since the Food and Drug Administration (FDA) has approved recombinant human growth hormone (rhGH) treatment of very short children with ISS (current and projected height <-2.25 standard deviation score), pediatricians are likely to be confronted with families seeking rhGH for their child.

Is rhGH safe enough for these otherwise healthy children?

Following the startling discovery of pituitary-derived GH treatment transmission of Creutzfeldt-Jakob infection, industry-sponsored post-marketing safety surveillance of rhGH therapy was initiated. Twenty-five years of data from these studies show:

- certain adverse effects (AEs) associated with rapid growth (scoliosis progression, slipped epiphyses) and others of unknown mechanism (intracranial hypertension, pancreatitis) occur rarely;
- overt hyperglycemia is rare, but insulin sensitivity is reduced and a possible increase in risk for type 2 diabetes mellitus may be obscured by its rising general pediatric population incidence;
- when a child already at higher risk for sudden death dies during rhGH therapy, a possible contributing role of rhGH (e.g., reduced cortisol availability in hypopituitary children or airway compromise in children with Prader-Willi syndrome [PWS]) cannot be excluded; and
- rhGH does not increase risk for new malignancies in children without risk factors, but may slightly increase or hasten the onset of second malignancies in patients previously treated for cancer (*J Clin Endocrinol Metab*. 2010;95:167-177).

While this general safety record of rhGH treatment is reassuring, there are potential pitfalls in applying post-marketing surveillance study results to ISS patients:

- reporting of AEs depends on physician investigator compliance;
- descriptions of the AE as “related” or “unrelated” to rhGH therapy is subjective;
- rhGH dosages studied generally are lower than those currently used for ISS, and
- reporting of AEs covers only the period on rhGH treatment.

Further, with regard to safety, rhGH treatment of ISS deserves special scrutiny because 1) children with ISS are essentially healthy, 2) salutary outcomes usually require supra-physiologic dosages administered over several years, 3) actual height increases are moderate (~1 centimeter increase per year of rhGH treatment on average), with a substantial proportion of children responding to years of costly and invasive treatment with minimal increases in adult height, and 4) it remains unproven whether rhGH-mediated height increases translate into meaningful improvements in the child’s ultimate well-being.

From an ethics standpoint, therefore, it is problematic to present rhGH treatment for short stature: panacea or Pandora’s box?

Pediatricians confronted by families seeking recombinant human growth hormone (rhGH) for their healthy, but short child could convey that while the general safety profile is reassuring, the treatment deserves special scrutiny given its potential risks and costs. In addition, height increases typically are moderate and may not translate into meaningful improvements in a child’s well-being.
From a safety standpoint, even a small risk for a short- or long-term adverse effect may not be outweighed by an unpredictable and poorly defined benefit.

An honest and informed risk/cost/benefit assessment for rhGH treatment of ISS in obtaining “informed assent” for rhGH treatment. From a safety standpoint, even a small risk for a short- or long-term adverse effect may not be outweighed by an unpredictable and poorly defined benefit.

A recent consensus conference summarized the safety of rhGH treatment of ISS (inserts added): “The possible side effects in GH-treated children with ISS (at currently recommended doses of <0.37 mg/kg/week) are (qualitatively) similar to those previously reported in children receiving GH therapy for other indications, (and) the frequency of adverse events is generally less. No long-term adverse effects have been documented. Post-treatment surveillance with focus on cancer prevalence and metabolic side effects is recommended” (J Clin Endocrinol Metab. 2008;93:4210-4217).

The likelihood of further dose escalation to achieve greater height-promoting effects and the possibility that heightened GH, IGF-I and insulin exposure could have delayed and subtle adverse effects call for ongoing caution about rhGH treatment for ISS. To confirm the negligible risk considered tolerable in this situation, the global pediatric endocrine community must accept the responsibility to pick up where the post-marketing studies leave off, by conducting collaborative fol-

removed by the abundance of rhGH, the notion was put forth that, for height promotion, degree of disability and responsiveness to rhGH treatment, rather than the underlying etiology of short stature, should be the key to determining entitlement (J Pediatr. 1990;117:16-21). While subsequent FDA approval of rhGH treatment for several non-growth hormone deficiency (GHD) conditions validated that position, new questions have emerged about its justification when compared to costs and (known and unknown) risks.

Given the modest effects of rhGH on improving adult height in most patients without GHD, and still unproven beneficial effects on quality of life, the question posed then — will rhGH treatment for short stature be a panacea or Pandora’s box? — has been partially answered.

Growth hormone has its place but is not a panacea. Caution is still warranted when counseling and referring families with short children interested in such treatment.

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