Long-acting Growth Hormone Formulations: Structure and Activity

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Human growth hormone (hGH) has been available as a therapeutic agent since the middle of the 1950's (1). It is a 191 amino acid single chain peptide and was obtained from human pituitaries because animal growth hormones are inactive in primates (species specificity). For children, the main activity is to stimulate height velocity. In addition in children and those at adult height, hGH has extensive metabolic activities in part by the generation of insulin-like growth factor 1 on protein, carbohydrate, and adipose tissue.

Since the mid-1980's, virtually all hGH preparations have been biosynthetic, yielding a much greater supply and avoiding the prospect of Creutzfeldt-Jakob disease (2). Daily administration is quite non-physiologic, for it does not mimic the pulsatile nature of the secretion of hGH. It has a half-life of approximately 3.4 hours after subcutaneous injection. Daily administration of recombinant (r)hGH remains inconvenient for it may be painful and distressing to some patients. This may lead to non-compliance with reduced efficacy and thus increased health costs.

Long-acting endocrine drug formulations have long been part of the armamentarium of endocrinologists, for example, gonadotropin-releasing hormone agonist analogs, testosterone, medroxyprogesterone acetate, hCG (as long-acting luteinizing hormone), and multiple analogs of insulin. Pharmaceutical companies have used various strategies to lengthen the plasma half-life (and activity) of the native rhGH or an analog of it (3).

- Depot formulations with rhGH encapsulated in a biodegradable polymer or micro-particles of rhGH dispersed in a biodegradable polymer,

- PEGylation (PEG) specific site long chain polymers of PEG added to the native molecule,

- Pro-drug rhGH transiently bound to a PEG carrier with self-cleaving linker; a point mutation in rhGH to which a long chain with a terminal fatty acid is added. The latter interacts non-covalently with albumin,

- Fusion proteins: examples include hydrophilic amino acid tails (XTEN), the C-terminal peptide of hCG (CTP), albumin itself and several with immunoglobulin fragments.

Pharmaceutical agents in all classes are in at least phase 1 trials with many in phases 2 and 3 for children and adults.

Preliminary data indicate height velocities comparable to those noted with equivalent doses of rhGH obtained from the two very large registry data bases-National Cooperative Growth Study and Kabi International Growth Study. Each preparation appears safe and efficacious with a hint of less decline in height velocity in the second and perhaps third years as previously noted in virtually all studies with rhGH over 3 decades.

Virtually all agents require pivotal phase 3 studies before acceptance by the regulatory authorities. Given that the profiles (pharmacokinetic and pharmacodynamic) are even less "physiologic" than for daily therapy with rhGH and have addition biological material, long-term safety studies are mandatory.

References

1. Raben MS. Growth hormone. 2. Clinical use of human growth hormone. N Engl J Med 1962;266:82-86.
2. Hintz RL. The prismatic case of Creutzfeldt-Jakob disease associated with pituitary growth hormone treatment. J Clin Endocrinol Metab 1995;80:2298-2301.
3. Christiansen JS, Backeljauw PF, Bidlingmaier M, Biller BM, Boguszewski MC, Casanueva FF, Chanson P, Chatelain P, Choong CS, Clemmons DR, Cohen LE, Cohen P, Frystyk J, Grimberg A, Hasegawa Y, Haymond MW, Ho K, Hoffman AR, Holly JM, Horikawa R, Höybye C, Jorgensen JO, Johannsson G, Juul A, Katznelson L, Kopchick JJ, Lee KO, Lee KW, Luo X, Melmed S, Miller BS, Misra M, Popovic V, Rosenfeld RG, Ross J, Ross RJ, Saenger P, Strasburger CJ, Thorner MO, Werner H, Yuen K. Growth Hormone Research Society perspective on the development of long-acting growth hormone preparations. Eur J Endocrinol 2016;174:1-8. Epub 2016 Mar 23