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Long-Acting Growth Hormone Preparations in the Treatment of Children

Rayhan A Lal, MD[1,2] and **Andrew R. Hoffman, MD**[2,3]

[1]Division of Endocrinology, Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA

[2]Division of Endocrinology, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA

[3]Medical Service, VA Palo Alto Health Care System, Palo Alto, California, USA

Abstract

Human growth hormone (hGH), which had been in use since 1958, was supplanted by recombinant human growth hormone (rhGH) in 1985 for those with growth hormone deficiency (GHD). Adherence to daily subcutaneous growth hormone is challenging for patients. Thus, several companies have pursued the creation of long acting rhGH. These agents can be divided broadly into depot formulations, PEGylated formulations, prodrug formulations, non-covalent albumin binding GH and GH fusion proteins. Nutropin Depot is the only long acting rhGH ever approved by the U.S. Food and Drug Administration, and it was removed from the market in 2004. Of the approximately seventeen candidate drugs, only a handful remain under active clinical investigation or are commercially available.

Keywords

Long-acting; Growth hormone; Pediatric; Child; Children; Adult; Growth hormone deficiency; Drug formulation; Novel treatment

Background

In 1958, Raben reported the clinical use of human growth hormone that had been purified using glacial acetic acid from pituitary glands harvested at autopsy. By injecting this purified pituitary extract two-three times each week, he was able to achieve increased growth in a teenager with hypopituitarism (1). Subsequently, the National Pituitary Agency was formed to supervise the collection of human pituitary glands, to arrange for the extraction and purification of the human growth hormone (hGH) from these glands, and to distribute this precious, scarce hormone to pediatric endocrinologists for the treatment of children with GH

Corresponding author: Rayhan Lal, MD, Stanford University School of Medicine, Room G-313 Medical Center, 300 Pasteur Drive, Stanford, CA 94305, USA, Tel: 650-498-7351, Fax: 650-725-8375, inforay@stanford.edu.

Disclosure

Dr. Lal has consulted for GlySens Incorporated and Abbott Diabetes Care.

Dr. Hoffman has consulted for Ascendis, GeneScience, Genexine, NovoNordisk, Pfizer and Versartis

deficiency (GHD). While early preparations of this cadavericderived hGH contained GH polymers and other contaminating materials, the methodology for purification improved with increasing complexity over time (2). Pharmaceutical companies also entered this market, and ultimately, more than 30,000 people received pituitary-derived hGH.

In 1985, a 20-year-old man who was followed at the Stanford Endocrine Clinic for hypopituitarism and diabetes and who had received cadaveric hGH since the age of 3, died of CreutzfeldJakob disease. The NIH was quickly notified, and several other cases were soon identified, leading to the withdrawal of pituitary-derived hGH from use in the United States (3). Fortunately, a recombinant human GH (rhGH) with an added methionine was approved by the FDA and marketed by Genentech (South San Francisco, USA) in the same year, and subsequently, several companies introduced native rhGH to the market for use in both children and adults with GHD.

With the availability of unlimited amounts of rhGH, clinicians began to prescribe rhGH as a daily subcutaneous injection. Adherence to a daily injection has not been optimal, and it has been postulated that by facilitating increased adherence, a long-acting GH formulation that could be given weekly, biweekly or even more infrequently might lead to better growth in children (4). Studies in which rhGH was given as a constant subcutaneous infusion for as long as 6 months showed that IGF-I levels could be maintained, suggesting that desensitization of the GH receptor did not occur when it was exposed to constant GH levels (5). A number of pharmaceutical companies began to develop long-acting GH preparations. We will discuss a representative group of these novel GH formulations that have been tested in humans (6).

Depot Formulations

The first entry in the long acting rhGH field was Nutropin Depot, a product made by Genentech (South San Francisco, USA) and Alkermes (Dublin, Ireland), which consisted of rhGH that was encapsulated in microspheres composed of a poly(lactide coglycolide) copolymer that was fully biodegradable. In a study of 74 prepubertal children with GHD, monthly or twice monthly administration of Nutropin Depot led to annualized growth rates of 8.4 cm/year after 6 months of therapy, and this drug was approved by the FDA for use in children with GHD (7). However, it was necessary to deliver large volumes of this viscous medication, and often more than one injection at a time was needed to deliver the proper dose to children. The injections required a large bore needle, and a large lump was apparent for several days after the injection. In a subsequent study of adults with GHD, Nutropin Depot was shown to be effective in decreasing truncal and visceral adipose tissue (8). The drug was never approved for adults, and it was removed from the market in 2004.

Declage or Somatotropin Biopartners (LB03002) is produced by BioPartners (Los Angeles, USA) in conjunction with LG Life Sciences (Seoul, South Korea). It is an rhGH incorporated into sodium hyaluronate which is suspended in an oil base of medium-chain triglycerides (MCT) before injection. Hyaluronidase present in tissue degrades the microspheres, releasing rhGH. The pharmacokinetics and pharmacodynamics were first evaluated by Bidlingmaier and colleagues in 2006 among 6 men and 3 women with adult

GHD on a stable daily rhGH regimen. Participants underwent a 4-week washout followed by weekly LB03002 administration for five weeks. Maximal serum GH concentration doubled, dose-normalized area under curve was not significantly different, mean maximal serum IGF-1 was 34–41% greater and normalizedto-rhGH-dose IGF-1 area under curve was comparable (9). In 2009 a randomized, comparator-controlled, assessor masked phase 2 study was performed on 37 pre-pubertal, rhGHnaïve children. They received rhGH 0.03mg/kg for 7 days, followed by a 3-week washout then one of three different doses of LB03002 weekly for 3 months. Maximal serum GH concentrations increased up to 4-fold, GH area under curve remained stable over 3 months, maximal IGF-1 progressively increased with normal IGF-1 standard deviation scores achieved after 3 months and normal IGFBP-3 scores after 1 week treatment (10). A 2011 placebo-controlled clinical trial of LB03002 for 26 weeks in 152 adults with GHD demonstrated significantly increased IGF-1 levels and reduced mean fat mass (11). These changes were sustained in a 1-year followup study (12). A prospective sub-study to the year-long phase III trial also showed reduction in fat mass with reduced leptin and increased ghrelin, but no change in glucose or lipid metabolism (13). In 2012, Péter and colleagues confirmed the efficacy and safety of LB03002 at doses 0.5–0.7 mg/kg/wk versus daily rhGH in a 3-year trial for GH-naïve prepubertal children with GHD (14). A 1-year pediatric trial in Korea compared weekly LB03002 to daily rhGH and demonstrated comparable mean height velocity, which was also shown in the 2 year phase III multinational trial (15–16). While LB03002 was approved in Europe, it has not been marketed there. It is available for use in children in South Korea.

PEGylated Formulations

The addition of polyethylene glycol (PEG) moieties to a protein has been shown to extend its half-life and even decrease its antigenicity. PEGylated drugs are currently being marketed for the treatment of numerous diseases, including anemia (Amgen PEGylated erythopoeitin) and neutropenia (Amgen PEGylated G-CSF). A PEGylated GH antagonist manufactured by Pfizer (New York City, USA), pegvisomant, is an effective therapy for acromegaly. Ambrx (La Jolla, USA) developed ARX201, a pegylated GH agonist that was effective in increasing serum IGF-I levels in patients with GHD (17). However, preclinical studies in primates showed at autopsy that the PEG was accumulating in the ependymal cells of the choroid plexus. While it is not clear whether this pathologic finding had any clinical significance, Ambrx stopped developing this drug. Both Novo Nordisk (Bagsværd, Denmark) and Pfizer (New York City, USA) also ended their programs of PEGylated GH molecules (NNCI126–0083 and PHA-794428, respectively).

One PEGylated formulation is currently in use for the treatment of GHD in children in China. GeneScience Pharmaceuticals' (Changchun, China) Jintrolong is a PEGylated long-acting rhGH designed to be injected weekly. This drug was first tested in 2015 during a phase 1 trial on 12 children with GHD. Participants received rhGH 0.0286 mg/kg daily for 7 days, followed by 4 week washout and 6 weeks of Jintrolong 0.2mg/kg weekly for 6 weeks. Elimination rate was slower than daily rhGH without significant accumulation and serum IGF-1 was comparable between treatment regimens (18). The phase 2 and 3 trials were conducted in 6 hospitals in China and published in 2017. Participants were treatment-naïve children with GHD; 108 were enrolled in the phase 2 trial and 343 in the phase 3 trial. The

phase 2 study demonstrated the safety and efficacy of Jintrolong at 0.2mg/kg weekly for 25 weeks versus 0.1mg/kg weekly dosing and daily rhGH. The 25 week phase 3 study revealed greater height velocity increase and standard deviation height scores for weekly Jintrolong versus daily rhGH (19).

Pro-Drug Formulations

Ascendis Pharma (Hellerup, Denmark) TransCon sustainedrelease rhGH is an inactive prodrug consisting of rhGH transiently bound via proprietary linker to an inert carrier, methoxypolyethylene glycol (mPEG). The linker undergoes controlled autohydrolysis dependent on pH and temperature. A phase 1 randomized trial among 44 healthy male subjects compared 4 different doses of weekly TransCon rhGH prodrug to 2 different doses of daily rhGH. They found no adverse events, injection site reaction differences and no binding antibody formation. Measures of GH and IGF-1 were comparable at similar doses (20). Follow-up phase 2 trials among 37 adults with GHD and 53 GH-naïve prepubertal children with GHD revealed similar safety and efficacy of TransCon weekly rhGH and daily rhGH (21–22). At the time of this writing, phase 3 testing is underway.

Non-Covalent Albumin Binding GH

Novo Nordisk's (Bagsværd, Denmark) Somapacitan (NNC0195–0092) is rhGH with a single point mutation to which a terminal fatty acid is attached with noncovalent albumin-binding properties. The albumin binding is predicted to increase half-life through reduced clearance (23). This is the same technology that is used in their long-acting insulin detemir. A 2014 randomized, placebo-controlled single center trial of 105 healthy male subjects was performed in Germany. The drug was well tolerated without immunogenicity concerns at the 4 doses tested and demonstrated a dose-dependent increase in measured IGF-1 (24). A phase 1 trial among 34 adult men with GHD also demonstrated tolerability and comparable efficacy to daily rhGH based on serum IGF-1 (25). Similar findings were reported in the phase 1 trial of 32 prepubertal children with GHD (26). A 26 week randomized, controlled phase 3 trial performed in 6 countries was recently published. 92 participants with adult GHD were treated with weekly Somapacitan or daily rhGH administered subcutaneously by pen. Participants felt dosing was more convenient, IGF-1 standard deviation scores were maintained within a therapeutic target, and the medication was well tolerated (27).

GH Fusion Proteins

The Korean biotechnology firm, Genexine (Seongnam, South Korea) in collaboration with Handok (Seoul, South Korea) has produced HyTropin (GX-H9), which is rhGH fused to Genexine's proprietary hybrid Fc (hyFc) platform. The hyFc is created from IgD, which provides the greatest hinge flexibility and low antibody-dependent cellular cytotoxicity, as well as IgG4 which binds to the protective neonatal Fc receptor and exhibits low complement-dependent cytotoxicity (28). Phase 2 trials with 7–14 day administration in adult and children have demonstrated acceptable tolerability without significant immunogenicity and comparable biochemical efficacy. The company is seeking FDA approval to begin phase 3 trials.

Teva Pharmaceutical Industries (Petah Tikva, Israel) studied a long acting GH analog (TV-1106) that fused rhGH to human serum albumin, a molecule that had been developed by Human Genome Sciences as albutropin (29). While this drug initially showed promise as an effective treatment for childhood GHD, the development of potentially blocking or inactivating antibodies led the company to abandon the drug.

MOD-4023 is a chimeric product generated by fusing three copies of the 28 carboxy-terminal residues of human chorionic gonadotropin (hCG) beta subunit to the coding sequence of hGH developed by OPKO Health (Miami, USA) and Pfizer (New York City, USA) (30). The phase 2 study in 54 GH-deficient adults with once weekly dosing demonstrated favorable safety and efficacy with IGF-1 values comparable to daily rhGH dosing (31), but the phase 3 trial did not show noninferiority to daily rhGH, and there are no ongoing studies in adults. Similarly, a multicenter, open-label, randomized, controlled phase 2 study among 53 prepubertal children with GHD receiving weekly MOD-4023 for one year revealed promising safety and tolerability with 6 month annualized height velocity above 12 cm/year (32). Subsequent pharmacokinetic and pharmacodynamic studies in children established that sampling 4 days following dose administration allowed best estimation of mean IGF-1 SDS (33). Studies are continuing for the treatment of GHD in children.

In order to extend the half-life of the GH molecule, Versartis developed Somavaratan or VRS-317, by adding long unstructured hydrophilic strings of amino acids were to the ends of the GH molecule. While this GH analog was able to increase height velocity in children with GHD when given weekly or even less frequently, a phase 3 study showed that it was inferior to daily rhGH in its ability to increase height, and therefore this product was also discontinued (34).

Conclusions/Future Directions

Many long-acting rhGH formulations have been designed and tested in children and adults with GHD, and while no product is currently available for use in the United States, a PEGylated GH is being used in China and a depot formulation is available in South Korea (table 1). Over the past few years, a number of long-acting rhGH molecules have been discontinued, either because they are less effective than daily rhGH or because of potential side effects or complications (35). While there is ample data testifying to the relative safety of daily rhGH therapy in children (36), it will be necessary for the companies that market the long-acting rhGH preparations and for the physicians who prescribe them to perform thorough postmarketing surveillance to determine the safety of these novel molecules (37). It will be vital to learn whether constant exposure to GH action leads to acromegaly in the long run. Moreover, it is possible that the modifications introduced on some of these preparations could cause new side effects that we have not seen with daily rhGH. Finally, it would be of great interest to learn if giving a long-acting rhGH preparation leads to better adherence and better growth.

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Table 1.

Summary of long-acting rhGH preparations

Class	Company	Product	Design	Status
Depot Formulations				
	Genentech / Alkermes	Nutropin Depot	Encapsulated in Polylactide-Coglycolide Microspheres	FDA Approved. Removed from market in 2004.
	BioPartners / LG Life Sciences	Declage LB03002	rhGH incorporated into sodum hyaluronate and suspended in MCT for injection	Available for use by children in South Korea. Approved in Europe but not marketed.
PEGylated Formulations				
	Ambrx	ARX201	30-kDa PEG incorporated into rhGH	Drug development stopped due to PEG accumulation in ependymal cells of choroid plexus.
	Novo Nordisk	NNCI126–0083	43-kDa PEG attached to rhGH	Drug development stopped.
	Pfizer	PHA-794428	Branched 40-kDa PEG attached to amino end of GH	Drug development stopped.
	GeneScience Pharmaceuticals	Jintrolong	40-kDa PEG attached to rhGH	Available for use by children in China.
Pro-drug Formulations				
	Ascendis Pharma	TransCon Growth Hormone	rhGH transiently bound to mPEG	In phase 3 testing.
Non-Covalent Albumin Binding GH				
	Novo Nordisk	Somapacitan NNC0195–0092	rhGH with a single po int mutation attached to a terminal fatty acid	In phase 3 testing.
GH Fusion Proteins				
	Genexine / Handok	HyTropin GX-H9	rhGH fused to IgD and IgG4	Pending phase 3 testing.
	Teva	TV-1106	rhGH fused to albumin	Blocking/inactivating antibodies developed, drug abandoned.
	OPKO Health / Pfizer	MOD-4023	rhGH fused to 3 copies of carboxy-terminal of hCG's beta subunit	Phase 3 studies in adults completed at end of 2016, phase 3 testing in children underway.
	Versartis	Somavaratan VRS-317	rhGH fused to hydrophilic strings of amino acids	Discontinued due to inferiority to daily rhGH in increasing height in children