International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 7(1): January-February 2017

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 16-01-2017; Revised: 30-01-2017; Accepted: 03-02-2017

CURRENT STATUS OF MARKETED AND DEVELOPING LONG ACTING GROWTH HORMONE PREPARATIONS

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Keywords:

Clinical trials, Long acting growth hormone, Plasma half-life, somatotropin, and Phase 1 study

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ABSTRACT

Growth hormone (GH) treatment has been an established therapy for growth hormone deficiency (GHD) in children's as well as in adults. Growth hormone preparations are found to increase the height, bone density and body composition of the body. Human growth hormone (somatotropin) is secreted by anterior pituitary gland and is no longer used because of the very short half-life of 25 min. Instead of short acting growth hormones preparations, long acting growth hormone (LAGH) preparations are used these days. Some of the marketed formulations of LAGH are Norditropin, Humatrope etc. These preparations also have some unmet medical needs like short plasma half-life, daily sub cutaneous and intramuscular injections etc. To overcome these problems many new LAGH preparations are developing. Some of the developing LAGH are VRS-317, ACP-001, etc. Many of them has completed their Phase 1 and Phase 2 studies. For example MOD-4023, a drug developed by OPKO health, has completed its phase 2 trial in children's. Out of these developing drugs, some show very promising features and are potential candidate in the LAGH market, like VRS-317. This molecule has once a month dosing schedule with a very few side effects. It is presently undergoing phase 3 clinical trials in children's.

1. INTRODUCTION:

There are at present, seven sets of release hormones (RH) or release inhibiting hormones (RIH; some referred to as factors) that originate in the hypothalamus and regulate the secretions of anterior pituitary [1]. Some hormones from anterior pituitary act directly on target organs. These include growth hormone (GH) and prolactin (PRL). Others regulate the function of related endocrine glands such as thyroid stimulating hormone (TSH), which controls the secretions from thyroid gland; adrenocorticotrophic hormone (ACTH), which influences the functions of adrenal cortex, and gonadotropins (follicular stimulating hormone-FSH; and luteinising hormone-LH) which controls the functions of gonads. [2]

Secretion of growth hormone is regulated by the action of growth hormone releasing hormone (GHRH) released from hypothalamus. If given intravenously (i.v.), subcutaneously (s.c.), or intranasally, GHRH causes secretion of GH instantly from somatotrophs with peak concentrations being achieved in one hour. However, relative potencies by these three routes are 300:10:1, respectively. [3]

Only human growth hormone (GH) exerts metabolic activity in man, and it was not until its isolation from human cadaveric pituitary glands by Raben and its subsequent purification in the late fifties that clinical use of the hormone became possible.[4]

2. GROWTH HORMONE (GH):

Growth hormone is a peptide hormone produced by the anterior pituitary. The most abundant pituitary form has a molecular weight of 22 kDa. Secretion of GH is high in the newborn till 4 years of age. It remains at intermediate level until after puberty (25 years of age) and then there is a decline with aging. Women have a higher level of baseline GH and more pulses than do men [5]. GH is secreted in pulses, most of which occur during sleep; however, the size and the numbers of pulses are influenced by several factors, including age, gender, acute and chronic illnesses, stress, and nutrition [6]. GH increases protein synthesis and promotes positive nitrogen balance (increase cellular uptake of amino acids). The anabolic and growth promoting effects of GH are indirect and are mediated by activating insulin like growth factors type-1 (IGF-1) [5], predominantly at open epiphyses of long bones-thus causing bone growth. This growth factor also called somatomedins (which include IGF-1 and IGF-2) [6]. The metabolic consequences of a pharmacologic dose of GH is an initial insulin like effect followed by an effect antagonistic to that of insulin i.e., a decrease in glucose uptake into the tissues and an increased release of glucose from liver, i.e., diabetogenic effects [7]. There is also increased mobilization of free fatty acids from adipose tissues (Lipolysis), thus predisposing toward the formation of ketone bodies

especially among diabetics [7]. IGF-1 (which is released from liver in response to GH) also has inhibitory effects on GH release from anterior pituitary and a positive feedback to GH-RIH release from hypothalamus [5].

Intracellular GH signaling is mediated by the GH receptor, a type 1 cytokine receptor, a single transmembrane receptor found on most cells in the body. The extracellular GH binding domain of the receptor is also found in the circulation where it serves as a GH binding protein (GHBP) [5]. The GH molecule has two receptor binding sites that bind a preformed receptor dimer, creating a conformation change in the receptor and triggering intracellular signaling and receptor internalization [8].

3. GROWTH HORMONE DEFICIENCY (GHD):

The incidence in adults with GHD onset has been reported to affect 1 per 100,000 people per year, with an estimated prevalence of 350/million [9], while the incidence in children has been estimated to be about 1 in 4000 [10].

The most common etiology for childhood onset GHD isidiopathic GHD [10], while the most common causes of adult-onset GHD are pituitary adenomas or other hypothalamic masses [11].ShortstatureisacardinalsymptominchildrenwithGHD[10].GHDinadultsischaracterizedbyanumber ofclinicalfeaturesincludingimpairedqualityoflife,reduced physical activity, increased body fat, decreased lean body mass, decreased bone mineral density and an adverse metabolic profile [12].

The diagnosis of GHD is established according to specific criteria for the maximal GH response to various different stimulation tests, genetic tests, multiple pituitary hormone deficiencies with low IGF-I levels [11].

4. TREATMENT OF GHD:

The indication for GH replacement in adults is an established diagnosis of profound GHD according to consensus guidelines[11, 13].The primary objective of GH replacement therapy in children with GHD is to normalize linear growth[10]. There are different, marketed preparations which are used in the treatment of GHD [Table1].

Table.1 Marketed preparations used for GHD

S.No.	Company	Marketed GH formulation
1.	Merck Serono	• Saizen • Serostim

2.	Pfizer	• Genotropin • GenotropinMiniQuick • Genotropin Pen
3.	Novo Nordisk	• Norditropin
4.	F.Hoffmann-La Roche	• Nutropin • Nutropin AQ • Nutropin AQ NuSpin
5.	Eli Lilly	• Humatrope
6.	Sandoz	• Omnitrope

5. CURRENT MARKET SCENARIO OF LONG ACTING GROWTH HORMONES:

The **Global Human Growth Hormone Market** is growing at a rapid pace and is expected to post a **CAGR of4.22 percent from 2015-2019[14].**Novo Nordisk, Eli Lilly and Pfizer are the leading brand leaders in growth hormone market while Merck Serono and Roche are also trying to cover the higher percentage in growth hormone industry. Current market share of different LAGH with theirmanufactures are given in Fig 1.

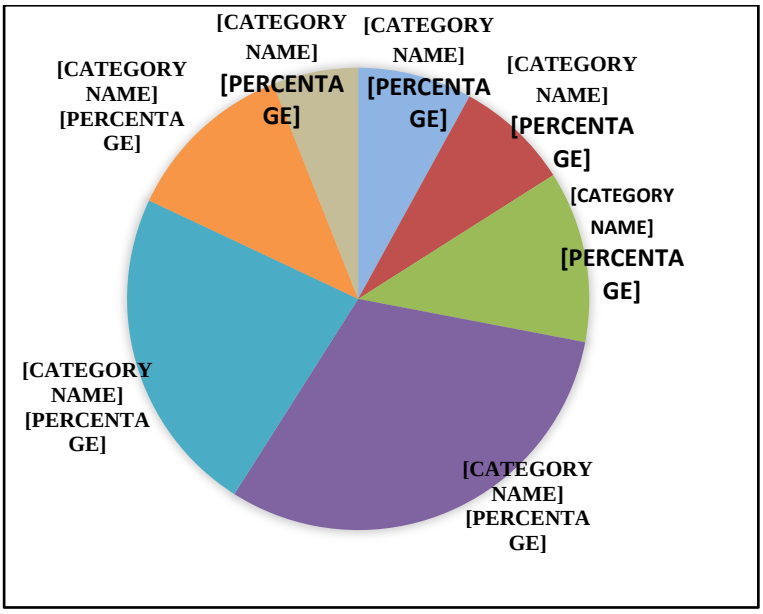

Fig. 1 Current market share of different LAGH with their manufactures

6. UNMET MEDICAL NEEDS WITH CURRENT THERAPIES:

GHhasaplasmahalf-lifeof3.4haftersubcutaneousinjectionand~20minafterintravenousinjection[15].Thepulsatileandvery irregularsecretionofGHseeninnormalpeopleareimpossibleto replicateclinically,evenwhentheGHisadministeredseveraltimeseachday.Inanimalmodels,pulsatilea dministrationofGHresultsin better growth and greater IGF-I generation than doescontinuousGHinfusion[16, 17]. Despiteongoingimprovementsininjectiondevicedesign,dailysub-cutaneous administration of GH remains inconvenient, painfulanddistressingformanypatients [18],leadingtononcompliance,reduced efficacy and increased health care costs. Compliance is a problem inupto75%ofteenagers,andgrowthvelocityisreducedinthechildren withpoorcompliance[18-20].Toaddressthisproblem,avariety of long-actingformulationsofGHhavebeendevelopedwiththehopeofachievingcomparableefficacyandsafety usingfewertotalinjections[21, 22](Table 2).

Table.2 Long acting preparations under developing phase:

S. No	Drug	Company	Phase-2	Phase-3	Phase-4
1	NNC0195-0092	Novo Nordisk	children's	adults	-
2	VRS-317	Versartis	children's	adults	-
3	MOD-4023	OPKO Health	children's	adults	-
4	TV-1106	Teva Pharmaceutical Industries Ltd	adults	adults	-
5	GX-H9	Handok and Genexine	adults	-	-
6	ACP-001	Ascendis Pharma	children's and adults	-	-
7	LB03002	Bio Partners	-	-	in Europe
8	Jintrolong	GenSci	-	-	in China

7. CHARACTERISTICS OF LAGH ASSESTS:

7.1 NNC0195-0092

NNC0195-0092, developed by Novo Nordisk, consists of a single-point mutation in the GH backbone to which a side chain with terminal fatty acid and non-covalent albumin-binding properties has been attached. The construction prolongs the absorption rate after subcutaneous injection and the non-covalent binding to circulating albumin reduces the clearance of the drug. Results from two placebo-controlled, double blind phase 1 studies have shown that NNC0195-0092 was well tolerated [23]. IGF-I levels increased in a dose dependent manner. Antibodies could not be measured and no clinically relevant difference in local tolerability between NNC0195-0092 and placebo occurred [23]. In total, 105 males were enrolled in the trials, which consisted of five cohorts receiving either a single dose (n=40) and five cohorts receiving four doses (n=65) of NNC0195-0092 or placebo [23]. In a phase 2 study short-term multiple dosing of NNC0195-0092 administered subcutaneously to adults with GHD was reported to be well-tolerated and without any serious safety issues [24]. Phase 3 studies are ongoing.

7.2 VRS-317

VRS-317, designed by Versartis for once monthly injections, is a fusion proteinwith amolecularmass of 119 kDa produced in Escherichia coli [25]. The pharmacologically active portion is the GH domain (22 kDa), and the pharmacologically inactive domains are long chains of natural hydrophilic amino acids, called XTEN. XTEN is added to the N- and C-termini of GH. XTEN enables extension of the half-life of GH by increasing the hydrodynamic size of GH and delaying receptormediated clearance through a reduction in receptor binding. The reduced rate of clearance significantly prolongs serum residence times of VRS-317, resulting in enhanced ligand time on target and potentially increasing the probability of a successful ligand-receptor interaction [25, 26]. In a placebo-controlled randomized single ascending study in 50 adults with GHD, VRS-317 doses of 0.05, 0.10, 0.20, 0.40 and 0.80 mg/kg were administered. The terminal elimination half-life of VRS-317 at the highest dose was 131 h [27]. A dose–response related IGF-I increase was observed. After a single dose of 0.80 mg/kg, serum IGF-I was maintained in the normal range for 3 weeks without overexposure to high IGF-I levels. No instances of lipoatrophy were recorded [27].

7.3 MOD-4023

MOD-4023 is being developed by Opko Health Inc. in conjunction with Pfizer. In MOD-4023 GH is fused to three copies of the carboxyterminal peptide (CTP) of the beta chain of human chorionic gonadotropin. MOD-4023 is developed for once-weekly administration [28]. In a phase 2 study, 39 adults (33 males and 6 females) with GHD were randomized to treatment with MOD-4023 for four weeks in doses equivalent to 30%, 45% or 100% of the patient's cumulative weekly GH dose [29].

MOD-4023 treatment resulted in a dose-dependent IGF-I response and with doses 45–100% of the weekly cumulative dose, IGF-I values comparable to daily GH injections were obtained. MOD-4023 was well tolerated [29]. In a randomized, controlled Phase 2 study, 56 pre pubertal, naive GHD children were randomized to MOD-4023 once weekly (0.25–0.66 mg/kg per week) or daily GH (34 μg/kg per day) for 12 months [30]. A dose dependent IGF-I response was observed. All cohorts demonstrated 6 month annualized height velocity above 12 cm/year, correlated with the PK/PD profile in those patients. No unexpected adverse events were observed [30].

7.4 TV-1106 (Albutropin)

TV-1106 is a long-acting GH developed by Teva Pharmaceutical Industries, Ltd. TV-1106 is comprised of human serum albumin (HSA), genetically fused to the N-terminus of GH. TV-1106 is produced using a yeast (Saccharomyces cerevisiae) that is genetically engineered to express the fusion protein. HSA is a carrier protein with no intrinsicenzymatic or immunologic activity but with a long circulating half-life. The fusion of HSA and GH extends circulation of GH and the pharmacologic activity of GH is retained while the duration of action is longer [31]. In healthy males a single subcutaneous administration of TV-1106 increased plasma IGF-I levels for up to 7 days [32]. Seven consecutive, daily subcutaneous injections of GHresulted in an increase in IGF-I equivalent to that induced by a single administration of TV-1106. TV-1106was well-tolerated. Phase 2 and phase 3 studies are ongoing.

7.5 GX-H9

GX-H9, co-developed by Handok and GenexineInc, uses an anti-body fusion technology. GX-H9 is an rhGH fused to hybrid Fc (hyFc). hy Fc is derived from hybridization of non-cytolytic immunoglobulin Fc portions of IgD and IgG4 without any site-directed mutagenesis. While hyFcextends the half-life of the Fc fused drug molecule mainly based on FcRn recycling mechanism, hyFc also minimizes the loss of bioactivity of the drug molecule, as IgD has the highest hinge flexibility among Igs. The junction site of IgD/IgG4 fusion is buried in the

unexposed region which prevents the adverse immunogenicity and cleavage by enzymes [33]. A phase 2 study is ongoing.

7.6 ACP-001/TransCon

ACP-001, which is developed by Ascendis Pharma, is a prodrug that releases unmodified GH by undergoing non-enzymatic cleavage solely dependent on physiological pH and temperature. ACP-001 is rapidly absorbed into the circulation, where it acts as a reservoir from which GH is released during a defined period of time. ACP-001 is designed for once-weekly subcutaneous injections. In a phase 1 study, ACP-001 was safe and well tolerated and demonstrated pharmacodynamics effects (IGF-I) at least comparable to daily hGH injections. In a single dose study, 37 adults with GHD were randomized to one of three dose levels of ACP-001 (equivalent to 0.02, 0.04 and 0.08 mg hGH/kg/week) injected weekly, or to daily hGH (0.04 mg/kg/week) for 28 days. All dose levels of ACP-001 were safe and well tolerated. A total of nine patients experienced injection site reactions, mostly mild erythema. No lipoatrophy at the injection site or treatment emergent antibodies occurred. IGF-I levels increased in a dose-dependent manner and demonstrated a similar response for ACP-001 0.04 mg/kg/week compared to the corresponding dose of daily GH (0.04 mg/kg/week) [34]. In a six month phase 2 study of TransCon in 52 prepubertal children with idiopathic GHD the increase in IGF-I levels was comparable to daily GH injections. The study showed good tolerability and safety [35].

Various features of developing long acting GH preparationslike technology used in its manufacturing and dosage schedule are given in a table (Table 3)

Table.3 Different LAGH with their method of preparation and dosing

S.no	Drug	Dosage	Technology used	Results
1	NNC0195-0092	Once/week, sc	Single point mutation in the GH backbone	Phase-3 Ongoing
2	VRS-317	Once/month, sc	Addition of hydrophilic amino acid to N and C terminal of GH	Comparable safety and efficacy in Phase-2
3	MOD-4023	Once/week, sc	GH is fused with carboxy terminal peptide of HCG	Comparable IGF-1 values

4	TV-1106	Once/week, sc	HSA is genetically fused to N-terminus of GH	Phase-2 and 3 Ongoing
5	GX-H9	Once/week, sc	Antibody fusion technology	Phase-2 Ongoing
6	ACP-001	Once/week, sc	Prodrug formation	Comparable IGF-1 values

8. CONCLUSION:

GH treatment has been a well-established therapy in adults and children with GHD for more than three decades. Efficacy and side effects of GH have been well described in numerous publications. Treatment is usually administered for many years in children and may be lifelong in adults, making compliance and adherence very important. Several studies have shown that poor compliance results in reduced efficacy [36].

Treatment with GH is still associated with discomfort for many patients despite careful injection education and advances in delivery devices. Several Long acting GH preparations have therefore been developed utilizing different techniques and with different pharmacodynamics and pharmacokinetic profiles. Some of the molecules like VRS-317 show very promising features like once a month dosing with least side effects [37]. While there is more to be learned, developing LAGH preparations have the potential to become a useful addition to the current available treatment options.

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