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Technology Trends of Growth Hormone and Development Strategies for Growtropin

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Recent research trends of human growth hormone (hGH) are divided into improved first-generation products, long-acting second-generation products, and biosimilar products. Among the improved first-generation products studies, studies of injection devices are being actively conducted. The long-acting second-generation products are focused on extending the half-life of hGH, and depending on the results of the clinical trials, the candidates are expected to lead the future hGH market. Finally, biosimilar has had less impact on the hGH market before now; however, expectations of low-cost products still remainas an opportunity.

Keywords: Growtropin, Human growth hormone (hGH), Biosimilar, Pen device, Long-acting product

Introduction

1. General information of Growtropin

Growtropin, a recombinant human growth hormone product released in 1995, is a biological product of Dong-A, for which the revenue is about 60 billion Won through domestic and global sales. The product is currently marketed as a lyophilized, liquid vial and liquid pen cartridge form. The main indication for Growtropin is pediatric growth hormone deficiency (GHD) and Idiopathic Short Stature (ISS).

2. Main subject

1) Trend of development: human growth hormone (hGH)

Recent development trends of hGH have been carried out in three directions (Fig. 1). The first trend is improving the first-generation hGH by upgrading the injection device needed for administration or improving the method of administration for the convenience of patients. The overall flow of this improvement hasled to an upgrade of the injection device; however, formulation development for oral and nasal administration is also being studied. The second trend is developing a long-acting second-generation hGH by extending the half-life of the first-generation

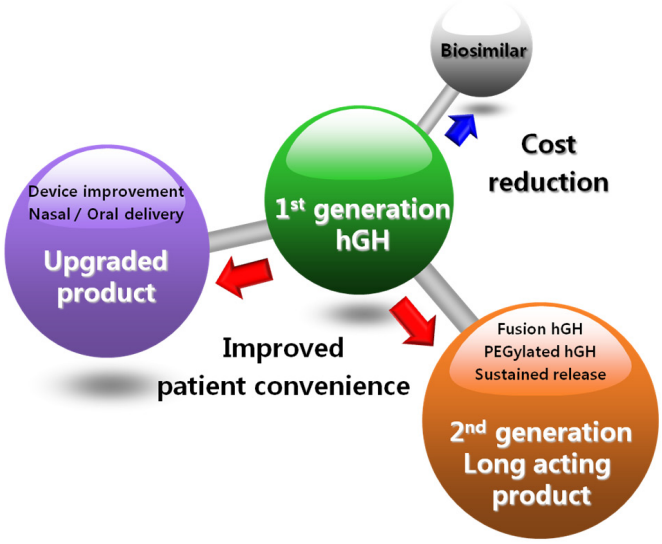

Fig. 1. Development trend of human growth hormone (hGH).

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hGH in order to reduce the administration frequency for the convenience of patients. The second-generation hGH development using Glycosylation, PEGylation, and Fc-fusion is actively being studied and is expected to be commercially available in the near future. The final trend is developing a biosimilar (similar biological product) product. The concept of the development of "biosimilar" is similar to that of the "generic products" of chemical drugs by supplying expensive biotherapeutics at a lower price for patients to give better treatment opportunities.

2) Upgraded products

The leading development plan of the upgraded product is improving the injection device. The main purpose of developing the injection device is to improve patients' convenience. The management of accurate administration and administration history are incidental purposes. The development of the injection device for insulin is carried out the most along with hGH. According to Feroz et al., the production of global insulin from 2007–2012 was driven by the cartridge-based pen injector[1]. It has also been reported that an important factor for production growth is the disposable pen in particular. This also appears in recent hGH-related patents. A number of hGH-related patents from global pharmaceutical companies are related to injection devices, and the number of hGH-related patents from Novo Nordisk, a latecome rhGH manufacturer, is overwhelming (Table 1). Some considerations when developing hGH pendevices are as follows: ① Ease of operation, ② Safety, ③ Eased reluctance, and ④ Eased storage conditions[2-6]. In conclusion, to achieve revenue growth, the development of an easy-to-use, safe pendevice should be considered to improve the accessibility of patients. Additionally, Genotropin (Pfizer), Humatrope (Eli Lilly), Nutropin (Genentech), and Norditropin (Novo Nordisk), which are the hGH originator drugs, as well as Omnitrope (Sandoz), a biosimilar product, are mainly sold as pen devices; among these products, Norditropin and Nutropin are supplied as disposable pen products (Table 2). In the case of Norditropin, despite being alatecomer, the market share from the world market in 2014 was 33.4%, making it the best seller for hGH (Fig. 2)[7]

Table 1. hGH-related patents

Company name	Product name	Patents (expiry date)	Patent type	Patent description
NOVO NORDISK	FlexPro Pen (New-type Pen)	US 7686786 (2026-08-03)	Device	Dial for dose control
		US 6899699 (2022-01-02)	Device	Automatic injection techonology
		US 6716198 (2021-06-05)	Device	Device including piston & ampoule
	NordiFlex Pen (NordiLet)	US RE41956 (2021-01-21)	Device	Device for dose contro
		US 6004297 (2019-01-28)	Device	Pen device
	Norditropin	US 5849700 (2015-12-15)	Method of use	Liquefied formulation
		US 5633352 (2014-05-27)	Process by product	Formulation
PHARMACIA	Genotropin	US 6152897 (2018-11-20)	Composition	Freeze-drying form & disposable syringe
		US 5435076 (2013-04-16)	Device	Reconstruction syringe
APPLIED RESEARCH SYSTEMS	Saizen	US 5898030 (2016-04-27)	Composition	Material
		US 5288703 (2011-10-07)	Method of use	Oral (not commercialization)
ELI LILLY	Humatrope	US 5612315 (2014-03-18)	Formulation	Formulation

Table 2. Device for hGH

	Norditropin FlexPro	Nutropin AQ NuSpin	Genotropin Pen	HumatroPen	Omnitrope Pen
Company	Novo Nordisk	Genentech	Pfizer	Eli Lilly	Sandoz
Needle protection	√	√	√	√	
Required mixing			√	√	
Exchangeable cartridge			√	√	√
Disposable	√	√			
Maximum dose	8 mg	7 mg	4 mg	6 mg	5.4 mg
Alarm after dose	√		√		

due to the following factors: ① Novel delivery device (disposable pen) and ② stable formulation (stable for 3 weeks at room temperature). It can be concluded that the device is having a significant impact on sales. Some examples ofthe development of the route of administration other than the device upgrade include oral delivery (Hanall BioPharma) and nasal delivery (Critical Pharmaceuticals)[8,9].

3) Second-generation products

The purposes of the development of the second-generation products are to extend the half-life of the biotherapeutics to reduce the dosing frequency for the convenience of patients and to increase patients' compliance. The major techniques include ① Glycosylation, ② PEGylation, and ③ Fc fusion, and products using these techniques are commercially available (Fig. 3).

(1) Glycosylation

Most of the biotherapeutics are glycoproteins composed of carbohydrate and protein. When the carbohydrate is bound to protein, the body clearance rate is reduced, which may extend the half-life. Amgen's Aranesp (Erythropoietin), an anemia drug, is a representative product using this principle. In the case of hGH, a study is being held by OPKO and Pfizer by connecting hGH to the carboxyl terminal peptide (CTP), a concentrated carbohydrate binding site, to improve glycosylation[10,11].

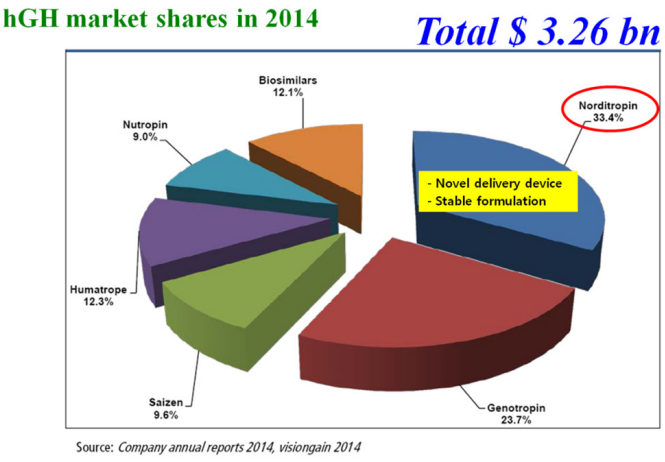


Fig. 2. Global hGH market in 2014.

(2) PEGylation

When coupling PEG (polyethylene glycol), a polymer compound, to a protein molecule, the half-life of the protein is extended and the clearance rate and immunogenicity in the blood is reduced. Using this principle, the PEGylation of therapeutic proteins with a short half-life is actively being studied, and Jintrolong, the world's first PEGylated hGH, has been released by GeneScience in China[12]. However, a PEGylated hGH that has been jointly studied by Ambrx and Merck has been halted and should be noted for future research trends.

(3) Fc Fusion

Antibodies have a much longer half-life than any other proteins due to the Fc region presentin antibodies. The second-generation biotherapeutics studies are being conducted by combining the antibody Fc region with normal proteins to extend the half-life. In the case of hGH, Genexine, a domestic company, is undertakinga Phase 2 clinical trial in Europe.

4) Biosimilar

The process and documents needed for the approval of biosimilar are relatively simple. It can be approved by proving comparability with formally approved and marketed originator drugs. The comparability testing should include physicochemical, nonclinical, and clinical studies. The advantage of biosimilar is that

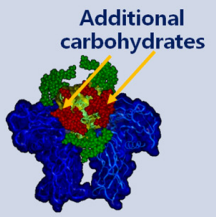
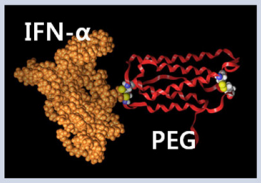
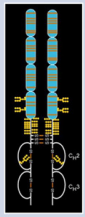
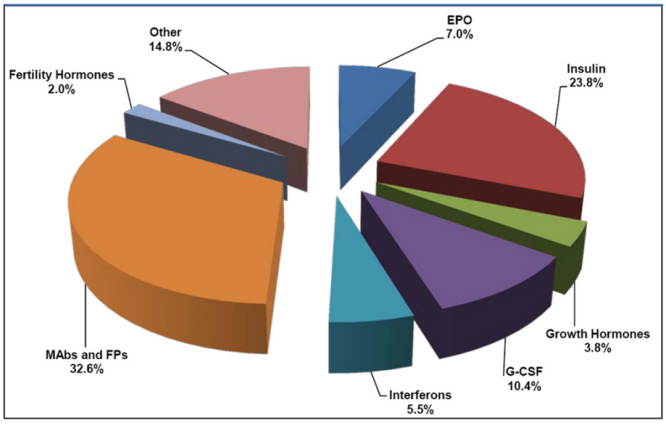
Technology	Glycosylation	PEGylation	Fc Fusion
Diagram			
Products	Aranesp® (EPO)/Amgen	Pegasys® (IFN-α)/Roche Neulasta® (G-CSF)/Amgen Mircera® (EPO)/Roche	Enbrel® (TNF-a)/Amgen Orencia® (CTLA-4)/BMS

Fig. 3. Representative technique for 2nd-generation products.

Table 3. Approved biosimilar products in the EU (– Jan 2015)

Reference	Molecule	Biosimilar	Manufacturer	Date marketing approval received
Neupogen	Filgrastim	Nivestim	Hospira	8 Jun 2010
		Zarzio	Sandoz	6 Feb 2009
		Filgrastim-Hexal	Sandoz	6 Feb 2009
		Ratiograstim	Ratiopharm	15 Sep 2008
		TevaGrastim	Teva	15 Sep 2008
		Biograstim	CT Aizneimittel	15 Sep 2008
		Grastofil	Apotex (w/Intas)	18 Oct 2013
		Accofil	Accord Healthcare	25 Jul 2014 (CHMP positive opinion)
Eprex	Epoetin zeta	Silapo	Stada	18 Dec 2007
		Retacrit	Hospira	18 Dec 2007
	Epoetin alfa	Binocrit	Sandoz	28 Aug 2007
		Epoetin alfa-Hexal	Hexal	28 Aug 2007
		Abseamed	Medice Arzneimittel Pütter	28 Aug 2007
Genotropin	Somatropin	Omnitrope	Sandoz	12 Apr 2006
Humatrope	Somatropin	Somatropin Biopartners	Biopartners	5 Aug 2013 (GHD)
Remicade	Infliximab	Inflectra/Remsima	Hospira/Celltrion	10 Sep 2013
Gonal-F	Follitropin alfa	Ovaleap	Teva	27 Sep 2013
	Follitropin alfa	Bemfola	Finox Biotech	27 March 2014
Lantus	Insulin glargin	Abasria (Basaglar, US)	Eli Lilly/BI	10 Sep 2014



Source: *visiongain 2014*

Fig. 4. Biosimilar market shares in 2013–2024.

the indications of the originator drug can be extrapolated by the comparative clinical phase 1 and phase 3 trials. Since 2006, after Omnitrope (Sandoz), the world's first biosimilar product, was approved, there haveso far been 19 approved biosimilar products-sold in Europe (Table 3). Among the biosimilar products, only two products Omnitrope and Somatropin Biopartners (BioPartners), are hGH products, and the product number and market share are relatively low compared with the first-generation biotherapeutics, such as filgrastim and epoetin (Fig. 4). The brand loyalty towards hGH products was the main reason such a matter was analyzed by Visiongain in 2014[7]. For hGH biosimilar market expansion in the future, improvement of the hGH injection device is required.

5) Development strategy for Growtropin

Dong-A is currently in progress to improve the Growtropin pen device and develop the second-generation hGH in order to improve domestic and global sales. The reusable pen device is expected to be changed to an easy-to-use disposable pen device, and extended half-life formulation research is being performed to develop a long-acting formulation. Through this, we expect to provide an opportunity for market expansion by extending the lifecycle of Growtropin.

Conclusion

The improvement of the first-generation hGH is being conducted using various methods worldwide. The research directions can be mainly classified asimproved products, long-acting

second-generation products, and biosimilar products. The development trends of the improved products are driven towards improving the injection device to enhance the convenience of patients, for which, in particular, the introduction of the disposable pen is an important factor. Studies of long-acting second-generation products aim to extend the half-life of hGH. For each of the candidates, the clinical trial results are important, and this is expected to drive the growth ofthe future hGH market. The market share of biosimilar products is still not significant, but if a low-cost product is launched by improving the injection device, the market share is expected to grow. Dong-A is currently proceeding with the introduction of the disposable pen device and development of second-generation productsin order to improve Growtropin.

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