The Development and Frontier Research of Growth Hormone

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Abstract: With the improvement of process technology, the safety and reliability of growth hormone products have been strengthened, and their clinical applications have become increasingly widespread, resulting in significant improvements in efficacy. However, there are still certain limitations in the clinical application of growth hormone product. It is necessary to have a broad understanding of the research dimensions and progress of growth hormone products, so as to have a more comprehensive grasp of the application value of the products. This article mainly elaborates on the development, evolution, and cutting-edge research progress of growth hormone, hoping to provide reference for the modernization of growth hormone development.

Keywords: Growth Hormone; Development and Evolution; Frontier Research

Each generation of growth hormone products has different advantages and disadvantages in terms of activity level, antibody level, onset speed, number of side effects, and long-term efficacy. However, safer medication, more reassuring treatment, and more satisfactory therapeutic effects remain the main direction for the continuous improvement of product production technology. Future growth hormone products still need to strengthen integration with high-tech production technology, continuously improve activity and purity, and have a wider and higher value in clinical applications, which is worth further research.

1. Analysis of the Development History of Growth Hormone

Human Growth Hormone (hGH) is a peptide hormone secreted by the anterior pituitary gland of the human body, consisting of 191 amino acids. Growth hormone has a significant impact on human growth and development, regulating substance metabolism, degrading fat, and promoting bone, visceral, and systemic growth. It is commonly used to treat childhood dwarfism and other conditions. Human pituitary growth hormone has undergone the following historical evolution from its application in 1958 to its synthesis through genetic engineering technology today:

1.1 The First Generation of Growth Hormone from the 1950s to the 1970s

The first generation of growth hormone refers to human pituitary derived growth hormone, which is the earliest growth hormone used clinically. It was successfully extracted from the human pituitary gland by Raben in 1958 and can be used to treat dwarfism in children. However, this growth hormone has the disadvantage of low production, and patients often find it difficult to achieve the desired elevation effect due to insufficient dosage; The human pituitary gland contains growth hormones of various molecular weights, and the 22kDa GH content in the product is low and the purity is low, resulting in a higher production of antibodies; Susceptible to hGH donor virus contamination, there have been reports of degenerative neurological diseases after use. The first group of patients treated with growth hormone were diagnosed with Creutzfeldt Jakob disease, a rare brain disease also known as "mad cow disease" or "mad cow disease", more than a decade later. The patient's brain may exhibit sponge like degeneration, visual loss, muscle atrophy, ataxia, dementia, and other symptoms. Subsequently banned by the US FDA.

1.2 Second Generation Growth Hormone in the Early 1980s

Genentech developed Met rhGH growth hormone using E. coli inclusion body technology in 1981, which contains a 192 amino acid recombinant human growth hormone. Compared to natural hGH, it has an additional methionine residue at the N-terminus, and the growth hormone secreted by the human

body is 191 amino acids. The antibody production rate of the product is as high as 64%, with low purity and activity. It also has disadvantages such as complex extraction process and easy contamination, which have a significant impact on the efficacy. It has not been widely used and promoted in clinical practice and was delisted in 2004.

1.3 Third Generation Growth Hormone from the Mid-1980s

The third-generation growth hormone is synthesized using ordinary E. coli gene expression technology and contains 191 amino acids. However, there are significant differences in protein structure compared to human pituitary growth hormone. The recombinant human growth hormone powder of the third generation growth hormone has been launched. Although its primary structure is the same as natural growth hormone, its secondary and tertiary levels are different. It has shortcomings such as high antibody production rate, complex extraction process, and easy contamination, especially easy to introduce impurities and cause allergic reactions. Due to the use of chemical modification methods for extraction, the operation process is cumbersome, and the market share is gradually shrinking, and it is being phased out in the European and American markets.

1.4 Fourth generation growth hormone in the late 1980s

The fourth generation growth hormone is a growth hormone synthesized using recombinant DNA technology from mammalian cells. It contains 191 amino acids and has a similar structure to natural growth hormone. However, it also has disadvantages such as high cell culture requirements, slow reproduction speed, susceptibility to adenovirus contamination, and contamination by proliferation promoting drugs. Therefore, it is currently only used by a very small number of manufacturers.

1.5 The Fifth Generation of Growth Hormone in the 1990s

The growth hormone synthesized using the secretory gene expression technology of Escherichia coli is directly secreted outside the bacterial cell. The fifth generation growth hormone has a protein structure and amino acid content, sequence, etc. that are completely identical to human pituitary growth hormone, which conforms to the pulsatile secretion pattern of human growth hormone. It has high biological activity, potency, purity, and absorption rate. At the same time, the product has low treatment cost and safe and reliable clinical application. The first recombinant human growth hormone powder injection, launched by Changchun Jinsai Pharmaceutical Co., Ltd. in 1998 in China, utilizes fifth generation technology to ensure high activity and purity performance; And in 2005, the first recombinant human growth hormone injection in Asia was launched. The aqueous solution can avoid the freezing and redissolution process of recombinant human growth hormone powder injection, and can maintain the natural state of growth hormone. The product has the advantages of few side effects, high activity, low antibody, and fast onset, and is widely used.

2. Frontier Research and Analysis of Growth Hormone

In 2014, China's independently developed polyethylene glycol long-acting growth hormone water solution emerged. The product is a growth hormone that uses natural peptide bonds to connect inert PEG with natural structures. The speed of filtration by the kidneys and the degradation effect of proteases on it are significantly reduced, and its stability in the human body is improved accordingly. Meanwhile, inert PEG and natural peptide bonds are harmless to the human body, ensuring the safety and effectiveness of the product. Long acting growth hormone water solution adopts methods such as microcapsules and microspheres, especially with the support of inert PEG, which slows down the drug elimination rate in the body and prolongs the metabolism time of growth hormone in the body. It can be injected once a week, reducing the pain of daily injections for patients. Long acting growth hormone water simulates the biological effects generated by pulses, which is significantly different from short-term effects. Nowadays, growth hormone has fully entered the era of weekly treatment.

In clinical applications, growth hormone products include powder, water, long-acting formulations, and other types. The main

components of recombinant human growth hormone for injection are recombinant human growth hormone and excipients. The components of recombinant human growth hormone injection are recombinant human growth hormone injection and protective agent. The main component of polyethylene glycol recombinant human growth hormone injection is polyethylene glycol recombinant human growth hormone. Grasping the indications, contraindications, and dosage of clinical applications is more conducive to improving overall efficacy. With the increasing research on high-dose recombinant human growth hormone therapy for children with idiopathic short stature, the relationship between growth hormone therapy and tumor risk in childhood cancer survivors, the effects of recombinant human growth hormone combined with leuprorelin acetate on girls with central precocious puberty [1], the combination of Jianpi Zhuanggu Formula and growth hormone therapy for children with spleen kidney deficiency type idiopathic short stature, and the effects of growth hormone intervention on cardiovascular function and metabolic related indicators in children with non-alcoholic fatty liver disease [2], its clinical value and product advantages have been unanimously recognized by experts and scholars at home and abroad.

In terms of safety and efficacy, growth hormone is a protein drug, and a small number of patients may develop antibodies after use. Simultaneous use of glucocorticoids may inhibit hormone responses. To improve the safety of the therapy, it is necessary to strictly follow the execution standards and apply it cautiously according to the patient's condition. With the deepening of research on the abnormal expression of growth hormone releasing peptides and their receptors in tumor diagnosis and treatment, as well as the effects of growth hormone on the invasion and migration of colon cancer cells [3], people have gained a clear understanding of the safety and limitations of clinical application of growth hormone, which can serve as an important reference and starting point for the modernization and in-depth research of growth hormone.

In terms of research direction, the current research direction on growth hormone is broader, including exploring potential biomarkers of growth hormone based on non targeted proteomics, clinical observations of different time periods of recombinant human growth hormone on children with growth hormone deficiency after treatment, studies on the dose-response relationship of recombinant human growth hormone treatment for dwarfism, and analysis of the therapeutic effect of recombinant human growth hormone treatment on improving lipid metabolism in children after craniopharyngioma surgery. These broad research dimensions can make the theoretical basis for the clinical application of growth hormone more solid.

3. Conclusion

Growth hormone drugs are currently the only effective treatment for dwarfism and have been used in clinical practice for over half a century. The development process of growth hormone drugs is mainly divided into multiple stages, including pituitary derived growth hormone, recombinant growth hormone, and long-acting growth hormone. In the future, with the support of advanced technology, growth hormone will be widely applied and promoted in clinical practice due to its more precise efficacy and higher safety advantages.

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