Sustained-release recombinant human GH improves quality of life in adults with GH deficiency

Youngsook Kim

Department of Medicine

The Graduate School, Yonsei University

Sustained-release recombinant human GH improves quality of life in adults with GH deficiency

Directed by Professor Eun Jig Lee

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Youngsook Kim is approved.

Thesis Supervisor : Eun Jig Lee

Yoon-Sok Chung

Jong Eun Lee

The Graduate School

Yonsei University

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ABSTRACT

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Department of Medicine
The Graduate School, Yonsei University

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Background: As studies demonstrate, the administration of recombinant human GH (rhGH) in adults with GH deficiency has been known to improve metabolic impairment and quality of life (QoL). Patients, however, do have to tolerate daily injections of GH (rhGH).

Objectives: To evaluate the effects, safety, and compliance of weekly administered sustained-release recombinant human GH (SR-rhGH) supplement in patients with GH deficiency

Design: This is a 12-week prospective, single-arm, open-label trial

Intervention/Participants: Men and women aged ≥ 20 years with diagnosed GH deficiency (caused by pituitary tumor, trauma, other pituitary disease) are eligible for this study. Once a week each subject was given 2 mg (6 IU) of SR-rhGH, administered subcutaneously. Efficacy and side effects were assessed at baseline and within 30 days after the 12^{th} injection. Then a comparison between baseline values and those at end time was performed.

Measurements: We evaluated AGHDA (The Assessment of Growth Hormone Deficiency in Adults) score for quality of life and measured serum IGF-1 (Insulin-like growth factor-1) level.

Results: The mean baseline IGF-1 level of 108.67 ± 73.03 ng/ml was increased to 129.01 ± 68.37 ng/ml (P=0.0111) at week 12 and the mean baseline (AGHDA score) was decreased from 9.80 ± 6.51 to 7.55 ± 5.76 (P<0.0001) at week 12. Side effects included pain, edema, rash, and a warm sensation at the administration site, but during the investigation many side effects were gradually disappeared.

Conclusions: Weekly administered SH-rhGH for 12 weeks increased IGH-1 level effectively and improved quality of life in patients with GH deficiency without severe side effects.

Key words : growth hormone replacement, sustained-release recombinant human GH, quality of life

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I. INTRODUCTION

Growth hormone plays a critical role in longitudinal growth during and after the growth period as it has significant effects on protein, lipid, and carbohydrate metabolism. Growth hormone modulates adipose tissue differentiation; therefore growth hormone decreases fat deposits and increases lean body mass. Growth hormone affects hepatocytes and lipoproteins and therefore influences cardiovascular function. Additionally, growth hormone affects bone metabolism, protein synthesis, carbohydrate metabolism, and muscle strength.[1, 2]

Growth hormone deficiency leads to abdominal fat accumulation, decreased muscle mass, dyslipidemia, increased cardiovascular risk, increased death rate, and decline of quality of life in patients with acquired growth hormone deficiency. [3, 4] Studies in patients with hormone deficiency have clearly demonstrated the ability of human growth hormone to improve lipid profile, muscle mass, and reduce obesity.[2] The importance of growth hormone replacement has been underestimated.

Growth hormone replacement therapy has resulted in overall fat mass reduction, specifically in the abdominal region,[5-7] as well as increases in muscle mass, capacity for exercise,[5] and bone density.[1] The effects of growth hormone replacement have recently received considerable attention, and many studies have shown improved quality of life after growth hormone replacement, including improved mood and

energy level.[8, 9] In spite of these positive effects, the concerns about the side effects of recombinant human growth hormone (rhGH) replacement and the inconvenience of daily injections remain to be explored.[10-13]

A sustained release formulation of recombinant human growth hormone (SR-rhGH, Declage™ LG Life Sciences, Ltd., Seoul, Korea) using sodium hyaluronate microparticles were developed to be administered on a weekly basis.[14] In this study, weekly administration of Declage™ was continued until 12 weeks to patients with growth hormone deficiency and investigated the safety and efficiency of SR-rhGH. Similar to previous studies,[15] our results showed on sustained increase in growth hormone concentration for more than 48 hours with Declage™ administration. However, no difference in effectiveness was observed between Declage™ and daily recombinant human growth hormone. The mean level of maximum serum IGF-1 concentration was 34-41% greater with Declage™ than with daily recombinant human growth hormone, and the normalized AUC dose was seven-fold greater compared with other administration groups. After normalization to growth hormone dose, AUC for IGF-1 was comparable between Declage™ and daily rhGH administration. This new formulation was expected to have comparable efficiency with similar side effects but the results showed better patient compliance when compared to daily injections.

II. SUBJECTS AND METHODS

1. Study design

This was a multicenter, open, single-group phase IV clinical trial. Patients were required to visit twice (baseline-visit 1, end-visit 2). The end visit was within 30 days after the last injection. In addition to the baseline and end visits, patients could visit as needed.

Demographic data including first initial of their name, sex, date of birth, pregnancy status, height and body weight (within 30 days), and past medical history were collected. Growth hormone deficiency history was also collected from each patient,

including onset timing, etiology, and maximum serum concentrations of growth hormone. Other important factors, including other hormone deficiencies, growth hormone therapy within three months, and concomitant medications were also identified.

Total cholesterol, IGF-1 and AGHDA QoL scores were recorded at the baseline and end visits. Quality of life was evaluated using the AGHDA QoL score obtained from a questionnaire with 25 questions, with a high score indicating a low quality of life.

Test drug administration was started when patients were enrolled at the baseline visit (visit 1, week 1). Each patient received a weekly SR-rhGH injection by self administration during 12 weeks with a starting dose of 2 mg. Local reactions at the injection site were recorded every week using a diary card and questionnaire. Adverse effects and serum IGF-1 were used as a guide for dose optimization. A minimum effective dose was required, but in order to avoid carpal tunnel syndrome, the dose was decreased if patients complained of continuous edema or severe parethesia.

At visit 2 patients returned any unused mediation and all packaging including empty vials. The study administrator examined the returned medication and recorded the number of prescribed, used, and unused vials in the case notes. Visit 2, this figure is calculated based on the compliant subjects.

Compliance (%) = Used vial/Prescribed vial * 100

2. Subjects

To be eligible for this study patients had to be ≥ 20 years old and have a hormone deficiency disorder caused by a pituitary tumor, trauma, or other pituitary disorder. Growth hormone deficiency was diagnosed by at least two growth hormone secreting stimulation tests (insulin tolerance test, GHRH stimulation test, L-dopa stimulation test, arginine stimulation test, clonidine stimulation test, or glucagon level). Growth hormone deficiency was diagnosed when the maximum serum growth hormone level was under 5 ng/ml after stimulation (in the case of insulin tolerance test, subsequent testing was not required.

Subjects were excluded if they had proliferative vitreoretinopathy, active malignancy,

increased intracranial pressure, dwarfism caused by a brain tumor making pituitary function resistant to growth hormone secretion, hypersensitivity to this drug, or female patients who were pregnant and/or lactating, planning a pregnancy during the clinical trial, or were capable of becoming pregnant and did not use contraceptives (i.e. sterilization, intrauterine contraceptives, combined oral contraceptives and barrier contraceptive, other hormonal contraceptive delivery system in combination with a barrier contraceptive, contraceptive cream, jelly, or foam in combination with a diaphragm or condom) or those with acute diseases caused by complications accompanied by heart surgery, abdominal surgery, multiple accident trauma, acute respiratory insufficiency, or mental illness.

3. Statistical analysis

Normally distributed variables including IGF-1, total cholesterol, and AGHDA QoL score were compared using a paired t-test, otherwise Wilcoxon's signed rank test was used. Adverse events related to the medication were compared using the Chi-square test or Fisher's exact test. Multiple logistic regression analysis was used to identify factors associated with adverse reactions (SAS version 9.1).

III. RESULTS

1. Baseline characteristics

A total of 123 patients were enrolled in this study. Safety was evaluated in all patients. Of these, 109 patients finished the 12-week schedule, and efficacy was only assessed in these 109 patients. Ultimately, 23 of the 109 subjects were excluded for the following reasons: patient request (8), violation of the protocol (3), adverse reaction or unexpected accidents (7), loss to follow-up (3), and other reasons (2).

The mean age of the 123 subjects was 52.18 ± 14.82 years; there were 73 (59%) females and 50 (41%) males (Table 1). The mean weight of all subjects was 65.01 ± 13.39 kg (38-104 kg), and the mean height was 161.37 ± 9.40 cm (139.1-182.4 cm). The average calculated BMI was 24.83 ± 3.81 kg/m^2 (16.82-36.33). Growth hormone deficiency was diagnosed after the age of 20 years in 116 patients (94.3%) and during

childhood in 7 patients (4.7%). The most common cause of growth hormone deficiency was a non-secreting pituitary adenoma (54.5%). Sheehan's syndrome (18.7%) and craniopharyngioma (6.5%) were also noted. With the exception of nine patients, all were diagnosed with growth hormone deficiency before this study. With the exception of six patients, all subjects also had other hormone (ACTH, TSH, LH/FSH, ADH and others) deficiencies.

Table 1. Baseline characteristics (Safety set)

		Total (N=123)	
		n	(%)
Age (years)	Mean±SD	52.18	± 14.82
Gender	Male	50	(40.65)
	Female	73	(59.34)
Height (cm)	Mean±SD	161.37	± 9.40
Body weight (kg)	Mean±SD	65.01	± 13.39
BMI (kg/㎡)	Mean±SD	24.83	± 3.81
GHD onset	Child onset	7	(5.69)
	Adult onset	116	(94.30)
GHD cause[Ψ]	Hormone-secreting pituitary adenoma	1	(0.81)
	Sheehan's syndrome	23	(18.70)
	Idiopathic	1	(0.81)
	Nonsecreting pituitary adenoma	67	(54.47)
	Empty sella	6	(4.88)
	Craniopharyngioma	8	(6.50)
	Other	18	(14.63)
GHD diagnosed before	Yes	114	(92.68)
	No	9	(7.31)
Maximum serum GH level (ng/ml)	Mean±SD	0.92	± 1.47
Other hormone deficiency[Ψ]	None	6	(4.88)
	ACTH	95	(77.24)
	TSH	96	(78.05)
	LH/FSH	82	(66.67)
	ADH	20	(16.26)
	Other	4	(3.25)

Ψ: overlap answer
BMI, body mass index, GHD growth hormone deficiency

2. Efficacy

(1) Serum IGF-1 concentration

After administration of SR-rhGH, serum IGF-1 levels significantly increased from 108.67 ± 74.03 to 129.01 ± 68.37 ng/ml (P = 0.0111).

(2) Quality of life

The AGHDA score evaluating quality of life significantly improved (p<0.0001), decreasing from 9 to 7 after SR-rhGH treatment.

(3) Total cholesterol

The total serum cholesterol levels were decreased by 7.36 ± 35.29 (p-value 0.1588), the change was not significant.

Table 2. Efficacy

	n	Mean	±SD	p-value
Insulin-like growth factor-1(IGF-1)				
Baseline (ng/ml)	76	108.67	± 74.03	
End (ng/ml)	77	129.01	± 68.37	
Difference	58	21.77	± 68.32	0.0111
Total Cholesterol				
Baseline (mg/dl)	78	184.62	± 39.23	
End (mg/dl)	75	184.45	± 33.66	
Difference	57	-7.63	± 35.29	0.1588
QoL-AGHDA				
Baseline	108	9.80	± 6.51	
End	108	7.55	± 5.76	
Difference	107	-2.32	± 4.19	<.0001

Difference=End - Baseline

p-value: Wilcoxon signed rank test

3. Assessment of safety and tolerability (Table 3)

A total of 38 patients had 55 reported adverse side effects, 17 of which (11 patients) were drug-related showing adverse side effects. Edema and fatigue were reported in six cases, myalgia/arthralgia in three cases, headaches and dizziness in three cases, a rash in two cases, urticaria in two cases, ocular hyperemia in one case, and abdominal

pain in one case. Severe adverse events including appendicitis, pneumonia and angina pectoris were reported in three cases. These severe adverse events and use of SR-rhGH were likely unrelated, and all patients recovered completely.

Subgroup analysis revealed that the cause of growth hormone deficiency influences the rate of adverse side effects; patients with non-secreting pituitary adenomas had significantly more adverse reactions than patients with other causes of growth hormone deficiency (odds ratio: 4.565, P = 0.0021). Other variables including age, past medical history, and current medical history were not significantly associated with adverse events.

Table 3. Adverse drug reaction (ADR, safety set)

Adverse drug reaction	n(%)	[events]
Edema (Administration site)	4 (3.25)	[4]
Fatigue	1 (0.81)	[1]
Edema (Pheripheral)	1 (0.81)	[1]
Myalgia	2 (1.63)	[2]
Arthralgia	1 (0.81)	[1]
Headache	2 (1.63)	[2]
Dizziness	1 (0.81)	[1]
Rash	1 (0.81)	[1]
Rash macular	1 (0.81)	[1]
Urticaria	1 (0.81)	[1]
Ocular hyperaemia	1 (0.81)	[1]
Abdominal pain	1 (0.81)	[1]

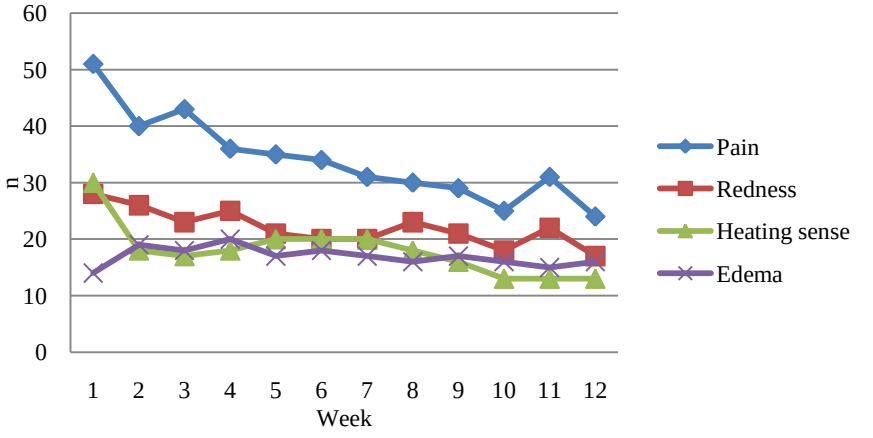
Dictionary: MedDRA (medical dictionary for regulatory activities) version 13.0

4. Local response at the administration site

We evaluated the local response at the administration site in patients receiving one or more injections. Each patient received between 1 - 12 injections. Side effects at the administration site included pain, warmth, edema, and rash. A total of 409 injections were given. All injections were painful, and warmth, rash and edema were reported with 216, 264, and 203 of the 409 injections, respectively (duplicated answer). During repeat injections, the incidence of pain, rash, and warmth gradually decreased, but

edema events showed no change. (Figure 1)

Figure 1. Administration site local reaction



IV. DISCUSSION

Growth hormone plays an important role in linear growth, lipid metabolism, bone metabolism, and body fat distribution. [1, 2] Growth hormone affects adipose tissue and liver and regulates the biosynthesis of lipoproteins and lipoprotein receptors. Hepatic LDL receptors are increased in growth hormone-deficient patients. These receptors remove cholesterol from the circulation, which may mediate growth hormone's cholesterol-lowering effect.[1, 15] Growth hormone promotes adipose tissue differentiation and lipolysis, specifically in abdominal adipose tissue, so fat deposits are decreased, resulting in a leaner body.[1, 16] Despite these effects, the use of growth hormone is limited because of concerns about local injection site reactions, adverse side effects, and the inconvenience of daily injections.

In this study, serum IGF-levels increased significantly while using weekly SR-rhGH injections. Our results were similar to those from studies using daily growth hormone injections.[11, 17, 18] As AGDHA increased as a result of weekly use of the sustained - release rhGH, improving the the patients' quality of life. This result is not unique, and has been demonstrated in previous studies of daily rhGH injections.[8, 19, 20] The increase in quality of life provides stronger support than the serological changes for

maintaining growth hormone use.

The reduction in serum cholesterol as a result of rhGH has been shown in previous studies[21, 22] but was not seen in our study. The relevance of GH deficiency and hypercholesterolemia have been demonstrated in previous studies,[21, 22] and replacement of growth hormone in growth hormone-deficient patients has led to an increase in HDL, LP(a) and decrease in LDL levels.[23-25] In our study, serum cholesterol did not decrease significantly after rhGH treatment. Furthermore, some patients showed increase in serum cholesterol levels. It is possible that this result was due to other medications that the patients were taking (e.g., sex hormones, hormone medications, lipid lowering drugs). Most patients had other pituitary hormone deficiencies so they had been prescribed other hormone drugs such as synthyroid (90 patients) and steroids (93 patients), which can affect the serum lipid profile. Sex hormones also have an effect on the lipid profile; 60 patients were using medication-related sex hormones. Other medications used by study patients included minirin (19 patients), antihypertensive drugs (34 patients) and antithrombotic agents (26 patients). Lipid lowering drugs are the most important medication that could have affected the results, and 50 patients were using lipid lowering drugs [statins (49) and fenofibrate (1)]. Patients using lipid lowering drugs were not excluded from the study to avoid biasing the results regarding cholesterol. Although we did not see a positive effect on lipid metabolism in this study, previous studies have demonstrated that the use of growth hormone has positive effects on lipid metabolism, including decreased total and LDL cholesterol levels.

In this study, we evaluated adverse side effects related to GH use. If the local injection site reactions of SR-rhGH were more severe than the ones with daily injections, the use of SR-rhGH would be limited. However, a weekly versus daily injection schedule still has obvious appeal to patients. Some patients complained of swelling, warmth, edema, and pain at the site of injection. These side effects were reported in similar previous studies as well. In previous studies, if the local side effects were not severe, the injections were continued but at a reduced dosage.[10] It is

important to note that the number of patients who complained of local reactions decreased as the weeks passed (Figure 1). This could be attractive to patients who need to use GH for an extended of period of time.

There were three patients who had pneumonia, appendicitis, or angina pectoris, but the relevance of the events and their relationship with growth hormone injection was low. These side effects may have been the result of other concomitant hormone replacement therapies as most patients (117/123) had other hormone deficiencies. Thus it is difficult to determine the exact cause of these severe side effects. The relationship between age and the incidence of adverse side effects was not significant in this study ($p = 0.4077$), although other studies have reported that younger patients have a lower incidence of side effects. [10]

In summary, several studies have validated the effects of growth hormone in growth hormone-deficient patients,[2] but GH replacement has been limited in its success as a result of the inconvenience of daily injections and concerns regarding side effects. Our research on the efficacy and safety of weekly SR-rhGH instead of daily rhGH will help to increase compliance, decrease side effects, and, thus, increase overall health. Increased serum IGF-1, improved quality of life, but no differences in serum cholesterol were demonstrated after SR-rhGH administration. There were no severe adverse side effects related to SR-rhGH use, while local injection site reactions decreased over time. The results of this study affirm that weekly SR-rhGH injections can be used in place of daily GH injections, and that in terms of efficacy. Weekly SR-rhGH has an advantage in that it minimizes the discomfort associated with GH daily injections.

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ABSTRACT (IN KOREAN)

성인 성장 호르몬 결핍 환자에서 서방형인성장호르몬의 삶의 질 개선 효과

김영숙

연세대학교
대학원 의학과

(지도교수 이은직)

배경 : 이전의 연구에서 인성장호르몬의 사용이 환자들의 대사적인 문제와 삶의 질을 개선시킨다는 것이 알려져있다. 그러나 인성장호르몬을 매일 사용하는 경우에는 환자들은 이로 인한 불편을 호소하였다.

목적 : 일주일에 한번 사용하는 서방형인성장 호르몬의 효과를 평가하기 위한 연구를 시행하였다.

설계 : 12 주 간의 다기관, 단일군, 전향적, 개방형 연구

중재/대상 : 20 세 이상의 후천적 원인에 (뇌하수체 종양, 외상, 이외 뇌하수체 질환) 의한 성장 호르몬 결핍이 진단된 환자를 대상으로 2 mg (6 IU)의 서방형인성장호르몬을 피하주사로 12 주간 매주 주사하였다. 유효성과 부작용에 대해 주사 시작 전 방문시와 12 번의 주사를 종료한 후 30 일 이내에 평가하였으며 이 두 번의 방문시에 측정한 검사치를 비교하였다.

측정 : 삶의 질에 대한 평가를 위해 AGHDA score 를 측정, 혈중 IGF-1 수치 측정

결과 : 평균 IGF-1 은 108.67 ± 73.03 ng/ml 에서 129.01 ± 68.37 ng/ml (P=0.0111)으로 상승하였고 AGHDA score 의 평균은 9.80 ± 6.51 에서 7.55 ± 5.76 (P<0.0001)으로 감소하였다. 약물 주사부위에 나타난 약물과 관련된 통증, 부종, 발적, 열감 등은 주사를 시작한 후 시간이 지남에 따라 점차 감소하였다.

결론 : 12 주간의 매주 서방형인성장호르몬 사용은 심각한 부작용 없이 환자들의 삶의 질을 개선시켰다.

핵심되는 말 : 성장 호르몬 보충, 서방형인성장호르몬, 삶의 질