

Efficacy and Safety of Sustained-Release Recombinant Human Growth Hormone in Korean Adults with Growth Hormone Deficiency

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Purpose: The administration of recombinant human growth hormone in adults with growth hormone deficiency has been known to improve metabolic impairment and quality of life. Patients, however, have to tolerate daily injections of growth hormone. The efficacy, safety, and compliance of weekly administered sustained-release recombinant human growth hormone (SR-rhGH, Declage™) supplement in patients with growth hormone deficiency were evaluated. **Materials and Methods:** This trial is 12-week prospective, single-arm, open-label trial. Men and women aged ≥ 20 years with diagnosed growth hormone deficiency (caused by pituitary tumor, trauma and other pituitary diseases) were eligible for this study. Each subject was given 2 mg (6 IU) of SR-rhGH once a week, subcutaneously for 12 weeks. Efficacy and safety at baseline and within 30 days after the 12th injection were assessed and compared. Score of Assessment of Growth Hormone Deficiency in Adults (AGHDA score) for quality of life and serum IGF-1 level. **Results:** The IGF-1 level of 108.67 ± 74.03 ng/mL was increased to 129.01 ± 68.37 ng/mL ($p=0.0111$) and the AGHDA QoL score was decreased from 9.80 ± 6.51 to 7.55 ± 5.76 ($p<0.0001$) at week 12 compared with those at baseline. Adverse events included pain, swelling, erythema, and warmth sensation at the administration site, but many adverse events gradually disappeared during the investigation. **Conclusion:** Weekly administered SR-rhGH for 12 weeks effectively increased IGF-1 level and improved the quality of life in patients with GH deficiency without serious adverse events.

Key Words: Growth hormone deficiency, sustained-release recombinant human GH, quality of life

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INTRODUCTION

Growth hormone plays a critical role in longitudinal growth during the growth period and has also significant effects on protein, lipid, and carbohydrate metabolism

thereafter. Growth hormone modulates adipose tissue differentiation; therefore growth hormone decreases fat deposits and increases lean body mass. Furthermore, growth hormone affects hepatocytes and lipoproteins, thus influencing 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 (QoL) 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 and muscle mass, and to reduce obesity.²

Growth hormone replacement therapy results 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 QoL after growth hormone replacement, including improved mood and energy level.^{8,9} Despite these positive effects, the concerns about the adverse events 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 Since the suggested formulation is supposed to afford the convenience of patients, the study has designed to confirm the efficacy and the safety during formulation usages. QoL used as a major evaluating provision for growth hormone is appraised, especially for Korean adults. The safety has also been confirmed, which has influence on compliance for sustained usage.

In this study, weekly administration of SR-rhGH was continued until 12 weeks in patients with growth hormone deficiency and efficacy and safety of SR-rhGH were investigated. Similar to previous studies,¹⁵ our results showed sustained increase of serum growth hormone concentration for more than 48 hours after SR-rhGH administration. The mean level of maximum serum IGF-1 concentration was 34–41% greater with SR-rhGH than with daily recombinant human growth hormone, and the normalized AUC dose was seven-fold greater compared with daily rhGH administration groups.

After adjustment to replaced growth hormone dose, AUC for IGF-1 was comparable between SR-rhGH and daily rhGH administration.¹⁵ This new formulation was expected to have comparable efficacy with similar adverse events, however, better patient compliance is expected, compared to daily injections.

Consistent with the previous studies, this study confirmed the efficacy of SR-rhGH and proceed to verify the safety in Korean adults.

MATERIALS AND METHODS

Study design

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

Demographic data including gender, date of birth, pregnancy status, height, body weight (within 30 days), and past medical history were collected. Growth hormone deficiency history was also collected from each patient, including onset time, etiology, and maximum concentrations of serum growth hormone. Other important factors, including other hormone deficiencies, growth hormone therapy within the past three months, and concomitant medications were also identified.

Total cholesterol values, serum IGF-1 levels and AGHDA QoL scores were recorded at the baseline and at the end visits. QoL 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 events and serum IGF-1 levels were used as a guide for dose adjustment. In order to avoid carpal tunnel syndrome, the dose was decreased when patients complained of continuous swelling or severe paresthesia. However, the minimum effective dose was retained as required.

At visit 2, patients were required to return any unused medication and all packages including empty vials. The study administrator examined the returned medication and

recorded the number of prescribed, used, and unused vials in the case report form. Visit 2; this figure was calculated based on the compliant subjects.

$$\text{Compliance (\%)} = \frac{\text{Used vial}}{\text{Prescribed vial}} \times 100$$

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 disorders. Growth hormone deficiency was diagnosed by at least two growth hormone secreting stimulation tests (insulin tolerance test, GHRH stimulation test, and arginine stimulation test). Growth hormone deficiency was diagnosed when the maximum serum growth hormone level was lower than 5 ng/mL after stimulation (in the case of insulin tolerance test, subsequent test-

ing 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.

Table 1. Baseline Characteristics (Safety Set)

	Total (n=123)
Age (yrs)	52.18±14.82
Gender	
Male	50
Female	73
Height (cm)	161.37±9.40
Body weight (kg)	65.01±13.39
BMI (kg/m ²)	24.83±3.81
GHD onset	
Child onset	7
Adult onset	116
GHD cause*	
Hormone-secreting pituitary adenoma	1
Sheehan's syndrome	23
Idiopathic	1
Nonsecreting pituitary adenoma	67
Empty sella	6
Craniopharyngioma	8
Other	18
GHD diagnosed before	
Yes	114
No	9
Maximum serum GH level (ng/mL)	0.92±1.47
Other hormone deficiency*	
None	6
ACTH	95
TSH	96
LH/FSH	82
ADH	20
Other	4

BMI, body mass index; GHD, growth hormone deficiency; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; LH/FSH, luteinizing hormone/follicle-stimulating hormone; ADH, argipressin.

*Overlap answer.

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).

RESULTS

Baseline characteristics

A total of 131 patients were enrolled in this study. Of these, 123 patients were included in the safety analysis, 109 patients were included in the efficacy analysis. One hundred patients completed the 12-week schedule, and 23 out of the 123 subjects were withdrawn due to 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 body mass index was 24.83±3.81 kg/m² (16.82–36.33 kg/m²). Growth hormone deficiency was diagnosed after the age of 20 years in 116 patients (94.3%) and during childhood in 7 patients (5.7%). 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. Nine patients were newly diagnosed with growth hormone deficiency at the screening periods of this study and the others had been diagnosed before. With the exception of six patients, all subjects also had other hormone (ACTH, TSH, LH/FSH, ADH and others) deficiencies.

Efficacy (Fig. 1)

In case of the IGF-1 and total cholesterol, the efficacy is assessed only for the cases of patients who have taken 12 times injection and have baseline and week 12 results. AGHDA was analyzed with 107 patients who took the AGHDA survey at both beginning and closing points, even including patients with single injection on non-sustained cases.

Change of serum IGF-1 concentration from baseline at week 12

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

Change of quality of life

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

Change of total cholesterol

Baseline value of total cholesterol was 186.02 ± 41.86 and decreased by 7.36 ± 35.29 mg/dL ($p=0.1588$), which was not statistically significant.

Assessment of safety and tolerability

A total of 36 patients had 55 reported adverse events, 17 of which (11 patients) were drug-related. Edema and fatigue were reported in six cases, myalgia/arthritis 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. Serious adverse events including appendicitis, pneumonia and angina pectoris were reported in three cases. These serious 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 influenced the rate of adverse events; patients with non-secreting pituitary adenomas had significantly more adverse reactions than patients with other causes of growth hormone deficiency (odds ratio: 4.565, $p=0.0021$). However, due to small number of subjects, we consider that there could be undesirable bias that caused these differences. Since the differences of prevalent age and gender can affect the results, further research on this subject is desirable. Other variables including age, past medical history, and current medical history were not significantly associated with adverse events.

Local tolerability 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. Adverse events at the administration site included pain, warmth, erythema and swelling. A total of 409 injections were given. 58.53% of patients had pain at the injection site, and warmth, erythema

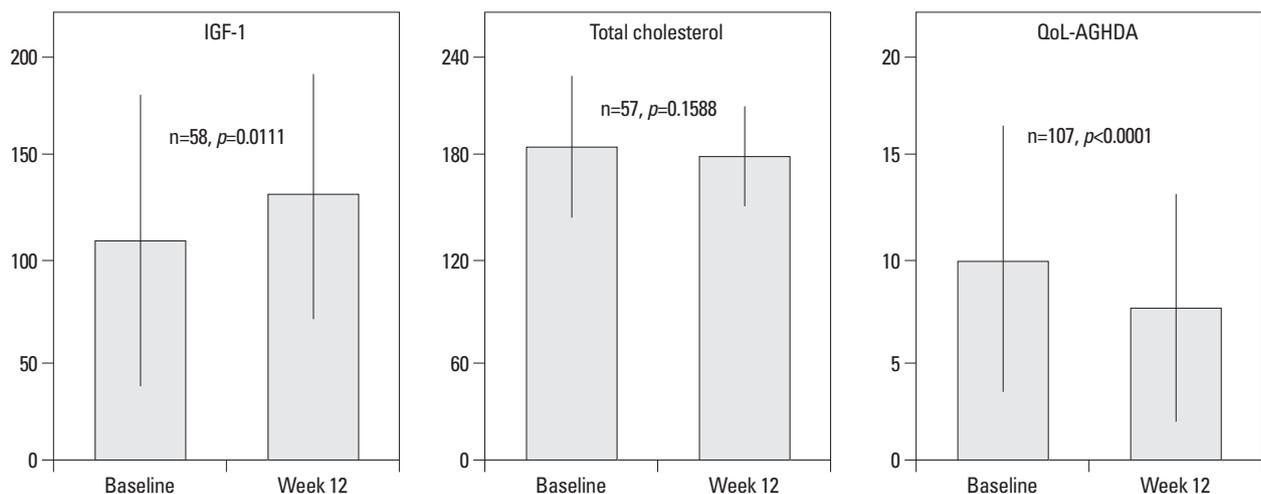


Fig. 1. Efficacy at week 12 compared with baseline. The differences between baseline and week 12 show statistical significance in IGF-1 and QoL-AGHDA but not in total cholesterol.

and swelling were reported with 216, 264, and 203 of the 409 injections, respectively (multiple choices). During repeat injections, the incidence of pain, erythema, and warmth gradually decreased, but swelling events showed no change (Fig. 2).

DISCUSSION

Growth hormone plays an important role in linear growth, lipid metabolism, bone metabolism, and body fat distribution.^{1,2} It 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.^{1,16} Growth hormone promotes adipose tissue differentiation and lipolysis, specifically in abdominal adipose tissue, therefore, fat deposits are decreased, resulting in a leaner body.^{1,17} Despite these effects, the use of growth hormone is limited because of concerns about local injection site reactions, adverse events, and the inconvenience of daily injections.

In this study, we found that serum IGF-levels were increased significantly while using weekly SR-rhGH injections. Our results were similar to those from studies using daily growth hormone injections.^{11,15,18} This result is not unique, and has been demonstrated in previous studies of daily rhGH injections.^{8,19,20} Actually, Biller, et al.²¹ reported the effect of SR-rhGH in growth hormone deficient patients over 6 months' period. Using the same SR-rhGH agent,

they reported that patients were well tolerated with significant increase of IGF-1 and lean body mass. However, most patients consisted of white ethnicity in the previous report. As a phase IV study, we evaluated the effectiveness of SR-rhGH in Korean patients.

To our best knowledge, no studies have been reported on the validation of AGHDA scale for Asian population. However, the AGHDA scale is one of the most widely used protocol in evaluating the QoL, especially in growth hormone deficient patients.^{22,23} Recently, one group in Canada reported the validity of AGHDA in four Slavic languages populations. Actually, the AGHDA scale has been used frequently in Korean studies since the early in 1990s and been approved to have no clinical limitation applying to Korean populations.

In this study, we evaluated adverse events related to growth hormone 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 injection schedule still has obvious appeal to patients compared to daily use. Some patients complained of swelling, warmth, erythema, and pain at the sites of injection. These adverse events have been reported also in previous studies as well. In previous studies, if the local adverse events 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 (Fig. 2). This could be attractive to patients who need to use growth hormone for an extended 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 were low.

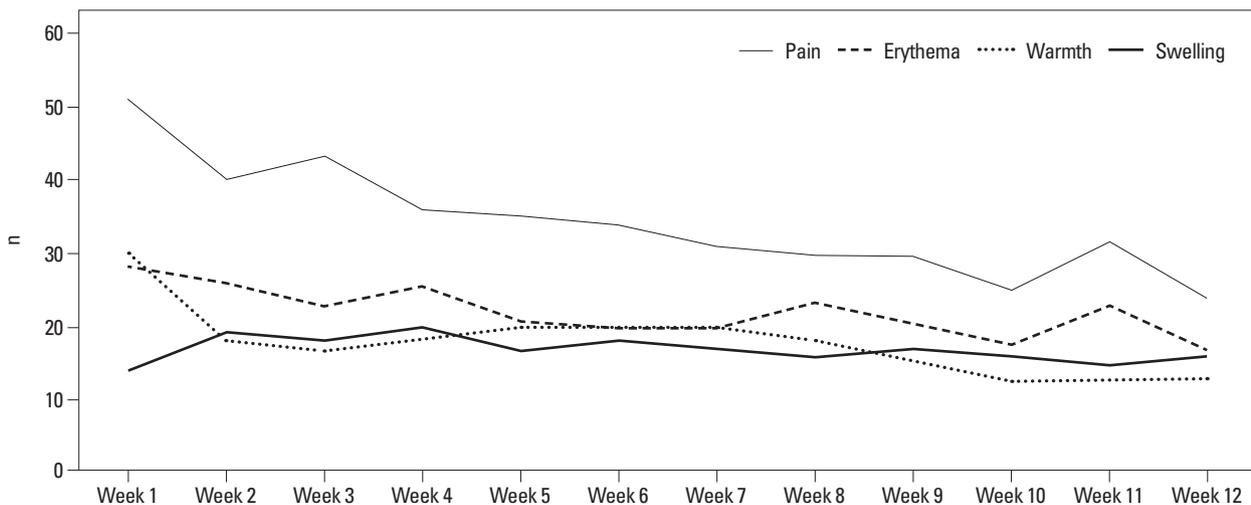


Fig. 2. Administration site local reaction weekly result summary (safety set). Side effects included pain, edema, rash, and a warm sensation at the administration sites, but most of the side effects disappeared during the investigation.

These adverse events 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 exact cause of these serious adverse events. The relationship between age and the incidence of adverse events was not apparent in this study ($p=0.4077$), although other studies have reported that younger patients have a lower incidence of adverse events.¹⁰

In summary, several studies have validated the effects of growth hormone in growth hormone-deficient patients,² however, the success of growth hormone replacement has been limited due to inconvenience of daily injections and concerns regarding adverse events. Our research on the efficacy and safety of weekly SR-rhGH concludes that, compared to daily rhGH, weekly SR-rhGH treatment will help increase compliance, decrease adverse events, and increase overall health. Increased serum IGF-1, improved QoL, but no differences in serum cholesterol were demonstrated after SR-rhGH administration. There were no serious adverse events related to SR-rhGH treatment, while local injection site reactions decreased over time. The results of this study confirm that weekly SR-rhGH injections can be used in place of daily rhGH injections. Weekly SR-rhGH has an advantage in minimizing the discomfort associated with rhGH daily injections.

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REFERENCES

1. Strobl JS, Thomas MJ. Human growth hormone. *Pharmacol Rev* 1994;46:1-34.
2. Carroll PV, Christ ER, Bengtsson BA, Carlsson L, Christiansen JS, Clemmons D, et al. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. *J Clin Endocrinol Metab* 1998;83:382-95.
3. Verhelst J, Mattsson AF, Luger A, Thunander M, Góth MI, Koltowska-Häggström M, et al. Prevalence and characteristics of the metabolic syndrome in 2479 hypopituitary patients with adult-onset GH deficiency before GH replacement: a KIMS analysis. *Eur J Endocrinol* 2011;165:881-9.
4. Ahmad AM, Hopkins MT, Thomas J, Ibrahim H, Fraser WD, Vora JP. Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. *Clin Endocrinol (Oxf)* 2001;54:709-17.
5. Jørgensen JO, Pedersen SA, Thuesen L, Jørgensen J, Ingemann-Hansen T, Skakkebaek NE, et al. Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet* 1989;1:1221-5.
6. Amato G, Carella C, Fazio S, La Montagna G, Cittadini A, Sabatini D, et al. Body composition, bone metabolism, and heart structure and function in growth hormone (GH)-deficient adults before and after GH replacement therapy at low doses. *J Clin Endocrinol Metab* 1993;77:1671-6.
7. Snel YE, Doerga ME, Brummer RJ, Zelissen PM, Zonderland ML, Koppeschaar HP. Resting metabolic rate, body composition and related hormonal parameters in growth hormone-deficient adults before and after growth hormone replacement therapy. *Eur J Endocrinol* 1995;133:445-50.
8. McKenna SP, Doward LC, Alonso J, Kohlmann T, Niero M, Prieto L, et al. The QoL-AGHDA: an instrument for the assessment of quality of life in adults with growth hormone deficiency. *Qual Life Res* 1999;8:373-83.
9. Webb SM. Measurements of quality of life in patients with growth hormone deficiency. *J Endocrinol Invest* 2008;31(9 Suppl):52-5.
10. Holmes SJ, Shalet SM. Which adults develop side-effects of growth hormone replacement? *Clin Endocrinol (Oxf)* 1995;43:143-9.
11. Cohn L, Feller AG, Draper MW, Rudman IW, Rudman D. Carpal tunnel syndrome and gynaecomastia during growth hormone treatment of elderly men with low circulating IGF-I concentrations. *Clin Endocrinol (Oxf)* 1993;39:417-25.
12. Baum HB, Biller BM, Finkelstein JS, Cannistraro KB, Oppenheim DS, Schoenfeld DA, et al. Effects of physiologic growth hormone therapy on bone density and body composition in patients with adult-onset growth hormone deficiency. A randomized, placebo-controlled trial. *Ann Intern Med* 1996;125:883-90.
13. Attanasio AF, Lamberts SW, Matranga AM, Birkett MA, Bates PC, Valk NK, et al. Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. Adult Growth Hormone Deficiency Study Group. *J Clin Endocrinol Metab* 1997;82:82-8.
14. Kim SJ, Hahn SK, Kim MJ, Kim DH, Lee YP. Development of a novel sustained release formulation of recombinant human growth hormone using sodium hyaluronate microparticles. *J Control Release* 2005;104:323-35.
15. Bidlingmaier M, Kim J, Savoy C, Kim MJ, Ebrecht N, de la Motte S, et al. Comparative pharmacokinetics and pharmacodynamics of a new sustained-release growth hormone (GH), LB03002, versus daily GH in adults with GH deficiency. *J Clin Endocrinol Metab* 2006;91:2926-30.
16. Binnerts A, Swart GR, Wilson JH, Hoogerbrugge N, Pols HA, Birkenhager JC, et al. The effect of growth hormone administration in growth hormone deficient adults on bone, protein, carbohydrate and lipid homeostasis, as well as on body composition. *Clin Endocrinol (Oxf)* 1992;37:79-87.
17. Vijayakumar A, Novosyadlyy R, Wu Y, Yakar S, LeRoith D. Biological effects of growth hormone on carbohydrate and lipid metabolism. *Growth Horm IGF Res* 2010;20:1-7.
18. Amato G, Mazziotti G, Di Somma C, Lalli E, De Felice G, Conte

- M, et al. Recombinant growth hormone (GH) therapy in GH-deficient adults: a long-term controlled study on daily versus thrice weekly injections. *J Clin Endocrinol Metab* 2000;85:3720-5.
19. McGauley G, Cuneo R, Salomon F, Sönksen PH. Growth hormone deficiency and quality of life. *Horm Res* 1996;45:34-7.
 20. Murray RD, Skillicorn CJ, Howell SJ, Lissett CA, Rahim A, Smethurst LE, et al. Influences on quality of life in GH deficient adults and their effect on response to treatment. *Clin Endocrinol (Oxf)* 1999;51:565-73.
 21. Biller BM, Ji HJ, Ahn H, Savoy C, Siepl EC, Popovic V, et al. Effects of once-weekly sustained-release growth hormone: a double-blind, placebo-controlled study in adult growth hormone deficiency. *J Clin Endocrinol Metab* 2011;96:1718-26.
 22. Valassi E, Brick DJ, Johnson JC, Biller BM, Klibanski A, Miller KK. Effect of growth hormone replacement therapy on the quality of life in women with growth hormone deficiency who have a history of acromegaly versus other disorders. *Endocr Pract* 2012;18:209-18.
 23. Mukherjee A, Tollhurst-Cleaver S, Ryder WD, Smethurst L, Shalet SM. The characteristics of quality of life impairment in adult growth hormone (GH)-deficient survivors of cancer and their response to GH replacement therapy. *J Clin Endocrinol Metab* 2005;90:1542-9.