Growth Hormone & IGF Research 36 (2017) 36–43

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Assessment of quality of life on 4-year growth hormone therapy in Japanese patients with adult growth hormone deficiency: A post-marketing, multicenter, observational study

Hitoshi Ishii[a,*], Akira Shimatsu[b], Hiromi Nishinaga[c], Osamu Murai[c], Kazuo Chihara[d]

[a] Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8521, Japan
[b] National Hospital Organization Kyoto Medical Center, 1-1 Fukakusamukaihata-cho, Fushimi-ku, Kyoto 612-8555, Japan
[c] Novo Nordisk Pharma Ltd., 2-1-1 Marunouchi, Chiyoda-ku, Tokyo 100-0005, Japan
[d] Akashi Medical Center, 743-33, Yagi, Okubo-cho, Akashi, Hyogo 674-0063, Japan

ARTICLE INFO

Keywords:
Adult Hypopituitarism Questionnaire
Quality of life
Growth hormone
Japanese adult growth hormone deficiency

ABSTRACT

Objective: Improvement of quality of life (QOL) by growth hormone (GH) therapy was not demonstrated in Japanese adult growth hormone deficiency (AGHD) patients by either the QOL Assessment of Growth Hormone Deficiency in Adults or the Questions on Life Satisfaction-Hypopituitarism, which are widely used to evaluate QOL in Western AGHD patients. We therefore evaluated QOL in Japanese AGHD patients receiving recombinant GH, Norditropin® (Novo Nordisk A/S, Denmark), using the newly developed Adult Hypopituitarism Questionnaire (AHQ).

Design: This multicenter, non-interventional, observational study in Japanese patients with severe AGHD was conducted from 1 October 2009 to 30 September 2014. Patients with severe AGHD already receiving somatropin and somatropin-naïve patients were included. GH therapy (Norditropin®) was initiated as injections of 0.021 mg/kg/week divided into 6–7 doses/week, and was adjusted according to clinical responses. Demographic/clinical data were obtained from medical records or by patient recall. QOL was assessed using the AHQ at baseline; 3, 6, and 12 months; and annually up to 4 years.

Results: Of 387 registered patients, 161 were eligible for QOL analysis. AHQ scores significantly improved after 3 months of treatment. Improvements in the psycho-social and physical domains were statistically significant throughout the 4-year study period. Although the GH dose was increased in females such that insulin-like growth factor-1 levels reached those of males, QOL improvements in females did not reach those of males. Despite the greater GH dose in child-onset patients, limited QOL improvements were observed in child-onset vs adult-onset cases.

Conclusions: Four-year GH treatment in Japanese AGHD patients elicits sustained improvement in QOL as assessed by AHQ scores.

1. Introduction

Adult growth hormone deficiency (AGHD) is characterized by abnormal body composition, including increased trunk fat, reduced lean body mass, and dyslipidemia, which increases the risk of cardiovascular and cerebrovascular morbidity and mortality [1]. GHD also has an important impact on quality of life (QOL), including effects on memory, body image, energy levels, mood, depression, anxiety, social interaction, and self-control [2,3].

The QOL Assessment of Growth Hormone Deficiency in Adults (QOL-AGHDA) [4] and Questions on Life Satisfaction-Hypopituitarism (QLS-H) [5] have been developed as disease-specific questionnaires to assess the QOL of AGHD patients. Clinical studies in Europe and the United States reported that growth hormone (GH) replacement therapy improves the QOL of AGHD patients [6–10]. However, in Japanese clinical studies assessing the QOL of Japanese AGHD patients using either the QOL-AGHDA [11] or QLS-H [12], no significant improvement was demonstrated by either of the measures compared with

Abbreviations: AGHD, adult growth hormone deficiency; AHQ, Adult Hypopituitarism Questionnaire; GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor-1; LOCF, last observation carried forward; QLS-H, Questions on Life Satisfaction-Hypopituitarism; QOL, quality of life; QOL-AGHDA, QOL Assessment of Growth Hormone Deficiency in Adults; SD, standard deviation; SDS, standard deviation score

* Corresponding author.
E-mail address: hits1@naramed-u.ac.jp (H. Ishii).

http://dx.doi.org/10.1016/j.ghir.2017.08.005
Received 24 January 2017; Received in revised form 10 August 2017; Accepted 24 August 2017
Available online 01 September 2017
1096-6374/

placebo-treated controls. Possible explanations for these findings include the lack of sensitivity of translated questionnaires to accurately assess QOL in Japanese patients. In addition, the QLS-H assesses mental function through most of its nine questions, but lacks specific questions related to physical and social functions. Although this view is not widely accepted, the QOL-AGHDA reportedly failed to differentiate AGHD from acromegaly, thus lacking disease specificity [13]. Therefore, there may be room for improving these QOL measures [14].

To overcome the limitations of the QOL-AGHDA and QLS-H, we developed and validated the Adult Hypopituitarism Questionnaire (AHQ), a disease-specific QOL questionnaire not only for AGHD patients but also for patients with hypopituitarism in general [15]. Yamada et al. [16] reported deterioration of the AHQ score in Japanese patients with acromegaly who presented severe GHD after surgery compared with patients without GHD, suggesting the clinical utility of the AHQ score to evaluate the QOL of GHD patients. In addition, preliminary data suggesting the usefulness of the AHQ in a small number of AGHD patients were reported by Ikeda et al. [17]. However, no study has been conducted in a substantial number of Japanese AGHD patients to verify whether the AHQ is useful to assess improvement in QOL by GH treatment in the clinical setting.

Norditropin® (Novo Nordisk A/S, Denmark) is a recombinant DNA-derived somatropin, administered by injection [18]. In Japan, it was approved for the treatment of AGHD in September 2009. Originally, this post-marketing observational study was designed to evaluate the efficacy, safety, and QOL of patients treated with somatropin; thus, we enrolled patients already receiving somatropin as well as somatropin-naïve patients. These patients were included in the efficacy and safety analyses reported elsewhere. In this report, we only focused on evaluating improvements of QOL by GH treatment with Norditropin® in Japanese AGHD patients using the AHQ. We also sought to establish whether there were sex- or age-related differences in QOL outcomes.

2. Materials and methods

2.1. Study design and setting

The present study was a multicenter, non-interventional observational study in patients with severe AGHD. The study was conducted at 92 centers in Japan, and was conducted from 1 October 2009 to 30 September 2014. Enrolment was from 1 October 2009 to 30 September 2012, with an observation period of 2–5 years.

The study subjects comprised patients already receiving somatropin and somatropin-naïve patients. All somatropin-naïve patients were started on Norditropin® only. Patient recruitment was on a sequential basis. Patients with severe AGHD were included. Severe AGHD was defined according to the latest diagnosis and treatment guidelines for adult growth hormone deficiency in Japan [19] as a peak GH response of < 1.8 ng/mL (< 9 ng/mL if growth hormone releasing peptide-2 was used) in GH stimulation tests using arginine, insulin, glucagon, and growth hormone-releasing peptide-2 [20]. The main exclusion criteria of the study were as follows: patients with known or suspected allergy to the study product or related products, diabetes mellitus, malignancy, pregnancy or a likelihood of becoming pregnant during the study period. These exclusion criteria were based on the drug contraindications noted in the Japanese package insert [21].

Norditropin® was administered as injections of 0.021 mg/kg/week divided into six to seven doses, based on the treatment guidelines in Japan [21]. The dosage could be increased incrementally to 0.084 mg/kg/week according to clinical response. Specifically, the dose could be increased once every 4 weeks according to the clinical symptoms and insulin-like growth factor-1 (IGF-1) levels of each patient. The dose was adjusted as needed to prevent adverse drug reactions and to maintain blood IGF-1 levels within the normal range for age and sex. The maximum daily dose was not to exceed 1 mg. Treatment compliance was assessed on a scale of 1 to 4 (1: 90% or more of planned injections administered; 2: 70%–90% of injections administered; 3: 50%–70% of injections administered; and 4: < 50% of injections administered).

2.2. Data collection and measurements

Measurements were taken at baseline and at 3, 6, and 12 months, then yearly until the end of the study. Data were collected from the patients' medical records. The survey questionnaire was handed to the patients by the physicians at enrollment. The QOL survey sheets were completed at home by the patients, and returned by post. The data collected included the following: demographic data (date of birth, sex, concomitant illness, past medical history, allergies, and smoking status); height, weight, and vital signs (including blood pressure); family history (including diabetes mellitus, pituitary tumor, cardiovascular disorders, and osteoporosis, among others); results and diagnoses of any underlying disease; laboratory assessments (e.g., endocrinological tests including serum IGF-1 concentration at the time of diagnosis, GH secretion stimulation test, and secretion of other pituitary hormones; blood chemistry; lean body mass; body fat percentage; and bone mineral density); treatments (Norditropin® and concomitant medications including hormone replacement therapy, cholesterol-lowering statins, and other drugs) and treatment adherence; edema and details of the tumor; other adverse events; and QOL, assessed using the self-administered Japanese AHQ [15].

The AHQ has two domains: a psycho-social domain with six sub-domains (depressed mood, limitation in social activities, vigor, sleep, anxiety about treatment, and interpersonal relationships) and a physical domain with seven sub-domains (control of body temperature; physical strength; immunity, digestive tract, and musculoskeletal system; urination; skin condition and visual acuity; body weight; and sexual function). The psycho-social domain comprises a 37-item questionnaire, and the physical domain, a 40-item questionnaire; in total, the questionnaire requires an average of ~12 min to complete [15]. The primary feature of the AHQ is that the questionnaire allows a more multifaceted assessment of QOL for all pituitary diseases. The response to each question is recorded on a 7-point (from 0 to 6) Likert scale. A higher score means a better QOL [15]. Incomplete questionnaires were handled according to the method reported by Ishii et al. [15]. Briefly, when a missing response was found to a question item attributed to a sub-domain, the following procedures were employed: 1) when the number of items with a missing response in a sub-domain was < 50% of the total number of items in the sub-domain, the mean was calculated by imputing the missing responses based on the mean of the non-missing items; 2) when the number of items with a missing response in a sub-domain was > 50% of the total number of items in the sub-domain, the sub-domain score was not calculated. If a sub-domain score was not available, the domain score was not calculated.

2.3. Statistical methods

Categorical variables were summarized in frequency tables, and continuous variables were summarized as descriptive statistics and analyzed by the paired *t*-test. Correlations between variables were measured by the Pearson correlation coefficient. The influence of predictor variables on the change in outcome variables was evaluated by analysis of covariance models for continuous outcome variables, and logistic regression models for discrete outcome variables. All statistical analyses were performed using SAS, Version 9 (SAS Institute, Cary, NC, USA). A 5% significance level was used for all statistical analyses, and tests were two-sided. No corrections for multiple testing were performed. Missing data were handled using the last observation carried forward (LOCF) method.

2.4. Ethical considerations

The study was conducted in accordance with the Declaration of