CLINICAL STUDY

Healthcare utilization, quality of life and patient-reported outcomes during two years of GH replacement therapy in GH-deficient adults – comparison between Sweden, The Netherlands and Germany

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Abstract

Objective: This study set out to determine the change in quality of life (QoL) and healthcare utilization during 2 years of growth hormone (GH) replacement therapy in adults with GH deficiency. Data were compared from three European countries.

Design: Analysis was made from KIMS, the Pfizer International Metabolic Database on adult GH deficiency.

Methods: QoL and healthcare utilization were measured at baseline and after 1 and 2 years of GH replacement in patient cohorts from Sweden ($n=302$), The Netherlands ($n=103$) and Germany ($n=98$). QoL was assessed by the QoL-Assessment in Growth Hormone Deficient Adults (QoL-AGHDA) questionnaire, and the KIMS Patient Life Situation Form was used to evaluate healthcare utilization.

Results: QoL improved significantly ($P<0.0001$) and comparably in all three cohorts. The improvement was seen during the first year of treatment and QoL remained improved during the second year. The number of days in hospital was reduced by 83% ($P<0.0001$) during GH replacement. There were no country-specific differences either at baseline or during follow-up. The same was true for the number of days of sick leave (reduction of 63%; $P=0.0004$). Significant reductions were recorded in the number of doctor visits in each of the three cohorts after 2 years of GH replacement ($P<0.05$).

Conclusions: This study provides a detailed comparative analysis of GH replacement therapy in GHD patients in three European countries. Despite some differences in treatment strategies, the beneficial effects on QoL, patient-reported outcomes and healthcare utilization are essentially similar in the healthcare environment of Western European countries.

European Journal of Endocrinology 154 843–850

Introduction

The beneficial clinical effects of growth hormone (GH) replacement therapy in hypopituitary adults with GH deficiency (GHD) have been established from numerous clinical trials (1–13). Data are also available from KIMS – the Pfizer International Metabolic Database – a large pharmacoepidemiological survey started in 1994 to look at the long-term safety and outcomes of GH replacement therapy with Genotropin in adults with GHD.

This database contains comprehensive clinical information on more than 10,000 hypopituitary adults with GHD from 28 countries. The database has confirmed the efficacy of GH replacement, including improvements in well-being and quality of life (QoL), which have previously been shown by Hernberg-Ståhl *et al.* to be accompanied by a reduction in healthcare utilization (14). That study was based on patient data from a wide range of countries with different healthcare environments. As socioeconomic evaluations depend on the

particular system of healthcare employed by different countries, analysis of country-specific data is necessary before results can be used for further health-economic evaluations. Such a single-country analysis, from Sweden (15), confirmed the previous multinational findings (14).

The aim of the present study was to investigate and compare the effect of GH replacement on QoL, patient-reported health outcomes and healthcare utilization in Sweden, The Netherlands and Germany, and to analyse whether changes in QoL scores correlate with changes in patient-reported outcomes and healthcare utilization. There are similarities between the three countries with respect to their cultural background, their healthcare policy as well as the approval and reimbursement criteria for GH replacement therapy in hypopituitary adults.

Subjects and methods

Patients

The study was based on data from 503 patients with GHD due to pituitary or hypothalamic disease, who were consecutively enrolled in KIMS in Sweden ($n = 302$), The Netherlands ($n = 103$) and Germany ($n = 98$). Diagnosis of GHD was based on a GH peak $< 3 \mu\text{g/l}$ in well-accepted GH stimulation tests. Indication for GH replacement therapy was at the discretion of the

responsible physician. Local approval and reimbursement criteria were similar for the three countries and do not require proven GHD in the presence of hypopituitary or hypothalamic disease.

Inclusion criteria for the study included GH replacement therapy for at least 2 years and the absence of treatment with GH before inclusion in KIMS. The baseline characteristics of the patient populations, together with the causes of GHD, are given in Table 1.

The majority of patients had multiple pituitary hormone deficiencies, and were receiving standard hormone replacement therapy (Table 2). Interestingly, the percentage of women receiving estrogen replacement was essentially different between the three countries, ranging from 21% in The Netherlands to 54% in Germany. The percentages of other replaced hormones were similar.

Assessments

Healthcare utilization and QoL were assessed by self-administered questionnaires at baseline and after 1 and 2 years of GH replacement therapy.

Quality of life. QoL was evaluated by the QoL-Assessment in Growth Hormone Deficient Adults (QoL-AGHDA) questionnaire. The QoL-AGHDA has been developed as a disease-specific instrument for the detection of deficits in areas that are affected in adults

Table 1 Baseline characteristics of 503 GH-deficient adults enrolled in KIMS – the Pfizer International Metabolic Database – in Sweden, The Netherlands and Germany. Values are means $\pm$ S.D. or 10th to 90th percentiles unless indicated otherwise.

	Swedish cohort ($n = 302$)	Dutch cohort ($n = 103$)	German cohort ($n = 98$)
Age at enrolment (years)**	51.1 $\pm$ 12.8	46.6 $\pm$ 13.5	46.7 $\pm$ 13.3
Males/females	151/151	50/53	57/41
Body mass index (kg/m^2)	27.5 $\pm$ 4.9	27.7 $\pm$ 4.3	27.6 $\pm$ 5.2
Cause of GH deficiency			
Pituitary adenoma	202 (66.9%)	61 (59.2%)	55 (56.1%)
Craniopharyngioma	22 (7.3%)	7 (6.8%)	15 (15.3%)
Other pituitary/hypothalamic tumours	9 (3.0%)	9 (8.7%)	5 (5.1%)
Non-pituitary, non-hypothalamic cranial tumours	8 (2.6%)	4 (3.9%)	2 (2.0%)
Treatment for malignancy outside the cranium	0 (0.0%)	4 (3.9%)	0 (0.0%)
Idiopathic GH deficiency	26 (8.6%)	5 (4.9%)	11 (11.2%)
Other causes	35 (11.6%)	13 (12.6%)	10 (10.2%)
Adult-onset GH deficiency*	283 (93.7%)	91 (88.3%)	95 (96.9%)
Isolated GH deficiency*	25 (8.3%)	15 (14.6%)	4 (4.1%)
Time since diagnosis of pituitary disease (years)*	10 (1.3–23.3)	9.4 (1.2–22.5)	7.2 (1.1–7.7)
Time since diagnosis of GH deficiency (years)	1.5 (0.2–2.7)	2.0 (0.2–5.3)	1.9 (0–5.2)
Pituitary surgery performed	207 (68.5%)	72 (69.9%)	71 (72.4%)
Time since last pituitary surgery (years)	7.7 (0.0–20)	8.2 (2–18)	5.6 (0–16)
Radiotherapy performed***	113 (37.4%)	57 (55.3%)	7 (7.1%)
Time since last radiotherapy (years)	12.6 (2–24)	9.4 (0–20)	9.4 (2–32)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ for heterogeneity between countries.

Table 2 Hormone replacement therapy in addition to GH replacement in adult GH-deficient patients enrolled in KIMS – the Pfizer International Metabolic Database – in Sweden, The Netherlands and Germany.

Hormone substituted	Number of patients		
	Sweden	The Netherlands	Germany
Sex steroids			
Males (testosterone)	134 (88.7%)	34 (68.0%)	50 (87.7%)
Females (oestrogens)	68 (45.0%)	11 (20.8%)	22 (53.6%)
Hydrocortisone	210 (69.6%)	68 (66.0%)	78 (79.6%)
Thyroid hormone	246 (81.5%)	75 (72.8%)	71 (72.4%)
Antidiuretic hormone	61 (20.2%)	20 (19.4%)	25 (25.5%)

with GHD (16). The questionnaire consists of 25 questions with 'yes' or 'no' answers, a 'yes' answer indicating that the patient perceives a problem. The sum of the number of 'yes' answers is used as a measure of QoL, with a high score denoting an impaired QoL.

From the three countries included in the analysis, reference data for QoL-AGHDA in the general population are available for Sweden with a mean score adjusted to age 50 of 3.8 (17, 18).

Patients' personal situations. The KIMS Patient Life Situation Form was used to record each patient's personal situation (marital status, education, employment and other data) and use of social care and healthcare resources. At the baseline visit, the patients were asked about number of days of sick leave, number of days in hospital and number of visits to a doctor, other than routine endocrine visits, during the last 6 months before entry into KIMS. At the follow-up visits, patients completed the same questionnaire for the period since their last visit. Analyses of sick leave have been performed only for patients at work and for students.

Patient-reported outcomes. Each patient's perception of treatment since their last visit was recorded using a five-point scale, where 1 corresponds to the answer 'I feel much improved', and 5 corresponds to the answer 'I feel much worse'.

P_{kern-2}physical activity during leisure time and satisfaction with that physical activity were measured using a visual analogue scale (VAS). High numerical values indicate high levels of physical activity and a greater degree of satisfaction. The need for assistance with daily activities was assessed using a 'yes/no' response variable.

Assays

Serum concentrations of insulin-like growth factor I (IGF-I) were determined by radioimmunoassay after HCl/ethanol precipitation of binding proteins (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA).

Intra-assay, inter-assay and total coefficients of variation were less than 9% in the concentration range 125–1046 µg/l. The assay detection limit was 13.5 µg/l. IGF-I values were analysed using age-specific reference ranges and are expressed as standard deviation scores (SDS).

Statistical methods

Descriptive statistical results are given as means $\pm$ s.d. or 10th to 90th percentile (for skewed distributions), or percentages. Statistical analyses of effects in terms of different outcome variables (changes in mean values over time) were performed by repeated-measurement regression and maximum likelihood estimation. The general structure of the regression model was outcome=function of (visit, country, age at baseline, gender, visit*country) where the variable country was used to test the difference in mean levels between studied countries, and the interaction term visit*country was used to test if these differences had changed or not during the treatment period. The significance level was set to 5%. Age and gender fulfilled as adjustment variables. The within-patient dependency of the data over visits was modelled by assuming unstructured variance-covariance matrixes. Comparisons of mean values at the 2-year visits versus baseline values were performed assuming identity link and a normal distribution (QoL-AGHDA score and VAS score scale variables) or a log link and a Poisson distribution (days of sick leave, days in hospital and number of doctor visits) or a logit link and a binomial distribution (need for assistance with daily activities and subjective improvement). Statistical tests for heterogeneity were performed using one-way ANOVA, χ^2 tests, Fisher's exact test (baseline characteristics) or F-tests and/or Walds' criteria (regression analyses). Confidence intervals were calculated assuming Walds' criteria.

The relationship between the change in QoL and change in other variables was calculated using linear and logistic regression.

Analyses were made using SAS software. PROC MIXED and PROC GENMOD were used for repeated measurement regression. PROC GLM and PROC GENMOD were used for linear and logistic regression.

All reported doctor visits, days in hospital and days on sick leave were standardized to 1 year and comparisons based on these 1-year values.

Results

Baseline characteristics

The baseline characteristics of the three cohorts were comparable with respect to gender distribution and the underlying pituitary disease. Mean age at the start of GH replacement was highest in the Swedish cohort (51.1 years compared with 46.6 years in the Dutch cohort and 46.7 years in the German cohort; $P < 0.01$). Radiotherapy had been performed significantly more frequently in the Dutch (55.3%) and Swedish (37.4%) patients than in the German patients (7.1%). All details about country-specific differences at baseline are given in Table 1.

Dose of growth hormone and levels of IGF-I

In all cohorts, the mean dose of GH increased during the first year and then stabilized (Table 3). This was associated with an increase in the IGF-I SDS to normal levels after 1 year of GH treatment, again followed by stabilization (Fig. 1). In Sweden and the Netherlands, females received higher doses of GH after 1 and 2 years of treatment. Nevertheless, males had higher mean IGF-I levels at baseline and during follow-up. In Germany, males received slightly higher GH doses than females resulting in even higher mean IGF-I levels.

In addition to these country-specific differences, there were also differences in the mean GH dose depending on the time when GH therapy was started. Mean maintenance dose was 0.40 mg/day in patients who started treatment between 1995 and 1997 and 0.33 mg/day in patients with treatment initiation between 1998 and 2001.

Quality of life and healthcare utilization

QoL, as assessed using the QoL-AGHDA, significantly improved during 2 years of GH replacement therapy

Table 3 GH doses during 2 years of GH replacement therapy in 503 GH-deficient adults enrolled in KIMS – the Pfizer International Metabolic Database – in Sweden, The Netherlands and Germany. Values are means $\pm$ s.d.

	GH dose (mg/day)		
	Sweden	The Netherlands	Germany
First-year visit			
Males	0.31 $\pm$ 0.17	0.34 $\pm$ 0.16	0.38 $\pm$ 0.23
Females	0.37 $\pm$ 0.19	0.47 $\pm$ 0.21	0.36 $\pm$ 0.18
Second-year visit			
Males	0.32 $\pm$ 0.21	0.31 $\pm$ 0.20	0.36 $\pm$ 0.27
Females	0.39 $\pm$ 0.25	0.52 $\pm$ 0.27	0.35 $\pm$ 0.25

Figure 1 Insulin-like growth factor I (IGF-I) SDS during 2 years of GH replacement therapy in 258 men and 245 women with GH deficiency enrolled in KIMS – the Pfizer International Metabolic Database – in Sweden, The Netherlands and Germany. Values are given as means $\pm$ S.E.M.

($P < 0.0001$). Baseline scores were significantly different between the three countries ($P = 0.03$) with the highest values, denoting the lowest baseline QoL, in Dutch patients. Nevertheless, the improvement in QoL during GH replacement was comparable between the three groups (Fig. 2).

In the whole cohort, improvements in QoL-AGHDA scores were significantly related to baseline scores, i.e. patients with the highest scores at baseline indicating the poorest QoL improved most during follow-up ($P = 0.0066$). In all countries, males had a slightly better QoL-AGHDA-score at baseline than females (Sweden: 7.82 vs. 9.59, The Netherlands: 8.87 vs. 11.19, Germany: 8.97 vs. 9.97). However,

Figure 2 QoL-Assessment in Growth Hormone Deficient Adults (QoL-AGHDA) questionnaire scores during 2 years of GH replacement therapy in 503 adult patients with GHD enrolled in KIMS – the Pfizer International Metabolic Database – in Sweden, The Netherlands and Germany. Values are given as means $\pm$ S.E.M.

a statistically significant difference in the rate of change between gender was seen neither over all countries ($P = 0.28$) nor when each country was evaluated separately ($P = 0.58$).

The number of doctor visits (excluding visits for routine monitoring of therapy) was significantly different between the three countries at baseline ($P < 0.0001$) and showed a significant overall reduction during GH treatment ($P < 0.0001$) which, again, was significantly different between the countries ($P = 0.005$) (Table 4). The most significant reduction in doctor visits was seen in the German population, which, at baseline, showed the highest number of doctor visits (mean 9.5 visits/year). With a mean of 3.2 visits/year, the Swedish patients had the lowest number of doctor visits at baseline and subsequently had the smallest percentage reduction during GH replacement. This still, however, reached statistical significance ($P < 0.05$).

The number of days in hospital were slightly but not significantly different between the countries at baseline (Germany 11.1 days/year, the Netherlands 7.3 days/year, Sweden 3.8 days/year, $P = 0.06$) and was also significantly reduced (by 83%; $P < 0.0001$) during GH replacement. There were no country-specific differences during follow-up. The same was true for the number of days of sick leave (baseline 30.6 days/year (Germany), 22.2 days/year (the Netherlands), and 29.7 days/year (Sweden) respectively, reduction of 63%; $P = 0.0004$).

Apart from these country-specific differences, healthcare utilization at baseline was significantly related to the underlying diagnosis which caused GHD. The number of days in hospital was highest in the non-functioning pituitary adenoma group (mean 8.1 days) and lowest in the idiopathic GHD group (mean 2.5 days). The number of doctor visits was highest in the craniopharyngioma group (mean 10.2) and again lowest in the idiopathic GHD group (mean 5.8). No significant differences were seen between the various aetiologies of GHD with respect to changes of healthcare utilization during follow-up.

Patient-reported outcomes

After 2 years of GH treatment, subjective improvements in general well-being were reported by 79.0% of the Swedish patients, by 75.8% of the Dutch patients and by 75.0% of the German patients (Fig. 3). The reported

subjective improvement was not significantly different between the three countries.

At baseline, the VAS scores for physical activity during leisure time were higher in the Swedish patients (41.0) than in the German (37.6) and Dutch (27.1) patients (P for heterogeneity < 0.0001). No country difference was seen for baseline satisfaction with physical activity. During GH replacement therapy, both parameters improved significantly (VAS score for physical activity: +5.0, VAS score for satisfaction with physical activity +7.9, $P < 0.0001$), with similar improvements in the three countries.

At baseline, 12.9% of the Swedish patients, 24.9% of the Dutch patients and 13.2% of the German patients needed assistance with daily activities. These country differences were statistically significant ($P = 0.01$). In all countries, the percentage of patients needing assistance was higher in female than in male patients (Sweden, 17.8% versus 6.4%; The Netherlands, 42.3% versus 7.0%; Germany, 14.2% versus 12.2%). In all countries, the need for assistance with daily activities showed a slight, but not significant, decrease during GH replacement therapy (-14%).

Relationship between Quality of Life-Assessment in Growth Hormone Deficient Adults scores and other variables

The changes in QoL-AGHDA scores after 2 years of GH replacement are significantly related to the change in leisure-time physical activity, satisfaction with physical activity, and subjective improvement in general well-being (Table 5). These results were pooled, as estimates were relatively homogenous between the three countries.

No association was found between the change in QoL-AGHDA scores and changes in healthcare utilization, i.e. number of doctor visits, number of hospital days, and days of sick leave.

Discussion

The present study confirms that GH treatment in adults with GHD is associated with a significant improvement in QoL, in conjunction with a significant reduction in healthcare utilization. Such beneficial changes have

Table 4 Number of doctor visits during 2 years of GH replacement therapy in 503 GH-deficient adults enrolled in KIMS – the Pfizer International Metabolic Database – in Sweden, The Netherlands and Germany.

	Baseline	Second-year visit	Percentage change	P value
Swedish cohort	3.2 (2.7–3.8)	2.6 (2.2–3.1)	–19.7 (–34.7 to –1.4)	0.037
Dutch cohort	7.0 (5.6–8.8)	3.3 (2.1–5.0)	–53.9 (–71.4 to –25.7)	0.002
German cohort	9.5 (7.3–12.3)	4.1 (3.1–5.5)	–56.7 (–70.0 to –37.6)	
				< 0.0001

To account for the impact of gender and age, the results have been adjusted and are expressed for 45-year-old patients at baseline and assuming 50% males and 50% females (mean values, with 95% confidence intervals in parentheses).

Figure 3 Patient-reported subjective improvements during 2 years of GH replacement therapy in 503 adult patients with GH deficiency enrolled in KIMS – the Pfizer International Metabolic Database – in Sweden, The Netherlands and Germany.

been reported previously in multinational (14) and single-country (15) analyses. In addition, differences in QoL between several European populations have been reported in the general population as well as in patients with GHD (19–21). The present study provides a comparative analysis of the course of QoL and healthcare utilization during GH replacement therapy in three well-defined European populations.

The doses of GH and the increases in IGF-I levels were similar in each country. In all populations investigated, females had lower IGF-I levels than males, which has been previously reported in several other studies (22–24). From these reports it is well known that women require higher doses of GH than men. In fact, to reach the same IGF-I concentrations, women need almost

a 20% higher GH dose than men, and a 125% higher dose is needed in women receiving oral oestrogens (25, 26). Therefore, the results of the present study indicate that in all countries investigated, women with GHD were not receiving the optimum replacement dose of GH. This is most striking in the German cohort, where males received even higher doses than females, but, interestingly, also applies to the Dutch cohort, where females received higher doses than in the other countries.

Baseline characteristics, including the underlying pituitary disorders, were very similar between the countries, with the exception that radiotherapy was used significantly less often in Germany. Slight, but significant, between-country differences at baseline were seen for parameters such as QoL, physical activity during leisure time, assistance with daily activities and number of doctor visits. The differences in doctor visits at baseline reflect the officially reported national data for each country with a mean number of approximately nine visits in Germany, six visits in The Netherlands, and three visits in Sweden each year for the last 5 years (27–29).

Despite a similar mean age of the three populations and very similar percentages of other replaced hormones, striking differences were found in the percentage of female patients receiving oestrogen replacement therapy. Since sex-steroid replacement has been found to be associated with outcome in hypopituitary patients, this fact needs further investigation (30).

Despite these differences between the three populations at baseline, QoL and healthcare utilization improved by a similar extent in each cohort during GH replacement therapy. Similar results have been reported from another multinational study (21). The QoL-AGHDA-scores after 2 years of treatment seem still to be higher than in the normal population.

Table 5 Change in QoL-Assessment in Growth Hormone Deficient Adults (QoL-AGHDA) questionnaire scores and some Patient Life Situation Form scores between baseline and 2 years of GH treatment in 503 GH-deficient adults enrolled in KIMS – the Pfizer International Metabolic Database – in Sweden, The Netherlands and Germany.

Change in QoL-AGHDA score ¹	Change in physical activity VAS score	Change in satisfaction with physical activity VAS score	Percentage of patients who reported improvement	Percentage of patients no longer requiring assistance	Change in number of doctor visits	Change in number of hospital days	Change in days of sick leave ²
0 (no change) (n = 133)	–1.8 (2.4)	–0.5 (2.8)	56.4 (46.9–65.6)	1.4 (0.3–5.8)	–2.3 (0.8)	–5.0 (2.6)	–23.3 (13.1)
–1 to –3 (n = 109)	3.3 (2.7)	6.6 (3.1)	76.4 (66.6–84.0)	4.9 (2.1–11.1)	–4.3 (0.8)	–11.3 (2.7)	–24.7 (13.9)
–4 to –7 (n = 103)	12.0 (2.7)	12.4 (3.1)	86.2 (77.5–91.9)	10.1 (5.3–18.5)	–4.1 (0.8)	–9.0 (2.7)	–22.7 (14.5)
–8 to –18 (n = 86)	12.0 (2.9)	20.1 (3.4)	90.0 (82.0–95.7)	9.7 (4.7–19.0)	–3.6 (0.9)	–3.2 (2.8)	–16.0 (16.1)
Trend over categories	<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> = 0.002	<i>P</i> = 0.25	<i>P</i> = 0.55	<i>P</i> = 0.7

Data are given as mean and s.e.m. or as mean and 95% CI.

¹Total 431; 72 missing due to lack of data at either baseline or 2 years or both.

²Among those working full- or part-time at both the baseline and 2-year visit (n = 221).

This, however, can only be evaluated for the Swedish population, where normative data for the QoL-AGHDA are currently available (17, 18).

According to previous reports (3, 21, 31), most of the improvements in QoL during GH replacement therapy were observed during the first year of treatment and these improvements were maintained during follow-up. There was a significant association between baseline QoL and improvement in QoL during follow-up, i.e. better improvements were seen in patients with poorer QoL at baseline.

Improvements in QoL seem to be related to physical activity, satisfaction with physical activity, patient-reported improvement in health and a reduced requirement for assistance with daily activities, but not to changes in healthcare utilization. Therefore, the data indicate that QoL is not a good predictor of reduction in healthcare use in this population.

It is well-established that exercise capacity and physical activity are improved following GH replacement in adults (7, 32). The improvement is probably multifactorial, involving improved cardiac function as well as increased muscle mass and strength (7, 32, 33). An increase in oxygen transport capacity due to a stimulatory effect of IGF-I on erythropoiesis may also contribute to increased physical activity (34).

Furthermore, adults with GHD have previously been shown to experience improvements in psychological functioning and QoL during GH replacement therapy (3, 35, 36). This has also been shown, using the QoL-AGHDA questionnaire, in patients in KIMS treated for up to 3 years with GH (14, 15, 22).

In addition, some studies have shown improvements in cognitive function with GH replacement therapy (1, 12, 37). Effects on psychological functioning may be mediated by direct GH effects on the brain, as well as indirectly through effects on body composition and cardiovascular parameters. GH can cross the blood-brain barrier, and the GH receptors found in the choroid plexus have been proposed as the site of passage of GH into the central nervous system (37). GH has been shown to influence neurotransmitters known to affect mood, such as dopamine and β -endorphin (38, 39).

Conclusion

This study provides a detailed comparative analysis of the effects of GH replacement therapy in GH-deficient adults in three European countries, which have a similar cultural background and healthcare policy. Under the conditions of clinical practice, there were some significant differences between the characteristics of the patient populations receiving GH replacement therapy and between the strategies of hormone replacement therapies. However, the beneficial effects of GH replacement on QoL, patient-reported outcomes and healthcare utilization were essentially similar. These results provide

important information for further socioeconomic evaluations of GH-replacement therapy in the healthcare environments of Western European countries.

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Received 15 December 2005

Accepted 23 February 2006