Targeting either GH or IGF-I during somatostatin analogue treatment in patients with acromegaly: a randomized multicentre study

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Abstract

Context: Discordant GH and IGF-I values are frequent in acromegaly. The clinical significance and its dependence on treatment modality and of glucose-suppressed GH (GH_{nadir}) measurements remain uncertain.

Objective: To evaluate the effects of targeting either IGF-I or GH during somatostatin analogue (SA) treatment.

Patients and Methods: 84 patients with controlled acromegaly after surgery ($n=23$) or SA ($n=61$) underwent a GH profile including an OGTT, at baseline and after 12 months. SA patients were randomized to monitoring according to either IGF-I ($n=33$) or GH_{nadir} ($n=28$). SA dose escalation was allowed at baseline and 6 months.

Main outcome measures: GH_{nadir} and IGF-I at baseline and 12 months, and disease-specific Quality of Life (QoL).

Results: IGF-I and fasting GH levels were comparable between the surgery and the SA group, whereas GH_{nadir} ($\mu\text{g/L}$) was lower in the surgery group (GH_{nadir} 0.7 ± 0.1 vs 0.3 ± 0.1 , $P<0.01$). SA dose increase was performed in 20 patients in the GH group and in 8 patients in the IGF-I group ($P=0.02$), which increased the number of concordantly controlled patients ($P=0.01$). QoL was only mildly affected at baseline in all groups and did not change consistently during the study.

Conclusion: (1) Discordant values in terms of high GH levels are prevalent in SA patients and more so if applying glucose-suppressed GH_{nadir}; (2) targeting discordant levels of either GH or IGF-I translates into SA dose increase and improved biochemical control; (3) even though QoL was not improved in this study, we suggest biochemical assessment of disease activity to include glucose-suppressed GH_{nadir} also in SA patients.

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Introduction

Acromegaly is a rare but debilitating disease, which in most cases originates from a benign somatotroph adenoma from the anterior pituitary gland (1). The phenotype is caused by excess production of GH and IGF-I in addition to expansion of the tumour in the pituitary fossa. If left untreated, the disease is associated

with excess morbidity and mortality (1, 2, 3). Surgical adenomectomy remains first line treatment, which is effective in approximately 60% (4). Medical treatment with somatostatin analogues (SA) has stood the test of time as secondary treatment when surgery is either insufficient or ineligible (5).

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The definition of disease control includes biochemical criteria, and normalization of IGF-I in combination with suppression of GH levels to a certain nadir level (GH_{nadir}) following an oral glucose load (OGTT) are generally accepted therapeutic targets (6). However, a number of controversies remain, such as the frequent occurrence of discordant serum levels of GH and IGF-I in individual patients (7). The reasons for discordance are many including analytical variation (8) and difference in GH cut-off levels, in addition to treatment-specific differences in the biochemical response. The clinical implications are uncertain, but it has been observed that elevated GH levels in the presence of normalized IGF-I in newly operated patients may be associated with the increased risk of disease recurrence (9). No longitudinal or experimental studies are reported in SA-treated patients in whom discordantly elevated GH levels are frequently encountered (10).

It is also controversial whether OGTT-based GH_{nadir} levels in SA-treated patients offer useful information as compared to random or fasting GH measurements (10). However, we have observed in two retrospective studies that measuring GH levels during OGTT may unmask potential under-treatment with SA despite IGF-I levels within the target range (11, 12).

We therefore conducted a controlled trial in SA-treated patients, who were randomized to biochemical monitoring according to either IGF-I or GH_{nadir} levels during a 12-month period. The study design included fasting GH (GH_{fasting}) as well as GH_{nadir} measurements and a comparison with a group of surgically cured patients followed during the same period.

Patients and methods

Patients and design

Eighty-four patients with acromegaly were recruited for this investigator-initiated, randomized, prospective, single-blinded multicentre study. The patients were considered controlled at the discretion of the physicians in charge for at least >6 months after either surgery-alone ($n=23$; 'surgery group') or during continued SA treatment (Sandostatin LAR, Novartis, Switzerland) in an unchanged dose ($n=61$; 'SA group'). All patients were studied during a 12-month period with GH profiles and concomitant insulin, glucose and free fatty acid (FFA) levels, single IGF-I measurements and questionnaires ($t=0$ and $t=12$ months). All hormone and metabolite

analyses were undertaken centrally at a single laboratory (Medical Research Laboratory, Aarhus University Hospital, Aarhus, Denmark). The GH profiles were performed after an overnight fast at the hospital. Blood was sampled between 8 and 11 h with 10-min intervals during the first hour ($t=-60$ min to $t=0$ min), followed by an oral glucose load (75 g) at $t=0$ and sampling at $t=30$, 45, 60, 90 and 120 min. After completion of the first profile, the SA patients were randomized to biochemical monitoring with *either* IGF-I ($n=28$) *or* GH_{nadir} ($n=33$) for 12 months using cut-off levels derived from an in-house reference material in 55 subjects (27M/28F, mean $\pm$ s.e. age 49 ± 1.6 year). Serum IGF-I levels in the reference cohort were age- but not sex-dependent translating into the following therapeutic target levels: <260 μ g/L in patients aged <50 years, and <190 μ g/L in patients aged >50 years. The corresponding GH_{nadir} levels during an OGTT were sex- but not age-dependent, and the following target levels were defined: <0.3 μ g/L in males and <0.4 μ g/L in females. In patients with aforementioned target values at baseline ($t=0$), an SA dose escalation was implemented, and an additional dose escalation was possible based on GH or IGF-I measurements after 6 months (Fig. 1). Where appropriate, the SA dose was increased by 10 mg Sandostatin LAR/4 weeks or by shortening the treatment interval, with a maximum dose of 50 mg/4 weeks.

The study was registered at Clinical Trials (ID:SOM-2012-01) and approved by the Danish Ethical Committee (no. 1-10-72-284-12), the Danish Data Protection Agency (no: 2012-41-0668) and the Regional Ethical Committee South East Norway (REK 2012/1383).

Hormones and metabolites

All serum IGF-I and GH concentrations were determined centrally using the IDS-iSYS system automated chemiluminescence immunoassays as previously described (16, 17). IGF-I standard deviation scores (SDS) at the time of acromegaly diagnosis were calculated *post hoc* based on IGF-I data from each patient record using the corresponding age-related cut-off levels. Serum levels of insulin, glucose and FFA were measured as previously published (13).

Patient-reported symptoms and quality of life (QoL)

We used the Patient-assessed Acromegaly Symptom Questionnaire (PASQ) and the AcroQoL questionnaires. The latter comprises 22 questions each of which has 5 possible answers scored 1–5, with a total maximum

Figure 1

Flow chart of the 61 somatostatin analog (SA) treated patients (n=61) in the study. Left panel depicts randomisation of the patients to either GH or IGF-I monitoring; mid panel depicts SA dosing during the trial (no increase vs increase in dose) and right panel depicts mean levels of GH (μg/l) and IGF-I (μg/l) at baseline and after one year. For further information see text.

score of 110 and expressed as a percentage. The questions are divided into two main categories: physical and psychological functions. The psychological dimension is subdivided into appearance and personal relationships. The score of 110 reflects the best possible QoL (14). The Patient-assessed Acromegaly Symptom Questionnaire (PASQ) is a disease-specific questionnaire, which consists of six questions scoring 0–8 and a seventh question addressing the overall health status, based on the other six questions, scoring 0–10. The first six questions measure the following symptoms: headache, excessive sweating, joint pain, fatigue, soft tissue swelling and numbness or tingling of the extremities. A high PASQ score reflects large symptom burden (15, 16).

Statistical analysis

Histogram and qq-plot were used to examine continuous variables for normal distribution. If data

were not normally distributed, log transformation was applied. Data are expressed as mean $\pm$ s.e. or as geometric mean $\pm$ CI for log-transformed data. Student's paired or unpaired *t*-tests were used to compare variables within or between groups, respectively. Correlation analyses were performed using Pearson's correlation coefficient. Non-parametric data were expressed as median (range). Wilcoxon matched-pairs signed-ranks test or Wilcoxon rank-sum test were used to compare non-parametric data within or between groups, respectively. Spearman's rank correlations were performed to analyse correlations between non-parametric data. Fischer's exact test was used to test differences in cross-tables and the Chi-square goodness of fit test was used to test whether observed percentages for a categorical variable were significantly different from expected percentages. Area under the curve (AUC) was calculated by the trapezoidal rule. A *P*-value <0.05 was considered statistically significant.

Results

Biochemical monitoring of patients treated with surgery and SA

Demographics and clinical disease control were comparable in the two groups of patients at the time of diagnosis except for pituitary adenoma size, with significantly larger adenomas in the SA group (Table 1). In spite of comparable lowest GH_{fasting} levels (µg/L) (0.9 ± 0.7 (SA) vs 0.8 ± 0.8 (surgery), $P=0.74$), SA patients exhibited significantly higher GH_{nadir} levels during OGTT compared to surgery patients (0.7 ± 0.1 (SA) vs 0.3 ± 0.1 (surgery), $P<0.01$) (Fig. 2A). In addition, the relative reduction (%) in GH (ΔGH) in response to OGTT was more pronounced among surgery patients (46 ± 7 (Surgery) vs 19 ± 4 (SA), $P<0.01$).

Based on the predefined cut-off levels for GH_{nadir} and IGF-I, each patient was categorized into one of the four groups: concordantly normalized GH and IGF-I levels (controlled), concordantly elevated GH and IGF-I levels (uncontrolled), elevated GH and normalized IGF-I levels (high GH) and elevated IGF-I and normalized GH levels (high IGF-I).

In the surgery group, 65% were controlled, 4% were uncontrolled, 26% had high GH and 4% had high IGF-I (Fig. 2B). When applying the GH_{fasting} value (cut-off <1 µg/L) in the surgery group, the following figures were obtained: 70% (controlled), 4% (uncontrolled),

22% (high GH) and 4% (high IGF-I). The proportion of patients in each of these categories in the surgery group was comparable when using GH_{nadir} versus GH_{fasting} ($P=0.97$) (Fig. 2B).

In SA patients, 31% were controlled, 23% were uncontrolled, 43% had high GH and 3% had high IGF-I. When applying GH_{fasting} in the SA group the following figures were obtained: 57.5% (controlled), 13% (uncontrolled), 16.5% (high GH) and 13% (high IGF-I).

In contrast to the surgery group, the distribution into the 4 categories in SA patients was significantly different when using GH_{fasting} as compared to GH_{nadir} ($P<0.01$). The distribution was also significantly different between surgery and SA when using GH_{nadir} ($P<0.01$), but not when using GH_{fasting} (Fig. 2B).

Biochemical status during SA dose titration

Thirty-three SA patients were randomized to GH_{nadir} targeting and 28 to IGF-I (Fig. 1). These two SA subgroups were comparable at study start as regards demographics and disease control (Gender: 15F/18M vs 15F/13M; age (year): 55 ± 1.9 vs 56 ± 1.6 ; GH_{fasting} (µg/L): 0.8 ± 0.1 vs 0.9 ± 0.1 ; GH_{nadir} (µg/L): 0.8 ± 0.1 vs 0.9 ± 0.1 ; IGF-I (µg/L): 159 ± 10 vs 183 ± 12 (all NS)). All patients with elevated target hormone levels at baseline ($n=28$) were increased in SA dose, but only patients in the GH target group required an additional dose increase at 6 months ($n=8$).

Table 1 Baseline characteristic data are presented as total numbers or mean $\pm$ s.e.

	All	Treatment		P-value
		Surgery	SA	
Patients				
Number	84	23	61	
Sex (F/M)	43/41	13/10	30/31	N.S.
At diagnosis				
Age (year)	44 ± 1.2	47 ± 2.9	43 ± 1.3	N.S.
Adenoma size (mm)	17 ± 1.2	12 ± 1.3	19 ± 1.5	<0.01
Macro adenoma (%)	77	63	82	N.S.
IGF-I (SDS)	5 ± 0.2	4.7 ± 0.4	5.3 ± 0.3	N.S.
At study start				
Age (year)	57 ± 1.1	61 ± 1.8	56 ± 1.3	0.04
IGF-I (µg/L)	164 ± 6.4	147 ± 10.1	171 ± 7.9	N.S.
IGF-I (SDS)	1.4 ± 0.1	1.2 ± 0.2	1.5 ± 0.1	N.S.
GH fasting (µg/L)	1.2 ± 0.1	1.1 ± 0.2	1.2 ± 0.1	N.S.
GH nadir (µg/L)	0.6 ± 0.1	0.3 ± 0.1	0.7 ± 0.1	<0.01
Treatment, before study start				
Long-acting SSA				
Duration (years)		0	10 ± 0.9	
Dosage (mg/month)		0	22 ± 1.1	
Pituitary surgery (%)		100	90	N.S.
Irradiation (%)		0	25	<0.01
Dopamin agonist (%)		0	11	N.S.

Figure 2

Panel (A) Mean $\pm$ s.e. serum levels of GH and IGF-I (insert) at baseline during an oral glucose tolerance test (OGTT) in surgery patients and somatostatin analogue (SA)-treated patients. Panel (B) The baseline distribution (%) of SA patients and surgery patients into one of the four predefined groups: concordantly elevated GH and IGF-I levels (uncontrolled), elevated GH and normalized IGF-I levels (high GH), elevated IGF-I with normalized GH levels (high IGF-I) and concordantly normalized GH and IGF-I levels (controlled). The upper part shows the distribution when using glucose-suppressed nadir GH levels, and the lower part shows the distribution when using fasting GH levels. Panel (C) Mean $\pm$ s.e. serum levels of GH and IGF-I (insert) at baseline and after 12 months during an OGTT among patients with increased SA dose. Panels (D) The distribution (%) into the same categories as defined in panel (B) of the SA patients undergoing SA dose increase at baseline and after 12 months.

The median Sandostatin LAR doses (mg/4 week) were increased from 20 (range 7–40) to 40 (range 20–50) and from 20 to 30 (range 20–40) in the GH target group and the IGF-I target group, respectively. Significantly, more patients in the GH group (20 vs 8, $P=0.02$) were increased with a significantly higher dose ($P=0.02$) compared to the IGF group (Fig. 1).

GH_{nadir} (μ g/L) as well as IGF-I (μ g/L) decreased in response to SA dose increase in both groups ((GH group: GH_{nadir} from 0.9 ± 0.13 to 0.7 ± 0.10 , $P=0.01$; IGF-I from 179 ± 14 to 148 ± 13 , $P=0.02$); (IGF group: GH_{nadir} from 1.2 ± 0.3 to 0.7 ± 0.2 , $P<0.01$; IGF-I from 245 ± 24 to 224 ± 24 , $P=0.22$)) (Fig. 2C). This translated into changes in the disease control classification with significantly more patients achieving concordant controlled values, such that 5 patients in the GH group and 2 patients in the IGF-I group changed from uncontrolled to controlled (Fig. 2D).

The OGTT-induced stimulation of insulin secretion was blunted in SA patients, and this was associated with less-suppressed FFA levels and higher glucose levels

(Fig. 3). These SA effects became further pronounced in the subgroup of patients, who underwent SA dose increase. AUC_{insulin} correlated positively with serum IGF-I in surgery patients, but not in SA patients (surgery: $r=0.42$, $P<0.01$; SA: $r=0.003$, $P=0.67$) (Fig. 4).

Spontaneous variation with time in serum GH and IGF levels among controlled patients

Fifty-six patients, including the entire surgery group ($n=23$) and 33 SA patients, did not undergo any change in acromegaly treatment during the study period. The circulating GH pattern did not change significantly between baseline and 12 months in either of these groups (Fig. 5). Likewise, no differences were recorded when comparing GH_{nadir} or IGF-I within the two groups at baseline and 12 months ((Surgery: GH_{nadir}: 0.33 ± 0.06 vs 0.27 ± 0.05 , $P=0.10$; IGF-I: 147 ± 10 vs 144 ± 9 , $P=0.63$); (SA: GH_{nadir}: 0.42 ± 0.07 vs 0.45 ± 0.07 , $P=0.48$; IGF-I: 153 ± 8 vs 156 ± 9 , $P=0.70$)). Moreover, significant positive correlations between GH_{nadir} at baseline and

Figure 3

Mean $\pm$ s.e. serum levels of insulin (A), Free fatty acid (FFA) (B) and glucose (C) after an oral glucose tolerance test (OGTT) in patients treated with surgery (filled circles) or SA (open circles).

Figure 4

Correlations between IGF-I and AUCinsulin (area under the curve) during an oral glucose tolerance test (OGTT) in patients treated with surgery (filled circles) and somatostatin analogue (SA, open circles). The solid line represents the regression line ($r = 0.42$, $P < 0.01$) for the surgery group. The dashed line represents the regression line for the SA group (NS).

12 months, and between IGF-I at baseline and 12 months were recorded in both groups ((Surgery: GH_{nadir} : $r = 0.81$, $P < 0.01$; IGF-I: $r = 0.65$, $P < 0.01$); (SA: GH_{nadir} : $r = 0.81$, $P < 0.01$; IGF-I: $r = 0.31$, $P < 0.01$)). The corresponding correlations between $\text{GH}_{\text{fasting}}$ at baseline and 12 months was weaker in both groups (Surgery: $r = 0.08$, $P = 0.18$; SA: $r = 0.60$, $P < 0.01$).

QoL

The patients at baseline reported only moderate complaints as judged by AcroQoL and PASQ with no significant differences between the two patient groups (surgery vs SA). Moreover, no consistent differences were recorded when comparing the changes in scores between baseline and 12 months in either group. Likewise, when comparing the scores between the SA group, who underwent a dose increase and the SA group, who continued on the same dose, no significant treatment effects were revealed. However, when comparing the scores obtained at 12 months between these 2 groups, the SA group undergoing a dose increase scored significantly better as regards 3 AcroQoL domains (Table 2).

Figure 5

Baseline vs 12 months GH levels (left panel) and correlations between GH levels (right panel) in surgery patients using GH_{nadir} values (A) and GH_{fasting} values (B), and in SA patients using GH_{nadir} values (C) and GH_{fasting} values (D). The GH values are presented as µg/L.

Discussion

Discordant serum levels of GH and IGF-I are observed in approximately 25% of the patients with acromegaly after treatment in cross-sectional studies (7), but the underlying mechanisms as well as the clinical implications remain unclear. To advance our understanding, we therefore conducted a clinical trial, where SA-treated patients were randomized to being monitored and dosed according to either GH or IGF-I for 12 months. The primary outcomes were the distribution of discordant GH and IGF-I values and disease-specific QoL as a function of time and treatment. In addition, we aimed to evaluate the utility of OGTT and assessed the spontaneous variation in biochemical control with time. The main findings of our study were as follows: (1) discordant values in terms of

high GH levels are prevalent in SA-treated patients and more so if applying OGTT-based levels; (2) targeting discordant levels of either GH or IGF-I translates into SA dose increase and improved biochemical control; (3) QoL among the patients was only mildly impaired at baseline and did not change consistently with either time or treatment.

The occurrence of discordant GH and IGF-I levels is a challenge since measurement of both peptides is recommended for the diagnosis and as biochemical endpoints (6). Numerous factors may potentially determine this phenomenon including analytical variation (e.g. assay sensitivity), test conditions (e.g. fasting vs glucose-suppressed GH levels and GH threshold definitions), acromegaly treatment modalities (surgery vs medical treatment), concomitant disease and medication (e.g. diabetes mellitus, liver disease, oestrogen treatment), GH receptor polymorphism (17), age, gender and body composition (18). Probably, the two most critical determinants are GH assay sensitivity and GH threshold definitions, which to some extent are interdependent (7). Lowering of the GH threshold with the availability of ultrasensitive assays will invariably increase the proportion of patients with 'high' GH not least bearing in mind that the 95% percentile GH_{nadir} value in healthy subjects ranges between 0.07 and 0.37 µg/L with modern assays (8). Current guidelines suggest a random GH < 1 µg/L as a pragmatic compromise since this threshold value is associated with reduced mortality in epidemiological surveys (6). It is also recommended to maintain the same GH and IGF-I assays throughout management (6) as in the present study, where we also used state-of-the-art GH and IGF-I assays (19). Our cut-off levels were based on data from a dedicated in-house reference cohort, which was relatively small but had the advantage of providing concurrent measurements of GH and IGF-I in the same individual.

Our observation of high GH levels as the most prevalent discordance is in agreement with some (10) but not all studies (7, 18). It is, however, problematic to compare discordant values between studies due to pronounced heterogeneity as regards patient populations, GH assays and threshold definitions. As an example, a recent meta-analysis reports that discordance during SA treatment mainly comprises high IGF-I, which, however, can be attributed to the use of high GH thresholds (7). The percentage of discordant results at baseline in our study ranged between 30 and 70%, which is quite large and mainly reflects our selection of low and gender-specific GH thresholds.

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Table 2 Quality of life questionnaire data presented as median (range).

Questionnaires	Surgical treatment†	SA treatment	Unchanged SA treatment		Increased SA treatment	
			Baseline	12 months	Baseline	12 months
AcroQoL (%)						
Global	77 (46–92)	74 (49–95)	74 (49–95)	71 (51–96)	78 (51–95)	79 (50–95)*
Physical	78 (45–100)	73 (38–95)	65 (38–95)	65 (33–100)	76 (43–95)*	78 (43–100)*
Psychological	77 (44–90)	76 (47–97)	74 (47–97)	71 (49–94)	81 (53–94)	78 (51–99)
Personal relationships	86 (43–100)	86 (46–100)	80 (49–100)	80 (49–100)	89 (46–100)	89 (54–100)*
Appearance	64 (31–86)	69 (43–100)	66 (43–94)	63 (49–97)	70 (43–100)	69 (37–100)
PASQ						
Headache	0 (0–6)	1 (0–8)	0 (0–7)	1 (0–7)	1 (0–8)	1 (0–8)
Excessive sweating	2.5 (0–7)	1 (0–7)	5 (0–7)	2 (0–7)	1 (0–6)	1 (0–7)
Joint pain	1.5 (0–7)	3 (0–8)	3 (0–8)	4 (0–8)	3 (0–8)	4 (0–6)
Fatigue	4 (0–7)	4 (0–8)	5 (0–8)	4 (0–8)	3.5 (0–8)	4 (0–7)
Soft tissue swelling	0 (0–7)	0.5 (0–8)	1 (0–8)	1 (0–6)	0 (0–5)*	0 (0–6)
Numbness or tingling	1 (0–6)	1 (0–7)	1 (0–7)	2 (0–7)	0.5 (0–7)	1 (0–5)
Overall health status	2 (0–7)	3 (0–10)	4 (0–7)	5 (0–9)	2.5 (0–10)*	3 (0–6)

†Baseline values; *Significant difference between the group of unchanged SA and increased SA treatment, $P < 0.05$.

A conspicuous observation from our study relates to the distinction between $\text{GH}_{\text{fasting}}$ and GH_{nadir} in SA patients. It has previously been reported that discordance in terms of high GH is independent of whether random or glucose-suppressed GH measurements are used (10). Therefore, it was concluded that OGTT-based measurements (GH_{nadir}) offer no additional information. That study, however, was based on quite high GH threshold levels and heterogeneity of assay methods. By contrast, we have previously observed that GH_{nadir} levels are significantly elevated in controlled SA patients compared to surgery patients despite comparable IGF-I and $\text{GH}_{\text{fasting}}$ levels, which were accompanied by worse symptoms and QoL (11). We have also reported that SA patients exhibit elevated GH_{nadir} levels in response to both OGTT and mixed meals as compared to controlled surgery patients carefully matched for IGF-I and gender (12). The reason why GH_{nadir} levels are elevated in SA patients in the presence of controlled IGF-I levels is not fully clarified. Suppression of GH in response to glucose is assumed to involve stimulation of hypothalamic somatostatin secretion (20), and this is likely to be perturbed in SA patients whose GH levels mainly originate from tumourous production. More importantly, it is well known that hepatic IGF-I production also depends on portal insulin stimulation, which is suppressed during SA treatment (21). It is also reported that somatostatin may directly suppress hepatic IGF-I production (22). It is therefore plausible that serum IGF-I levels in SA patients not only reflect acromegaly disease activity, but are also the result of a GH-independent hepatic IGF-I suppression. This is potentially important when considering that circulating IGF-I only accounts for a limited part of the overall effect of GH (23).

The observation that experimental SA dose escalation targeted according to elevated levels of either GH or IGF-I results in significant changes in biochemical disease activity is new. It was interesting that GH and IGF-I decreased in both groups, which implies that discordance is a dynamic phenomenon, which depends on SA dose. At the same time, the degree of discordance remained relatively constant with time in surgery patients and in SA patients not undergoing a dose increase. The timing of SA injections relative to the GH profiles was not fixed in our study, which is a source of potential pre-analytical variation, but it is unlikely to bias the results.

Thus, based on our biochemical endpoints, we suggest that a substantial proportion of SA patients are under dosed. This is in indirect accordance with recent observations from randomized trials that a surprisingly large proportion of SA patients fail to achieve biochemical

control (24, 25). On the other hand, we did not detect robust differences in symptom scores or disease-specific QoL between the different groups as a function of either time or treatment. This is in contrast with our observation from a cross-sectional study in which symptom relief was superior in patients controlled by surgery as compared to SA treatment despite comparable and controlled IGF-I levels (11). The latter observation is compatible with the literature (26). In general, the patients in our trial performed well as regards QoL and symptoms already at baseline, and the number of patients undergoing SA dose escalation was relatively low, which may be an explanation. It remains to be tested if a more prolonged study period will translate into detectable changes in QoL or other non-biochemical endpoints.

Our observations on insulin, FFA and glucose levels during the OGTT are in accordance with previous studies (11, 12, 13) and reflect the suppressive effects of SA on insulin secretion. It is also noteworthy that a positive correlation between insulin AUC during OGTT and IGF-I was recorded only in surgery patients, which indirectly supports a suppressive effect of SA on insulin-induced hepatic IGF-I. The clinical implications of this insulin suppression on glucose homeostasis are uncertain, since overt glucose intolerance appears to be a relatively rare occurrence during SA treatment (27).

In conclusion, elevated GH levels in the presence of controlled IGF-I levels are prevalent in SA-treated patients and this becomes accentuated when applying GH_{nadir} levels. Unbiased SA dose escalation is associated with an increased proportion of concordantly controlled patients. Even though an improvement in QoL was not detected in our study, we suggest the possibility that biochemical control of disease activity in patients with acromegaly includes assessment of GH levels during glucose suppression also in SA patients.

Declaration of interest

J O L J has received grants and lecture fees from Pfizer, IPSEN and Novartis. J D has received lecture fees from Novartis, Pfizer and IPSEN. U F R has received lecture fees and travel grants from Novartis, Pfizer and IPSEN and is a Member of Pfizer's KIMS advisory Board.

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References

- 1 Dal J, Feldt-Rasmussen U, Andersen M, Kristensen L, Laurberg P, Pedersen L, Dekkers OM, Sørensen HT & Jørgensen JOL. Acromegaly

- incidence, prevalence, complications and long-term prognosis: a nationwide cohort study. *European Journal of Endocrinology* 2016 **175** 181–190. (<https://doi.org/10.1530/EJE-16-0117>)
- 2 Dekkers OM, Biermasz NR, Pereira AM, Romijn JA & Vandenbroucke JP. Mortality in acromegaly: a metaanalysis. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 61–67. (<https://doi.org/10.1210/jc.2007-1191>)
- 3 Holdaway IM, Bolland MJ & Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *European Journal of Endocrinology/European Federation of Endocrine Societies* 2008 **159** 89–95. (<https://doi.org/10.1530/EJE-08-0267>)
- 4 Nomikos P, Buchfelder M & Fahlbusch R. The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. *European Journal of Endocrinology* 2005 **152** 379–387. (<https://doi.org/10.1530/eje.1.01863>)
- 5 Freda PU, Katznelson L, Lely Van Der AJ, Reyes CM, Zhao S & Rabinowitz D. Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4465–4473. (<https://doi.org/10.1210/jc.2005-0260>)
- 6 Katznelson L, Laws ER, Melmed S, Molitch ME, Murad MH, Utz A & Wass JAH. Acromegaly: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 3933–3951. (<https://doi.org/10.1210/jc.2014-2700>)
- 7 Kanakis GA, Chrisoulidou A, Bargiota A, Efsthadiadou ZA, Papanastasiou L, Theodoropoulou A, Tigas SK, Vassiliadi DA, Tsagarakis S & Alevizaki M. The ongoing challenge of discrepant growth hormone and insulin-like growth factor I results in the evaluation of treated acromegalic patients: a systematic review and meta-analysis. *Clinical Endocrinology* 2016 **85** 681–688. (<https://doi.org/10.1111/cen.13129>)
- 8 Arafat AM, Möhlig M, Weickert MO, Perschel FH, Purschwitz J, Spranger J, Strasburger CJ, Schöfl C & Pfeiffer AFH. Growth hormone response during oral glucose tolerance test: the impact of assay method on the estimation of reference values in patients with acromegaly and in healthy controls, and the role of gender, age, and body mass index. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1254–1262. (<https://doi.org/10.1210/jc.2007-2084>)
- 9 Freda PU. Significance of 'abnormal' nadir growth hormone levels after oral glucose in postoperative patients with acromegaly in remission with normal insulin-like growth factor-I levels. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 495–500. (<https://doi.org/10.1210/jc.2003-031316>)
- 10 Carmichael JD, Bonert VS, Mirocha JM & Melmed S. The utility of oral glucose tolerance testing for diagnosis and assessment of treatment outcomes in 166 patients with acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 523–527. (<https://doi.org/10.1210/jc.2008-1371>)
- 11 Ruback KZ, Madsen M, Andreassen CM, Fisker S, Frystyk J & Jørgensen JOL. Conventional and novel biomarkers of treatment outcome in patients with acromegaly: discordant results after somatostatin analog treatment compared with surgery. *European Journal of Endocrinology* 2010 **163** 717–726. (<https://doi.org/10.1530/EJE-10-0640>)
- 12 Christiansen Arlien-Søborg M, Trolle C, Alvarson E, Bæk A, Dal J & Jørgensen JOL. Biochemical assessment of disease control in acromegaly: reappraisal of the glucose suppression test in somatostatin analogue (SA) treated patients. *Endocrine* 2017 **56** 589–594. (<https://doi.org/10.1007/s12020-017-1258-9>)
- 13 Dal J, Høyer KL, Pedersen SB, Magnusson NE, Bjerring P, Frystyk J, Møller N, Jessen N & Jørgensen JOL. Growth hormone and insulin signaling in acromegaly: impact of surgery versus somatostatin analog treatment. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 3716–3723. (<https://doi.org/10.1210/jc.2016-1806>)
- 14 Webb SM, Prieto L, Badia X, Albareda M, Catalá M, Gaztambide S, Lucas T, Páramo C, Picó A, Lucas A *et al.* Acromegaly Quality of

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- Life Questionnaire (ACROQOL) a new health-related quality of life questionnaire for patients with acromegaly: development and psychometric properties. *Clinical Endocrinology* 2002 **57** 251–258. (<https://doi.org/10.1046/j.1365-2265.2002.01597.x>)
- 15 Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, Lely Van Der AJ, Dimaraki EV, Stewart PM, Friend KE, Vance ML *et al.* Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *New England Journal of Medicine* 2000 **342** 1171–1177. (<https://doi.org/10.1056/NEJM200004203421604>)
 - 16 LelyVan Der AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klibanski A, Herman-Bonert V, Melmed S, Vance ML *et al.* Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 2001 **358** 1754–1759. ([https://doi.org/10.1016/S0140-6736\(01\)06844-1](https://doi.org/10.1016/S0140-6736(01)06844-1))
 - 17 Bianchi A, Giustina A, Cimino V, Pola R, Angelini F, Pontecorvi A & De Marinis L. Influence of growth hormone receptor d3 and full-length isoforms on biochemical treatment outcomes in acromegaly. *Journal of Clinical Endocrinology and Metabolism* **2009** 94 2015–2022.
 - 18 Alexopoulou O, Bex M, Abs R, T'Sjoen G, Velkeniers B & Maiter D. Divergence between growth hormone and insulin-like growth factor-I concentrations in the follow-up of acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1324–1330. (<https://doi.org/10.1210/jc.2007-2104>)
 - 19 Clemmons DR. Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. *Clinical Chemistry* 2011 **57** 555–559. (<https://doi.org/10.1373/clinchem.2010.150631>)
 - 20 Giustina A & Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. *Endocrine Reviews* 1998 **19** 717–797. (<https://doi.org/10.1210/edrv.19.6.0353>)
 - 21 Neggers SJ, Kopchick JJ, Jørgensen JOL & Lely Van Der AJ. Hypothesis: extra-hepatic acromegaly: a new paradigm? *European Journal of Endocrinology/European Federation of Endocrine Societies* 2011 **164** 11–16. (<https://doi.org/10.1530/EJE-10-0969>)
 - 22 Murray RD, Kim K, Ren SG, Chelly M, Umehara Y & Melmed S. Central and peripheral actions of somatostatin on the growth hormone-IGF-I axis. *Journal of Clinical Investigation* 2004 **114** 349–356. (<https://doi.org/10.1172/JCI19933>)
 - 23 Roith D Le. The insulin-like growth factor system. *Experimental Diabetes Research* 2003 **4** 205–212. (<https://doi.org/10.1155/EDR.2003.205>)
 - 24 Shanik MH, Cao PD & Ludlam WH. Historical response rates of somatostatin analogues in the treatment of acromegaly: a systematic review. *Endocrine Practice* 2016 **22** 350–356. (<https://doi.org/10.4158/EP15913.RA>)
 - 25 Gadelha MR, Bronstein MD, Brue T, Coculescu M, Fleseriu M, Guitelman M, Pronin V, Raverot G, Shimon I, Lievre KK *et al.* Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. *Lancet: Diabetes and Endocrinology* 2014 **2** 875–884. ([https://doi.org/10.1016/S2213-8587\(14\)70169-X](https://doi.org/10.1016/S2213-8587(14)70169-X))
 - 26 Yoshida K, Fukuoka H, Matsumoto R, Bando H, Suda K, Nishizawa H, Iguchi G, Ogawa W, Webb SM & Takahashi Y. The quality of life in acromegalic patients with biochemical remission by surgery alone is superior to that in those with pharmaceutical therapy without radiotherapy, using the newly developed Japanese version of the AcroQoL. *Pituitary* 2015 **18** 876–883. (<https://doi.org/10.1007/s11102-015-0665-2>)
 - 27 Mazziotti G, Floriani I, Bonadonna S, Torri V, Chanson P & Giustina A. Effects of somatostatin analogs on glucose homeostasis: a metaanalysis of acromegaly studies. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1500–1508. (<https://doi.org/10.1210/jc.2008-2332>)

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