Effects of high-dose octreotide LAR on glucose metabolism in patients with acromegaly inadequately controlled by conventional somatostatin analog therapy

Gherardo Mazzotti, Teresa Porcelli, Fausto Bogazzi1, Giovanna Bugari2, Salvatore Cannavò3, Annamaria Colao4, Renato Cozzi5, Laura De Marinis6, Ettore degli Uberti7, Silvia Grottoli8, Francesco Minuto9, Marcella Montini10, Maurizio Spinello11 and Andrea Giustina

Abstract

Objective: In this study, the effect of high-dose octreotide LAR on glucose metabolism in patients with acromegaly was investigated.

Design: A post-hoc analysis of a clinical trial enrolling 26 patients with acromegaly not controlled by standard maximal somatostatin analog (SSAs) dose and randomized to receive high-dose (60 mg/28 days) or high-frequency (30 mg/21 days) octreotide i.m. injection (octreotide LAR) for 6 months.

Methods: Glucose metabolic status was defined as worsened when a progression from normoglycemia to impaired fasting glucose (IFG) or from IFG to diabetes occurred or when an increase of HbAlc by at least 0.5% was demonstrated. An improvement of glucose metabolism was defined in the presence of a regression from IFG to normoglycemia and/or when HbAlc decreased by at least 0.5%.

Results: Glucose metabolic status remained unchanged in a majority of patients (16/26 patients, 65.3%), worsened in six patients, and improved in four patients. Pre-existing metabolic status did not predict worsening of glucose metabolism, which, conversely, was significantly related to persistent biochemical activity of the disease. In fact, patients with worsened glucose metabolism exhibited a less frequent decrease in serum GH and IGF1 levels, compared with patients with improved or unchanged glucose metabolism (2/6 vs 18/20; \( P<0.01 \)).

Conclusion: An increase in octreotide LAR dose or frequency did not impact on glucose metabolism in most patients. Worsening of glucose metabolic status occurred in close relation with persistently uncontrolled acromegaly.

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Introduction

Acromegaly is a rare disease characterized by increased cardiovascular morbidity and mortality (1). Impaired glucose tolerance and diabetes mellitus are frequent complications, occurring in up to 50% of patients affected by acromegaly, and insulin resistance is an important factor in the development of cardiovascular complications in patients with acromegaly (2–4). The abnormalities of glucose homeostasis are closely associated with growth hormone (GH) hypersecretion, as GH opposes the effects of insulin on carbohydrate metabolism (2–4).

Long-acting somatostatin analogs (SSAs) are effective in the treatment of acromegaly and may correct GH/insulin-like growth factor 1 (IGF1) hypersecretion and control complications in a subset of patients (2, 3, 5–7). However, the activity of SSAs on several peripheral tissues can also cause undesired effects. In particular, SSAs may induce abnormalities of glucose metabolism due to inhibition of insulin secretion (8, 9). As study results to date have been equivocal, we recently performed a meta-analysis to assess the effects of SSAs on glucose metabolism. This analysis demonstrated that SSAs, when administered at conventional...
Materials and methods

This post-hoc analysis was performed on 26 patients with persistently uncontrolled acromegaly under maximal conventional SSA doses, who had been enrolled in a prospective multicenter, randomized, controlled, open-label study, the results of which have been published recently (11). The protocol was approved by the ethical committee of the Principal Investigator (A G: ethical committee of Spedali Civili di Brescia on behalf of the National Health Authority) and by all local ethical committees of each participating center. All patients provided written informed consent to participate in the study. The study was pre-registered at ClinicalTrials.gov: registration number: NCT00372697. The inclusion and exclusion criteria are detailed in the original publication (11).

Patients were randomized to receive octreotide LAR 30 mg administered every 21 days for 6 months (high-frequency group) or octreotide LAR 60 mg administered every 28 days for 6 months (high-dose group). Octreotide LAR 60 mg was administered as two 30 mg injections. The primary outcome measures were mean change in IGF1 and GH serum concentrations from baseline to month 6. The secondary outcome measures were the proportion of patients achieving IGF1 reduction ≥20% (to limit the confounding effect of assay variability), IGF1 normalization (according to pre-specified normal ranges for age), clinically relevant tumor shrinkage (tumor volume decrease of ≥20% versus baseline), and safety and tolerability evaluations. For the purpose of this post-hoc analysis, we analyzed the biochemical parameters of glucose homeostasis, which were collected during the study (i.e. serum glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), and fasting plasma insulin (FPI)) measured at enrollment and after 6 months of treatment. Patients were characterized as having diabetes mellitus if FPG levels were ≥126 mg/dl or if they were on active antidiabetic treatments (12). Impaired fasting glucose (IFG) was defined if FPG fell between 100 and 125 mg/dl (12). Patients were defined normoglycemic if FPG was <100 mg/dl and HbA1c values were ≤6% (12). Glucose metabolism was defined as worsened during high-dose or high-frequency octreotide LAR therapy when a progression from normoglycemia to IFG or from IFG to diabetes occurred or when an increase of HbA1c by at least 0.5% was demonstrated. An improvement in glucose metabolism was defined by the presence of a regression from IFG to normal glucose levels and/or when HbA1c decreased by at least 0.5%.

Statistical analysis

Data are expressed as median and range. Paired and unpaired data were compared using Wilcoxon’s and Mann–Whitney’s U tests respectively. Multiple comparisons were made by Friedman’s and Kruskal–Wallis’ tests, with post-hoc Bonferroni’s correction. Fisher’s exact test was used for unpaired comparison of proportions. Repeated frequencies were compared via the McNemar’s test. Pearson’s coefficient was used to assess correlations. To test the independent effects of FPI and GH/IGF1 changes on outcome of glucose metabolism during octreotide LAR treatment, the partial correlation coefficient was calculated. Statistical significance was considered to be P < 0.05.

Results

At the study entry (i.e. under conventional maximal SSA dose regimens), 7 patients (26.9%) had diabetes mellitus (three treated with metformin, one with insulin, and three on diet alone). 8 patients (30.8%) had IFG, whereas 11 patients were normoglycemic (Table 1). No significant differences in the prevalence of diabetes mellitus (33.3 vs 18.2%, P = 0.39) or IFG (26.7% vs 36.4%; P = 0.60) were observed in the high-frequency versus high-dose group respectively. In patients receiving high-dose octreotide, a significantly greater number of patients (10 out of 11, 91%) achieved a reduction (of any magnitude) in serum IGF1 concentration at 6 months than those in the high-frequency group (8 out of 15, 53%; P < 0.05) (Table 2). In the high-dose group, the median serum IGF1 concentration at month 6 was significantly lower (P = 0.02) than baseline. The percentage GH and IGF1 changes at the end of the study versus baseline were statistically significant in the high-dose group (−28 and −27% for GH and IGF1 respectively; P < 0.05 for both values), but not in the high-frequency group (+6 and −5% for GH and IGF1 respectively; P > 0.05 for both values).

According to the criteria reported in the Materials and Methods section, glucose metabolism remained unchanged in the majority of patients (16/26 patients, 65.3%), whereas changes in FPG and HbA1c were
observed in only ten patients (six worsened and four improved). At the study end, eight patients (30.8%) had diabetes mellitus ($P = 0.32$ versus baseline), and eight patients (30.8%) had IFG (NS versus baseline). No significant ($P = 0.62$) difference in the outcome of glucose metabolism was observed between the high-dose (Table 2) and high-frequency (Table 3) groups.

Pooling together data from high-dose and high-frequency groups, the rate of worsening in glucose metabolism was comparable between patients with pre-existing diabetes mellitus (2 out of 7, 28.6%) and those with IFG (2 out of 8, 25.0%) or normoglycemic (2 out of 11, 18.2%), whereas the improvement in glucose metabolism was more frequently ($P = 0.02$) observed in patients with pre-existing diabetes (3 out of 7, 42.9%) as compared to the other two groups of patients (0 and 9.1% for IFG and normoglycemic respectively).

Percent changes in GH and IGF1 values at the end of the study versus baseline were significantly different in the three groups. In fact, in six patients with worsened glucose metabolism, an increase in GH and IGF1 levels was observed, whereas GH and IGF1 decreased in patients whose glucose metabolism improved or did not change (Fig. 1A and B). Analysis of individual outcomes demonstrated that patients with worsened glucose metabolism exhibited a less frequent decrease (of any magnitude) in serum GH and IGF1 levels, compared with the other patients whose glucose metabolism either improved or did not change (2/6 vs 18/20; $P = 0.01$).

High-dose and high-frequency octreotide LAR treatment caused an increase in FPI (range from $1.2$ to $158.6\%$) in 14 patients and a decrease in FPI (range from $73.1$ to $20.2\%$) in the remaining 12 patients (Tables 2 and 3). The decrease in FPI occurred more frequently ($P = 0.03$) in patients with worsening in glucose metabolism (5 out 6, 83.3%) as compared to patients whose glucose metabolism improved or did not change (7 out of 20, 35.0%).

Reduction in FPI ($r = -0.59$; $P = 0.003$) and increase in GH ($r = 0.44$; $P = 0.03$) and IGF1 values ($r = 0.51$; $P = 0.008$), but not baseline glucose metabolism

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Table 1 Baseline demographical and clinical data of 26 patients with acromegaly randomized to high-dose or high-frequency octreotide LAR.

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<th>Duration (months)</th>
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<th>IGF1 ($\mu$g/l)</th>
<th>FPG (mg/dl)</th>
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M, male; F, female; LAN SR, lanreotide-sustained release; LAN ER, lanreotide-extended release; OCT, octreotide LAR; IGF1, insulin-like growth factor 1; FPG, fasting plasma glucose; FPI, fasting plasma insulin; IFG, impaired fasting glucose.

aDiabetes treated with metformin.
bDiabetes treated with diet alone.
cDiabetes treated with insulin.

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(r: 0.1; P = 0.63), baseline GH (r: -0.06; P = 0.76), and IGF1 (r: 0.21; P = 0.30) values, were significant predictors of worsened glucose homeostasis. The impact of increased serum IGF1 and/or GH values on worsened glucose metabolism remained significant even after correction for changes in FPI (r = 0.48; P = 0.01). Worsening of glucose metabolism during high-dose and high-frequency octreotide LAR was not significantly correlated with duration of conventional SSAs treatment prior to randomization (r: 0.1; P = 0.6).

**Discussion**

This post-hoc analysis of the results of a recently published randomized clinical trial (11) shows that an increase in octreotide LAR dose or frequency results in worsened glucose metabolism in ~25% of this population of patients with acromegaly poorly controlled by conventional SSA dose regimens. The observed worsening in glucose metabolism was correlated with decreased FPI at the study end, as well as persistently high serum GH and IGF1 values.

Abnormalities of glucose metabolism frequently occur in patients with acromegaly as a direct result of GH hypersecretion on glucose and lipid metabolism (2). Patients with acromegaly are insulin resistant either at the liver or at the peripheral level, displaying hyperinsulinemia and increased glucose turnover in the basal and post-absorptive states. SSA therapy has been shown to impair glucose metabolism in patients with acromegaly by inhibition of insulin secretion (13–15). However, previous results of studies investigating this issue have been controversial, and a meta-analysis of published data suggests that SSA treatment may have only a marginal impact on glucose metabolism in...
patients with acromegaly treated with conventional dosing regimens (10).

In a recent prospective, randomized study, we demonstrated that high-dose octreotide LAR (60 mg every 4 weeks) may provide beneficial effects in terms of an IGF1 decrease and normalization in patients with acromegaly who were inadequately controlled by conventional SSA dosing regimens, the compliance to which was assessed on the basis of clinical judgment in each participating center (11). At these high doses, octreotide LAR may produce biological effects that are different from those occurring at lower doses. In particular, it was hypothesized that high-dose octreotide LAR could exert its activity via receptor subtypes other than sst2, such as sst5, for which octreotide has a lower affinity (11). It is noteworthy that the sst5 receptor is involved in the regulation of insulin production by pancreatic β-cells, with potential negative effects mediated by SSA-dependent receptor activation (16). Indeed, it is still unclear whether inhibition of insulin secretion may result in impaired glucose metabolism in patients with insulin resistance, as is frequently the case in patients with acromegaly (10, 16–19).

An interesting finding of this analysis was the association between worsening in glucose metabolism and persistence of elevated serum GH and IGF1 values during high-dose and high-frequency octreotide LAR treatment. This association appeared to be independent of baseline metabolic condition and variation in insulin secretion during treatment. This finding is consistent with the hypothesis that GH hypersecretion is the main determinant of abnormal glucose metabolism in both untreated and treated acromegaly (3). Moreover, high-dose and high-frequency octreotide LAR showed comparable risk in terms of glucose metabolism impairment. It is noteworthy that patients treated with high-dose octreotide LAR received higher cumulative doses than patients treated with the high-frequency regimen and demonstrated better biochemical control (11). These findings confirm that impairment of glucose metabolism may not be correlated with the dose of SSAs, but may be dependent on the biochemical control of acromegaly.

Our study has some limitations. First of all, our study was not aimed to assess the overall effects of SSAs on glucose metabolism in acromegaly. No data were collected in this trial on the glucose metabolism status prior to the beginning of conventional SSA treatment. Therefore, no comparisons can be made between the glycometabolic effects of conventional versus high-dose SSA treatment. Moreover, the length of treatment with conventional doses was generally much longer than the duration of the high-dose trial making difficult any comparisons between the two schedules. Furthermore, glycometabolic status of our patients at the study entry was that expected based on epidemiological data (2, 3) as well as on meta-analytic evaluations suggesting a minor clinical impact of conventional somatostatin schedule on glucose metabolism (10). It cannot be excluded that any side effect of SSA on glucose metabolism had been established in sensitive patients during the first period of SSA treatment, such that an increase in dose as employed in the present paper would be less likely to promote additional deterioration (20, 21). In fact, this trial included only patients partially sensitive to SSAs. In terms of evolution of glucose metabolism, this may be a selection bias since patients resistant to SSAs, possibly with significantly altered glucose metabolism, may have been switched to other treatment modalities before enrollment (22). However, since these patients were all not controlled by SSAs,
it could be argued that this population represents a clinically relevant model to study the potential negative glycometabolic effects of high-dose SSAs, which is consistent with the hypothesis that these patients could be assumed to be at high risk of developing abnormalities in glucose homeostasis (10). Glucose homeostasis was investigated by assaying FPG and HbAlc, but information on the potential effects of high-dose and high-frequency octreotide LAR on plasma glucose during an oral glucose tolerance test was not available as this is not routinely assessed in the follow-up of acromegaly during SSA treatment (23). There is evidence that an impaired oral glucose tolerance test may occur more frequently than impaired FPG during SSA treatment (10). This limitation is partially compensated by the fact that in our study, we reported the outcome of HbAlc, which is an integrated measure of glucose homeostasis (12). Furthermore, criteria characterizing the worsening in glucose metabolism were arbitrarily defined, but were sufficiently strict to include subjects with changes of minor clinical significance in FPG and HbAlc. In fact, only two of the 26 patients enrolled in the trial had an increase in HbAlc ≥ 1% at 6 months. Finally, changes in glycometabolic control patients with acromegaly and diabetes may be influenced by other variables independent of GH/IGF1 levels, such as adherence to treatment, increase in body weight, and changes in diet.

Besides these limitations, our analysis may have interesting clinical implications. In particular, these data strengthen the concept that high-dose octreotide LAR is substantially well tolerated in acromegaly and may be a feasible therapeutic option even in the presence of pre-existing alterations of glucose metabolism. Further studies are needed to clarify the cost effectiveness of high-dose octreotide LAR as compared to pegvisomant, a GH receptor antagonist, which appears to have no negative effects on glucose homeostasis and can be used to treat patients with acromegaly who are not controlled with conventional SSA regimens (24–28). Our study also shows that, even if rare, a clinically significant worsening in glucose metabolism may occur with high-dose or high-frequency octreotide therapy, highlighting the need to monitor glycometabolic homeostasis during intensive regimens of octreotide LAR.

In conclusion, the increase in octreotide LAR dose or frequency did not have a detrimental effect on glucose metabolism in the majority of patients included in the trial. In the minority of patients who experienced impaired glucose homeostasis, this event occurred more frequently in those with persistently uncontrolled acromegaly, and it could not be predicted based on pre-existing abnormalities in glucose metabolism.

Declaration of interest
Prof. A Giustina is a consultant for Ipsen, Italfarmaco, and Novartis, and has received lecture fees from Pfizer, Ipsen, and Italfarmaco. Prof. A Colao has received research grant support from IPSEN, Italfarmaco, Novartis, and Pfizer; has received speaker fees from IPSEN, Italfarmaco, and Novartis; and has served on advisory boards for IPSEN and Novartis. M Spinello is employee of Novartis Farma, Italy. The remaining authors have no conflicts of interest.

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