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RESEARCH LETTER

Pasireotide versus pituitary surgery: a retrospective analysis of 12 months of treatment in patients with Cushing's disease

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Introduction

Pituitary surgery represents the first-line treatment for most patients with Cushing's disease (CD) [1, 2].

In the case of surgery failure, additional treatment options are required [3–6]. Pasireotide has shown favourable results in the first-line treatment of patients with CD, who are not candidates for surgery or in the second-line when surgery has failed [7–9]. The aim of the current study is to compare the effects of surgery and pasireotide treatment in a cohort of patients with CD, and to evaluate the differences in response rate in terms of hormonal and clinical control, and improvement of metabolic complications.

Materials and methods

This retrospective study analysed data of ten patients (8 F, 2 M; mean age 43.2 ± 11.8 years) with active CD despite a previous surgery, who were treated with pasireotide and 20 gender and age-matched naïve CD patients treated by transsphenoidal surgery.

According to the mean (m) of three urinary free cortisol (UFC) levels, in the pasireotide group 7/10 had mild [mUFC ≥ 1.5 and ≤2 times the upper limit of the normal range (ULN)], 2/10 moderate (mUFC > 2 and ≤5 ULN) and 1/10 had severe (mUFC > 5 ULN) CD. In the surgery group, 10/20 had mild, 6/20 moderate and 4/20 severe CD.

Before treatment with pasireotide, 8/10 patients were diabetic, metformin-treated, while 2/10 patients had normal glucose tolerance. Pasireotide was administered at the dose of 600 µg twice daily, with an increase to 900 µg twice daily, for those patients who did not normalise mUFC levels after 3 months.

The study protocol was approved by the local Ethics Committee and a written informed consent was obtained from all participants included in the study.

Body mass index (BMI) and waist circumference (WC), lipids, HbA1c, glycaemia and insulinaemia fasting and during oral glucose tolerance test were eveluated at baseline and after 12 months of treatment. Insulin secretion was evaluated by HOMA-β, the oral disposition index (DIo) and the area under the curve of insulin ($AUC_{2\text{-h insulin}}$), while insulin sensitivity was assessed by ISI Matsuda [10–12].

To evaluate the difference between surgery and pasireotide treatment in terms of efficacy, the Δ value was calculated as the difference between 12 months of therapy and baseline, for those parameters, which were statistically significant at the *t*-Student.

Insulin, glycaemia and lipids were measured using standard methods (Modular P800, Roche, Milan). HbA1c was determined by high performance liquid chromatography with an ion-exchange resin (Bio-Rad Laboratories, Milan, Italy). Adrenocorticotropic hormone (ACTH) and urinary free cortisol (UFC) were detected by electrochemiluminescence immunoassay (Elecsys, Roche, Milan).

Statistical analysis

The Statistical Packages for Social Science SPSS version 17 (SPSS, Inc.) was used for data analysis. Data were presented as mean ± SD for continuous variables, and rates and

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proportions were calculated for categorical variables. The differences between groups were evaluated with the *t*-Student for quantitative variables and χ^2 for trend for categorical variables. A p value <0.05 was considered statistically significant.

Results

Both surgery and pasireotide treatments resulted in a significant decrease of BMI ($p < 0.001$) and WC ($p < 0.001$ and $p = 0.003$) compared to baseline (Table 1).

A significant decrease in ACTH and mUFC levels was observed both after surgery (both $p < 0.001$) and pasireotide ($p = 0.014$ and $p = 0.001$, respectively) (Table 1).

In the pasireotide group, 8/10 patients normalised mUFC with the dose of 600 µg. Two patients did not normalise mUFC, despite the increase to 900 µg. One of them, who had moderate CD, had a decrease of approximately 60%, while the other one, who had severe CD, had a decrease of about 55% compared to baseline. In the surgery group, 2/20 patients, both with moderate disease, did not normalise mUFC levels. Additionally, surgery resulted in a significant decrease in Δ_ACTH ($p = 0.001$) and Δ_mUFC (p 0.019) compared to pasireotide.

When comparing the Δ_mUFC according to the severity of CD, no difference in Δ_mUFC was found between pasireotide and surgery in patients with mild and moderate hypercortisolism. In patients with severe hypercortisolism, surgery proved more effective in reducing mUFC levels than pasireotide ($p = 0.035$), though only one patient treated with pasireotide had severe hypercortisolism. Comparing the Δ_ACTH according to the severity of CD, surgery proved more effective in reducing ACTH levels in patients with mild ($p = 0.019$) and moderate ($p = 0.039$) CD than pasireotide, while no differences were observed in patients with severe disease (data not shown).

A significant reduction in total cholesterol (TC) was observed both after surgery ($p = 0.015$) and pasireotide ($p = 0.012$) (Table 1). Surgery resulted in a significant reduction in LDL-C ($p = 0.045$) and fibrinogen ($p = 0.009$) (Table 1). Conversely, pasireotide was associated with a significant increase in fasting glycaemia ($p = 0.002$), HbA1c ($p = 0.011$) and $AUC_{2h\text{-glycaemia}}$ ($p = 0.007$) concomitant to a significant decrease in fasting insulinaemia ($p = 0.018$), HOMAβ ($p = 0.002$) and $AUC_{2h\text{-insulinaemia}}$

Table 1 Clinical, hormonal, metabolic and clotting parameters, insulin secretion and sensitivity indexes, in patients treated by surgery and with pasireotide at baseline and after 12 months

	Surgery ($N = 20$)			Pasireotide ($N = 10$)		
	Baseline Mean ± SD	12 months Mean ± SD	p	Baseline Mean ± SD	12 months Mean ± SD	p
Clinical parameters						
BMI (Kg/m^2)	29.3 ± 3.9	25.4 ± 3.97	<0.001	38.6 ± 9.8	32.9 ± 8.1	<0.001
WC (cm)	100.5 ± 8.8	93.1 ± 9.09	<0.001	117.3 ± 15.7	110.1 ± 16.1	0.003
Hormonal parameters						
ACTH (pmol/l)	15.9 ± 4.6	5.3 ± 1.7	<0.001	14.8 ± 4.2	11.2 ± 4.6	0.001
mUFC (nmol/24 h)	1049.5 ± 637.2	310.1 ± 206.8	<0.001	683.1 ± 522.1	337.4 ± 254.1	0.001
Metabolic parameters						
TC (mmol/l)	5.57 ± 1.23	4.87 ± 1.24	0.015	5.41 ± 0.94	4.93 ± 0.73	0.012
HDL cholesterol (mmol/l)	1.31 ± 0.32	1.26 ± 0.36	0.699	1.56 ± 0.46	1.57 ± 0.43	0.928
Triglycerides (mmol/l)	1.83 ± 0.87	1.48 ± 0.59	0.169	1.45 ± 0.57	1.25 ± 0.55	0.194
LDL cholesterol (mmol/l)	3.3 ± 1.02	2.78 ± 1.15	0.045	3.17 ± 0.86	2.89 ± 0.74	0.214
Atherogenic index	0.11 ± 0.3	0.05 ± 0.31	0.619	−0.04 ± 0.3	−0.12 ± 0.29	0.179
Fasting glycaemia (mmol/l)	5.26 ± 1.99	4.79 ± 1.59	0.215	5.79 ± 1.1	7.19 ± 1.77	0.002
HbA1c (mmol/mol)	44.1 ± 11.1	44.9 ± 12.5	0.780	42.9 ± 5.8	50.2 ± 10.8	0.011
AUC $_{2h\ glycaemia}$ (mmol/l 120 min)	1255.6 ± 389.9	901.8 ± 212.7	0.146	944.5 ± 461	802.6 ± 430.9	0.007
Insulin secretion indexes						
Fasting insulinaemia (UI/ml)	13.3 ± 8.16	7.37 ± 3.43	0.056	18.5 ± 10.1	9.1 ± 5.34	0.018
HOMA β	153.1 ± 97.4	112.7 ± 45.1	0.233	141.18 ± 61.6	63.1 ± 36.1	0.002
DIo	1.05 ± 1.41	4.84 ± 4.88	0.358	2.29 ± 0.75	−0.34 ± 4.8	0.405
AUC $_{2h\ insulinaemia}$ (microU/ml 120 min)	9218.1 ± 6342.2	8805.1 ± 3992.7	0.907	9059.2 ± 3523.8	5893 ± 5418.1	0.047
Insulin sensitivity indexes						
ISI Matsuda	2.48 ± 0.54	6.71 ± 5.12	0.324	3.73 ± 1.08	8.67 ± 4.65	0.076
Clotting parameters						
INR	0.85 ± 0.19	0.98 ± 0.05	0.103	0.91 ± 0.07	0.92 ± 0.05	0.556
aPTT (sec)	25.9 ± 4.73	29.1 ± 2.15	0.075	27.1 ± 5.26	25.6 ± 4.75	0.177
Fibrinogen (mg/dl)	356.4 ± 71.1	248.8 ± 71.5	0.009	355.4 ± 111.8	326.5 ± 42.58	0.285

($p = 0.047$), without a significant effect on DIo and ISI-Matsuda (Table 1).

Discussion

The current study shows that 12 months of both pasireotide treatment and surgery result in effective control of hormonal and clinical parameters in patients with CD. However, pasireotide leads to an increase in glycaemic values and a decrease in insulin secretion, without any interference on insulin sensitivity, as already described [13]. The impairment of glucose metabolism in the group of pasireotide was more evident in patients with pre-existing diabetes mellitus, while one patient without pre-existing glucose metabolism defects did not experience hyperglycaemia. This may be related to the interaction of individual factors, such as age, genetic predisposition and lifestyle, and disease-related factors such as duration and degree of hypercortisolism, which may act in favouring diabetes mellitus [14, 15] and consequently may determine more susceptibility to the pasireotide hyperglycaemic effect.

We reported normalisation of mUFC and ACTH levels in 18/20 patients (90%) treated with surgery and in 8/10 (80%) treated with pasireotide. The good control of disease with pasireotide appears to be in disagreement with the results of the phase III study, which reported a 34.2% of full and partial control of disease [5]. However, the phase III study included 78% of patients with moderate to severe CD, while the current study focused especially on patients with mild disease, who might appear as the patients with highest benefit from pasireotide, while only a small number (20%) had moderate disease and only one patient had severe disease. Comparing surgery and pasireotide treatment, surgery proved more effective in reducing mUFC than pasireotide in patients with severe disease and, in reducing ACTH in patients with moderate and severe disease, while no differences between the two treatments, in terms of mUFC and ACTH decrease, were observed in patients with mild CD.

Surgery resulted in a decrease in LDL-C and fibrinogen, while no effect was observed in the pasireotide group, which maybe related to the hyperglycaemic effect [16–18].

As far as we know, this is the first study directly comparing pasireotide and surgery treatments. However, some study limitations should be considered. This study was performed on a small cohort of patients with CD. The period of observation was quite short and the most part of patients treated with pasireotide had mild hypercortisolism.

In conclusion, these preliminary data suggest that pasireotide and surgery are effective in CD control in terms of decrease of visceral obesity and hormonal parameters, which are strong cardiovascular risk factors [19]. Surgery efficacy appears to be comparable with pasireotide in patients with mild hypercortisolism, while it appears to be much stronger in patients with moderate and severe CD. Therefore, further larger studies are required to evaluate the long-term effects of both treatments on hormonal and clinical parameters, especially in patients with severe CD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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