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Endocrine (2014) 46:678–681
DOI 10.1007/s12020-013-0145-2

FELLOWS CORNER

Combined biological therapy with lanreotide autogel and cabergoline in the treatment of MEN-1-related insulinomas

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Received: 3 September 2013 / Accepted: 4 December 2013 / Published online: 3 January 2014
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Abstract Multiple endocrine neoplasia type 1 (MEN1) is a hereditary syndrome associated with the development of many endocrine tumors, involving mainly pituitary, parathyroids, pancreas, although a proliferative state interests all neuroendocrine system. MEN1 pancreatic neuroendocrine tumors (pNETs) are multiples and can secrete different hormones. The therapeutic approach is based on surgery which usually is followed by tumor relapse or persistence unless to be highly aggressive. Biotherapy with somatostatin analogs and dopamine agonists could be of great benefit to manage these patients without altering their life quality. We report a case of a 36-year-old MEN1 man affected with multicentric pNETs associated with insulinoma syndrome. Therapy with symptomatic agents (diazoxide), as well as biotherapy (lanreotide, cabergoline) was started. At 6-month follow-up, symptomatic agents were stopped and disease control was only based on lanreotide plus cabergoline. This combined biotherapy was able to control endocrine syndromes and tumor growth. Subsequently, a safer and selective surgical intervention on pNETs was performed. An excellent response to therapy with lanreotide autogel and cabergoline has been observed in a MEN1 patient with pNETs associated with insulinoma syndrome. The potential synergistic effects of lanreotide autogel and cabergoline on insulin-secreting neuroendocrine tumors are discussed.

Keywords Insulinoma syndrome · MEN1 syndrome · Neuroendocrine tumors · Somatostatin analogs · Dopamine agonists

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary syndrome predisposing to the development of many endocrine and neuroendocrine tumors (NETs) and/or hyperplasia, involving mainly pituitary, parathyroids, and pancreas [1]. In these patients, prognosis is mainly related to the behavior of tumors arising from pancreas [2]. Pancreatic NET (pNET) arising from islet cells may be non-functioning or functioning, with production of active hormones such as gastrin, insulin, vasoactive intestinal polypeptide, glucagon, and somatostatin [3]. Therapeutic approach in pNETs is based on surgery. However, in MEN1 there is a high risk of recurrence even after radical surgery and a considerable risk of morbidity and mortality associated with the surgical management [4, 5].

Somatostatin analogs (SSAs) have been demonstrated to induce symptomatic, biochemical, and antiproliferative effects in well-differentiated NETs [6, 7]. Unfortunately, neither sub-cutaneous nor long-acting slow release SSAs resulted in high rate of clinical and biochemical response in patients with insulin-secreting pNETs [8, 9]. Furthermore,

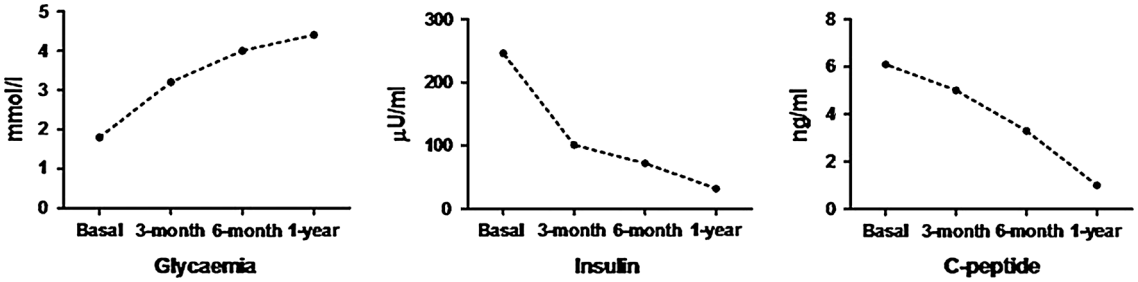

Fig. 1 Hormonal markers of insulinoma (serum glycaemia, insulin, and C-peptide) before and 3, 6, and 12 months after the beginning of treatment. Lanreotide treatment was started at basal, while cabergoline was started at 3 month

response duration is variable and side effects such as a paradoxical impairment of hypoglycemia, due to predominant suppression of contraregulator hormones, may occur [9, 10].

Dopamine agonists (DAs) are effective in controlling tumor growth and hormone secretion in pituitary tumors. DA activity in NETs is hypothesized on the basis of reported expression of dopamine receptors (DR2) in these tumors. Possible synergistic effects of SSAs and DAs could be of great benefit to manage MEN1-related pNETs, either arresting tumor growth or maintaining their unaltered quality of life.

In this case report, we describe a MEN1 man affected by multiple insulin-secreting and nonfunctioning pNETs experiencing an excellent response to the treatment with lanreotide autogel, a long-acting formulation of SSA. Since a concomitant therapy with cabergoline was given for a prolactin (PRL)-secreting pituitary adenoma, the potential synergistic effects of lanreotide autogel and cabergoline on insulinoma are discussed.

Case presentation

A 36-year-old man presented with symptoms of neuroglycopaenia. Physical examination revealed sweating and tachycardia. Biochemical assessment showed hypoglycemia and not suppressed insulin and C-peptide levels (Fig. 1). Fasting test confirmed the clinical diagnosis of insulinoma by revealing an insulin to glycaemia ratio of 0.6 and C-peptide serum concentrations of 6.0 ng/ml in condition of hypoglycemia. To localize the insulin-secreting primary tumor, a contrast-enhanced helical computed tomography (CT) was performed and detected 4 nodules ranging 10–25 mm along head, body, and tail of the pancreas. A complete hormonal and instrumental work-up was performed to characterize the pNETs and to screen for a MEN1 syndrome. High plasma levels of chromogranin A (not shown) and gastrin (>150 pmol/l) were found and associated, at the endoscopy, to an erosive gastro-duodenitis. A pituitary microadenoma was detected by magnetic resonance imaging and characterized by PRL hypersecretion (>3,000 mU/l), while primary hyperparathyroidism (PTH = 15.8 pmol/l) with a mild increase of serum calcium levels (2.6 mmol/l) was associated to a left inferior parathyroid adenoma at cervical Doppler ultrasonography and sestamibi SPECT scintigraphy. A whole body Indium-^{111}-DTPA-Phe1-octreotide scintigraphy (Octreoscan) pointed out a strong uptake corresponding to the greatest pancreatic lesion.

The diagnosis of insulinoma syndrome, Zollinger–Ellison syndrome, microprolactinoma, and primary hyperparathyroidism was made. This picture was consistent with the diagnosis of MEN1 syndrome. To confirm the diagnosis of MEN1, germline mutation in the menin gene was searched as previously described [11]. A novel heterozygote frameshift 335delA mutation in the exon 2 was revealed in this patient.

In order to control the Zollinger–Ellison syndrome, proton pump inhibitor (omeprazole) was prescribed (20 mg twice a day) followed by a rapid improvement of gastric symptoms. One week later, diazoxide (300 mg a day in 3 daily doses) and lanreotide (slow release formulation, 30 mg every 2 weeks) were introduced in the schedule treatment, in order to improve symptoms related to hyperinsulinemia the former and to inhibit gastrin and insulin hypersecretion the latter. A high hydratation regimen plus hydrochlorothiazide (25 mg a day) was recommended to achieve normocalcemia. During the first 3 months of therapy, a decrease of frequency and severity of hypoglycemic events occurred. At the 3-month hormonal follow-up, normalization of gastrin (<25 pmol/l), as well as marked decrease of C-peptide (Fig. 1) with normalization of the insulin to glycemia ratio was observed. No side effects were observed. Therefore, omeprazole treatment was stopped, diazoxide treatment was lowered (150 mg a day divided in 3 daily doses) and lanreotide was given at the dose of 60 mg every 4 weeks. Due to the progressive increase of PRL levels (>4,000 mU/l), a cabergoline schedule treatment was started. At 6-month follow-up, a stable normalization of gastrin levels, a further

decrease of insulin and C-peptide (Fig. 1) and a suppression of PRL levels were observed, allowing to stop diazoxide and to decrease cabergoline doses. At this time, lanreotide autogel 120 mg every 8 weeks was started in place of lanreotide 60 mg every 4 weeks. This hormonal picture remains unchanged at the 12-month follow-up (Fig. 1). These results paralleled the complete disappearance of hypoglycemic events and gastrointestinal disorders. A morphological evaluation of the pNETs was performed 1 year after the beginning of the treatment: compared to basal CT scan, the nodules were stable in size and number. Contrast enhancement of the pNETs, which was high and rapid at baseline, was then scarce after medical therapy.

Due to the complete and stable normalization of symptomatology, as well as the possibility to completely remove pNETs, the patient underwent distal pancreatectomy, tumor enucleation in the pancreatic head and duodenum and locoregional lymph node dissection. Histology and immunohistochemistry for chromogranin A and synaptophysin highlighted a diagnosis of well-differentiated pNET (G1) in a total of 16 nodules (size ranging 3–22 mm). Two insulin-positive pNETs were found in pancreas, while a gastrin-positive tumor was found in duodenum. All lymph nodes were unaffected.

After surgery, the patient recovered rapidly and was discharged without any therapy but cabergoline. Both basal and secretin-stimulated pancreatic hormone values were normal, and neither clinical symptoms nor tumor recurrence was after a 5 year follow-up.

Discussion

Surgery represents the treatment of choice for MEN1-related pNETs with significant benefits in terms of survival. However, this approach for small tumors is still controversial because pNETs < 2 cm seem to have a more indolent behavior. In particular, pNET surgery in MEN1 is associated with a higher risk of complications and mortality, as well as a high rate of recurrence [5].

SSAs represent the gold standard in the treatment of functioning NETs [9]. The PROMID study demonstrated also that octreotide LAR has antiproliferative effects in patients with metastatic NETs of midgut, significantly improving the time to progression as compared to placebo [7]. However, in insulin-secreting pNET, SSAs seem to difficultly control hormone secretion and proliferating activity [12]. In fact, even if SSAs inhibit insulin secretion and activity [13, 14], the SSA-induced inhibition of contraregulatory hormones (glucagon, GH, and IGF-1) may be higher than insulin suppression, resulting in scarce effectiveness in the improvement of hypoglycemia [15]. The inadequate control of insulin secretion by SSAs is likely a consequence of the low expression of SSTR2 and SSTR5 in insulin-secreting pNET, which also explains the low percentage of Octreoscan-positive tumors.

In the current case, a MEN1 patient with multiple pNETs associated with Zollinger–Ellison and insulinoma syndrome, after an initial clinical improvement on SSA, experienced a complete and stable clinical remission on SSA and DA therapy. At CT scan, pNETs were stable, while contrast enhancement was decreased revealing decreased tumor activity [16]. These findings could be imputable to the combined use of biotherapy with SSA and DA, even if it is difficult to exclude that only one of the two drugs was active. In this regard, it was previously reported in literature a case of a patient affected by prolactinoma and metastatic islet cell tumor secreting pancreatic polypeptide (PP), where DAs caused a decrease in PP levels and inhibited liver metastases [17]. Double-staining experiments showed that D2 colocalized with insulin-containing secretory granules and quinpirole, a D2-like receptor agonist, was able to inhibit glucose-stimulated insulin secretion, suggesting a potential implication of D2 on this activity [18]. Besides, it has been demonstrated that D2 are expressed in NET associated with ectopic ACTH syndrome and that cabergoline may be effective in controlling cortisol excess in a subgroup of these patients [19]. In NETs, D2 is frequently expressed in low- and intermediate-grade tumors, but it is to underlined that, in the majority of cases, it is coexpressed with SSTR2 and SSTR5 [20–22]. However, the in vivo efficacy of DA has not well-established yet in NET [22]. In the last years, basic research observations on the interaction of SSTR and DR2, and clinical reports of efficacy of combined SST and DA treatment in pituitary adenomas [23, 24], lead to the concept of creating chimeric molecules combining structural features of both compound classes. SSTR/DR2 chimeric compounds have recently been investigated also in NETs resulting in decreased cell viability in human midgut NET cells [25].

In conclusions, a combined therapy with SSA and DA was associated with complete normalization of a hyperinsulinemic hypoglycemia syndrome and tumor stabilization in a patient with MEN1 pNETs. In patients with insulinoma, particularly if associated with MEN1, SSA, and DA should be taken in account not only to normalize the functional syndrome but also to induce antitumoral effects.

Conflict of interest None.

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