

## CLINICAL STUDY

# Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycemia

Valérie Bernard, Catherine Lombard-Bohas<sup>1</sup>, Marie-Caroline Taquet<sup>2</sup>, François-Xavier Caroli-Bosc<sup>3</sup>, Philippe Ruszniewski<sup>4</sup>, Patricia Niccoli<sup>5</sup>, Rosine Guimbaud<sup>6</sup>, Cécile N Chougnet, Bernard Goichot<sup>2</sup>, Vincent Rohmer<sup>7</sup>, Françoise Borson-Chazot<sup>8</sup>, Eric Baudin for the French Group of Endocrine Tumors

Nuclear Medicine and Endocrine Oncology Unit, Department of Nuclear Medicine and Endocrine Oncology, Gustave Roussy Institute, University Paris Sud-XI, 114 Rue Édouard Vaillant, Villejuif F 94800, France, <sup>1</sup>Department of Oncology, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon F 69003, France, <sup>2</sup>Department of Internal Medicine, Endocrinology and Nutrition, University Hospital of Strasbourg, Strasbourg F 67098, France, <sup>3</sup>Department of Gastroenterology, University Hospital of Angers, Angers F 49933, France, <sup>4</sup>Department of Gastroenterology and Pancreatology, Beaujon Hospital, Clichy la Garenne F 92110, France, <sup>5</sup>Department of Endocrinology, University Hospital of Marseille, Marseille F 13000, France, <sup>6</sup>Department of Oncology, University Hospital of Toulouse, Toulouse F 31059, France, <sup>7</sup>Department of Endocrinology, University Hospital of Angers, Angers F 49933, France and <sup>8</sup>Department of Endocrinology, Hospices Civils de Lyon, University Lyon 1, Fédération d'Endocrinologie du pôle est, Lyon F 69003, France

(Correspondence should be addressed to E Baudin; Email: eric.baudin@igr.fr)

## Abstract

**Background:** Refractory hypoglycemia in patients with metastatic insulinoma is an important cause of morbidity and mortality. Everolimus could be a new therapeutic option.

**Methods:** Within the French Group, we conducted a retrospective, multicentric study of endocrine tumors to evaluate the time to the first recurrence of symptomatic hypoglycemia, after everolimus initiation, in patients with metastatic insulinoma and refractory hypoglycemia. Ongoing hyperglycemic medical options, tumor response, and safety information were recorded.

**Results:** Twelve patients with metastatic insulinoma and refractory hypoglycemia who were treated with everolimus between May 2007 and June 2011 were reviewed. Everolimus (starting dose, 10 mg/day, except in one patient, 5 mg/day) was given after a median of four previous therapeutic lines. Medication aimed at normalizing blood glucose levels in 11 patients. After a median duration of 6.5 months (range 1–35+ months), median time to the first recurrence of symptomatic hypoglycemia was 6.5 months (range 0 to 35+ months). Three patients discontinued everolimus because of cardiac and/or pulmonary adverse events at 1, 1.5, and 7 months after initiation, which led to two deaths. Three patients discontinued everolimus because of tumor progression at 2, 3, and 10 months after initiation, without recurrence of hypoglycemia.

**Conclusion:** Everolimus appears to be a new effective treatment for patients with metastatic insulinoma and refractory hypoglycemia. Tolerance should be carefully monitored.

*European Journal of Endocrinology* 168 665–674

## Introduction

Insulinomas are neuroendocrine tumors (NET) located within the pancreas, characterized by the presence of clinical symptoms due to the excessive secretion of insulin. These tumors are rare, with an estimated incidence of 1–3 per million per year. Although <15% are metastatic (1, 2), patients with malignant insulinomas display a poor prognosis, with an overall 5-year survival rate estimated between 16 and 55.6% (3, 4). Indeed, refractory hypoglycemia remains an important cause of morbidity and mortality and contributes to the poor prognosis of these patients. Current therapeutic options to control hormone-related symptoms include frequent carbohydrate-enriched meals, diazoxide, somatostatin analogs, and, in some cases, continuous

i.v. glucose infusion and/or nasogastric tube feeding (5). Antitumor options are discussed on a case-by-case basis, with the goals of tumor control and complete remission of hormone-related symptoms (5).

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that regulates cellular response to growth factor signaling and nutrients via the phosphatidylinositol 3-kinase (PI3K)/Akt pathway (6). This pathway has been shown to play a significant prognostic role in pancreatic NET (pNET) (7). In addition, the mTOR pathway plays a role in the control of glucose homeostasis (8). Indeed, mTOR activates cellular processes by phosphorylating p70 S6 kinase 1 (S6K1). Both mTOR and S6K1 are activated by insulin and nutrients through the insulin receptor/insulin receptor substrate (IRS)/PI3K/Akt pathway, leading to:

i) glucose transporter type 4 (GLUT4) translocation to the cell membrane, ii) increased peripheral glucose uptake, and iii) insulin secretion and insulin gene transcription. By contrast, chronic activation of the mTOR/S6K1 pathway increases IRS-1 serine phosphorylation, leading to a reduction in IRS-1 function and impaired activation of the PI3K/Akt pathway, thereby decreasing insulin action.

Everolimus, an oral mTOR inhibitor, has recently been shown to improve progression-free survival of patients with well-differentiated progressive metastatic pNET and has been approved as a new antitumor therapeutic option for this indication (8). In phase 2 and 3 trials, hyperglycemia has been recognized as a frequent adverse event which affects around 13% of the patients (8, 9). In a phase 1 dose-escalation trial, dose limitation due to hyperglycemia occurred at 10 mg/day (10). Everolimus-induced hyperglycemic adverse effects seem to be a class effect of mTOR inhibitors. Indeed, Bourcier *et al.* (11) reported the successful control of refractory hypoglycemia due to malignant insulinoma with the use of sirolimus, and a hyperglycemic effect with temsirolimus has been reported in patients treated for pNET and kidney cancer (12, 13, 14). To explain the occurrence of hyperglycemia in these patients, several hypotheses have been raised, including that a decrease in insulin production and release or an increase in peripheral insulin resistance may have been the cause (15, 16, 17, 18, 19).

Kulke *et al.* (20) first reported the symptomatic response of four patients treated with everolimus for uncontrolled hypoglycemia related to a metastatic insulinoma. All four patients exhibited normal glucose levels after everolimus treatment was begun and discontinued diazoxide and glucose infusion. In two of four patients, partial responses were observed at 16 and 29 months. Four other case reports mentioned successful efficacy of mTOR inhibitors in controlling hypoglycemia (11, 21, 22, 23), although failure to control hypoglycemic symptoms was reported in one case (24).

To better evaluate the benefit of this new therapy within a larger group of patients, we decided to retrospectively review the experience of the French Group of Endocrine Tumors in the use of everolimus for the treatment of refractory hypoglycemic symptoms related to metastatic insulinoma. The primary goal was to analyze symptom-free hypoglycemia survival (SFS) through clinical questioning. Secondary objectives were to evaluate objective tumor response (Response Evaluation Criteria In Solid Tumors (RECIST) 1.0) and the safety of everolimus treatment.

## Materials and methods

### Study population and data collection

All patients who were given the diagnosis of malignant insulinoma and treated with everolimus at one of the

treatment centers of the French Group of Endocrine Tumors were eligible for the study. Patients analyzed in this study were treated in the setting of the RADIANT-3 trial, compassionate use, or in an off-label setting on the basis of recommendations made by multidisciplinary staff members of the French Group of Endocrine Tumors network.

Patients with continued metastatic disease and refractory hypoglycemia after they had received conventional treatment were included. Malignancy was defined as the presence of distant metastatic disease diagnosed by pathologic and imaging reports (magnetic resonance imaging, computed tomography (CT), somatostatin receptor scintigraphy). Hypoglycemia was defined as the presence of symptoms of hypoglycemia associated with low plasma glucose concentrations ( $\leq 2.5$  mmol/l) and inappropriately high serum insulin ( $\geq 21$  pmol/l) or C-peptide ( $\geq 0.2$  nmol/l) demonstrated at least once in the course of disease management. Refractory hypoglycemia was defined by hospitalization or a severe impact on the patient's quality of life such as extreme limitation on daily living activities, including self-care. Patients for whom everolimus was prescribed for antitumor purposes only were excluded, as were patients for whom everolimus was initiated along with other antitumor or antisecretory therapeutic modalities.

All files were reviewed on-site by a single investigator (V B). Data collected at baseline included time since diagnosis of malignant insulinoma, as well as patient age, gender, and inherited status, World Health Organization (WHO) 2010 classification (25), International Union Against Cancer (UICC) pathologic tumor, node, metastasis (pTNM) classification (26), and metastatic locations, previous therapies, and starting dose of everolimus.

### Everolimus treatment and patient monitoring

All patients were started on everolimus at 10 mg/day, except one patient who received everolimus at 5 mg/day as a result of a decision by a local physician. In some of these patients, the dosage of everolimus was decreased later at the discretion of the local physician to 5 mg/day or 5 mg every other day to alleviate side effects. Patients were followed on-site, and the following parameters were recorded: frequency of daily symptomatic hypoglycemia as reported by the patient, the family, or another reliable person who answered questions in a real-time manner; RECIST evaluation (27) performed at least every 3–6 months; and safety assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4 (28).

According to the NCI CTCAE v4, grade 1 refers to asymptomatic or mild symptoms, and no intervention is indicated. Grade 2 refers to moderate or minimal

local symptoms, and noninvasive intervention is needed. Grade 3 refers to severe, nonlife-threatening symptoms, for which hospitalization may be indicated and daily living activities, including self-care, are extremely limited. Grade 4 refers to a life-threatening situation for which urgent intervention is required. Grade 5 signifies that death is associated with the adverse event.

### **Primary objective**

The primary objective of this retrospective study was SFS, as defined by the time from everolimus initiation to the first recurrence of symptomatic hypoglycemia after everolimus initiation. Control of symptomatic hypoglycemia was classified as complete or not. Complete hypoglycemia was defined by the disappearance of all symptoms previously related to a typical hypoglycemic event. A final follow-up for all patients was provided on December 31, 2011.

## **Results**

### **Patients and treatments before initiation of everolimus**

From May 2007 through June 2011, 17 files were reviewed at seven centers. Five patients were excluded because everolimus was prescribed only for tumor control purposes in asymptomatic patients at the time of everolimus initiation. Therefore, 12 patients with metastatic insulinoma and refractory hypoglycemia who were treated with everolimus were considered eligible for this study. Patient characteristics are given in Table 1. Seven women and five men, with a median age of 65 years (range 39–78 years) and with sporadic tumors, were enrolled. UICC pTNM classification was stage IV in all patients, including one patient with unresectable distant lymphatic node metastases. All patients except one had liver metastases, three patients bone metastases, and one patient lung metastases. Somatostatin receptor scintigraphy was positive in nine, negative in one, and not available in two of the 12 patients.

### **Everolimus treatment and outcome**

At the start of everolimus treatment, the median number of previous lines of treatment to control hypoglycemia-related symptoms and/or tumor growth was 5 (range 4–8). Four patients were on the fourth line of treatment, three on the fifth line, four on the sixth line, and one on the eighth line. Previous options included diazoxide in 11 patients, surgery for liver metastases in seven, liver transarterial chemoembolization in seven, cytotoxic chemotherapy in seven, octreotide in six, corticosteroid therapy in four, continuous or nocturnal glucose

infusion in three, interferon in two, and sunitinib in one. At the time of everolimus initiation, concomitant hyperglycemia medications were maintained in 11 patients, including diazoxide in nine patients, octreotide in three, continuous or nocturnal glucose infusion in three, and corticosteroid in two.

Patient outcome after everolimus initiation is detailed in Table 2. The median follow-up time from the start of everolimus treatment to the time of the last follow-up was 6.5 months (range 1–35+). The median SFS was 6.5 months (range 0–35+). Disappearance of hypoglycemic symptoms was observed in 11 patients and resulted in the discontinuation of at least one concomitant hyperglycemic agent, including glucose perfusion, in six of the ten patients receiving such therapies within 15 days (Table 2). Responses were observed immediately after everolimus initiation in these 11 responders. One patient did not experience a clinical response despite maintenance of everolimus for 2 months (patient 1). Comparisons of SFS under everolimus therapy with SFS under previous medical options are provided in Fig. 1. Everolimus was the most prolonged therapy in seven of the 12 patients. The median SFS of everolimus was 6.5 months (range 0–35 months) vs <1 month for the medical option that preceded everolimus therapy (range 0–21 months). During the follow-up, the treatment dose was reduced in four of the 11 responders to 5 mg/day (patients 2, 3, 7, and 11) without recurrence of hypoglycemia after a median follow-up of 4 months (range 3–9 months). It is interesting to note that one patient who received everolimus at 5 mg/day experienced the same quality of clinical response as was reported by ten others whose starting dose was 10 mg/day.

Ten patients underwent at least one radiographic evaluation every 3 months (range 2–6 months) for the evaluation of tumor response to everolimus according to the RECIST criteria. At the time of imaging at the last follow-up, conducted after a median of 7 months (range 2–32 months), seven patients experienced stable disease (70%) and three (30%) progressive disease.

Of the 11 patients who benefited from everolimus therapy, three (patients 4, 8, and 9) discontinued treatment because of pulmonary adverse events at 1, 1.5, and 7 months after initiation. At that time, RECIST evaluation had not been performed, except in patient 8, who had stable disease and experienced recurrence of hypoglycemia and progression of disease after everolimus withdrawal. One patient (patient 6) was censored after 3 months of everolimus treatment because he had to start depot octreotide to control a pulmonary embolism that was thought to be hyperglucagonemia related but was finally diagnosed as congestive cardiac failure. Two patients (patients 3 and 7) discontinued treatment with everolimus because of disease progression at 3 and 10 months after initiation and died as a result of tumor progression without recurrence of hypoglycemia within 1 month and at 2 months after everolimus withdrawal

**Table 1** Clinical characteristics of the patients treated with everolimus.

Patient	Age (years)	Gender	Time since diagnosis	WHO 2010 grade	UICC pTNM stage (tumor location)	Previous/ongoing therapies (by chronological order)	Glucose, insulin, and C-peptide levels <sup>a</sup>
1	42	F	21 months	2	IV (liver)	i.v. chemotherapy (adriamycin + streptozotocin, FOLFOX), transarterial liver chemoembolization/diazoxide	G: 2 mmol/l; I: 422 pmol/l; C-P: 1.7 nmol/l
2	78	F	6 months	1	IV (liver)	Depot octreotide, i.v. chemotherapy (FOLFOX)/diazoxide	G: 1.9 mmol/l; I: 126 pmol/l; C-P: 1 nmol/l
3	69	F	2 years	Unknown	IV (liver)	i.v. chemotherapy (adriamycin + streptozotocin, 5FU + streptozotocin), transarterial liver chemoembolization/diazoxide, glucose infusion, depot octreotide	G: 3.3 mmol/l (glucose infusion); I: 645 pmol/l; C-P: 2.6 nmol/l
4	54	M	21 months	1	IV (liver)	Transarterial liver chemoembolization, interferon, i.v. chemotherapy (adriamycin + streptozotocin)/diazoxide, nocturnal glucose infusion, corticosteroid therapy	G: 6.8 mmol/l (glucose infusion); I: 264 pmol/l; C-P: 2.2 nmol/l
5	61	F	4 years and 9 months	2	IV (liver, lungs, and bones)	Surgery, radio-frequency ablation, i.v. chemotherapy (adriamycin + streptozotocin), transarterial liver chemoembolization/depot octreotide	G: 2.9 mmol/l; I: 69 mmol/l; C-P: 0.1 nmol/l
6	73	M	3 years and 3 months	2	IV (liver)	Surgery, i.v. chemotherapy (5FU + epirubicin + dacarbazine, GEMOX), diazoxide, corticosteroid therapy, glucose infusion, transarterial liver chemoembolization	G: 2.8 mmol/l; I: 102 pmol/l; C-P: 0.77 nmol/l
7	75	F	4 years and 2 months	2	IV (liver and bones)	Interferon, depot octreotide/diazoxide	G: 2.4 mmol/l; I: 163 pmol/l; C-P: 1.3 nmol/l
8	61	M	8 months	NA <sup>b</sup>	IV (liver)	Surgery, transarterial liver chemoembolization/diazoxide	G: 1.7 mmol/l; I: 466 pmol/l; C-P: 3.1 nmol/l
9	71	M	18 years	Unknown	IV (liver and bones)	Surgery, transarterial liver chemoembolization, corticosteroid therapy/diazoxide, glucose infusion	G: 1.8 mmol/l (glucose infusion); I: 166 pmol/l; C-P: 1.9 nmol/l
10	48	F	3 years and 10 months	2	IV (liver)	Surgery, depot octreotide, sunitinib/diazoxide, corticosteroid therapy	G: 2.2 mmol/l; I: 186 pmol/l; C-P: 1.8 nmol/l
11	72	F	18 months	2	IV (liver)	Surgery, diazoxide/depot octreotide	G: 2.2 mmol/l; I: 108 pmol/l; C-P: 1.1 nmol/l
12	39	M	3 years and 5 months	2	IV (distant lymphatic nodes)	Surgery, depot octreotide, i.v. chemotherapy (adriamycin + streptozotocin)/diazoxide	G: 2.2 mmol/l; I: 107 pmol/l; C-P: 1 nmol/l

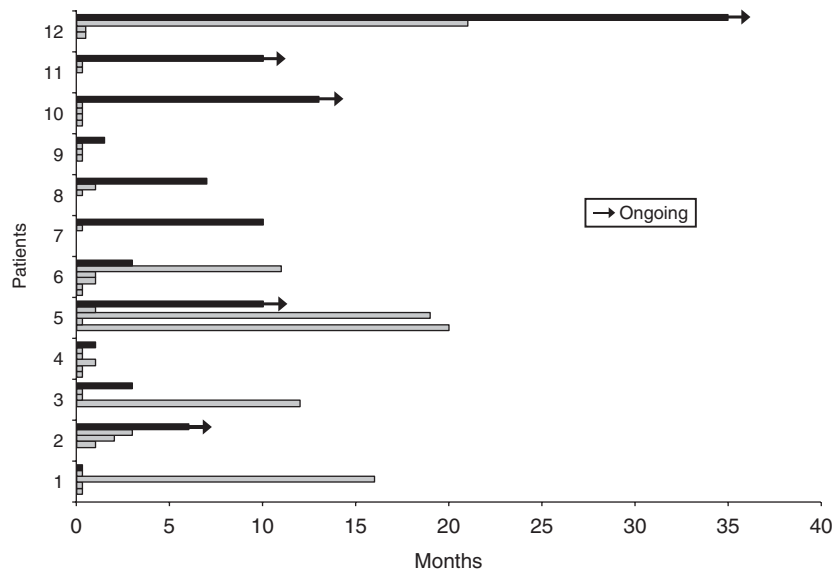
NA, not applicable; 5FU, 5-fluorouracil; FOLFOX, 5FU, folinic acid and oxaliplatin; GEMOX, gemcitabine and oxaliplatin; G, glycaemia; I, insulinemia; C-P, C-peptide.

<sup>a</sup>Levels prior to everolimus initiation.

<sup>b</sup>Well differentiated but Ki67 > 30%.

**Table 2** Clinical outcomes of patients treated with everolimus.

Patient	Complete symptomatic control	Duration of control (months)	Outcome of other hyperglycemic agents	RECIST 1.0	Safety	Reasons for everolimus withdrawal	Status at the last evaluation
1	No		Diazoxide increase	Progressive disease at 2 months	Noninfectious pneumonitis (grade 3), peripheral edema (grade 2), asthenia grade 2, ectopic Cushing's syndrome, hepatic cytolysis (grade 3)	Progression	Death, disease progression
2	Yes	6+	Diazoxide withdrawal	Stable disease at 6+ months			Alive, stable
3	Yes	3	Diazoxide and glucose infusion withdrawal	Progressive disease at 3 months	Biliary cyst rupture	Progression	Death, disease progression
4	Yes	1	Glucose infusion withdrawal	Non-evaluable	Pneumocystis pneumonia (grade 5), asthenia (grade 1), peripheral edema (grade 1), stomatitis (grade 2)	Toxicity	Death, drug-related toxicity
5	Yes	10+		Stable disease at 10+ months	Diarrhea (grade 2), asthenia (grade 2), stomatitis (grade 2), palmar-plantar erythrodysesthesia (grade 1)		Alive, disease progression
6	Yes	3		Stable at 3 months	Asthenia (grade 1), neutropenia (grade 1), skin rash (grade 1), hypertriglyceridemia (grade 2), cardiac failure (grade 3)	Censored	Alive, disease progression
7	Yes	10	Diazoxide decrease	Progressive disease at 10 months	Asthenia (grade 2), anorexia (grade 2), neutropenia (grade 2)	Progression	Death, disease progression
8	Yes	7	Diazoxide withdrawal	Stable disease at 7 months	Noninfectious pneumonitis (grade 1), stomatitis (grade 2)	Toxicity	Alive, disease progression
9	Yes	1.5	Glucose infusion withdrawal	Non-evaluable	Noninfectious pneumonitis and cardiac failure (grade 5)	Toxicity	Death, drug-related toxicity
10	Yes	13+	Diazoxide and glucose infusion withdrawal	Stable disease at 13+ months	Nausea and weight loss (grade 2)		Alive, stable
11	Yes	10+		Stable disease at 10+ months	Noninfectious pneumonitis and cardiac failure (grade 3), anorexia (grade 2), stomatitis (grade 2), diarrhea (grade 1), hepatic cytolysis (grade 2)		Alive, stable
12	Yes	32+		Stable disease at 32+ months	Hepatic cytolysis (grade 2), neutropenia (grade 1), stomatitis (grade 2)		Alive, stable



**Figure 1** Duration of symptom control with everolimus therapy compared with previous lines of treatment. Black lines refer to everolimus therapy and gray lines to previous medical options.

respectively. Finally, at the last follow-up, five patients (patients 2, 5, 10, 11, and 12) continued to show complete hypoglycemic response and were still receiving everolimus treatment at 6, 10, 10, 13, and 35 months respectively after everolimus initiation. These last five patients had stable disease at the last RECIST evaluation, which was performed after a median follow-up of 9 months (range 5–32).

### Safety

Adverse events of treatment are reported in Table 2.

**Pulmonary and cardiac toxicity** Six patients (patients 1, 4, 6, 8, 9, and 11) experienced pulmonary and/or cardiac adverse effects during everolimus treatment, including three who discontinued everolimus for safety reasons, which was recommended by local investigators. Two patients (patients 4 and 9) discontinued everolimus because of grade 4 pulmonary toxicity, but deaths occurred despite drug withdrawal. One of these two patients has been described recently in the RADIANT-3 publication (8).

- Patient 4 was a 54-year-old male with an insulinoma and liver metastases who was treated with everolimus as the sixth line of treatment within the setting of the RADIANT-3 trial. He had severe hypoglycemia, requiring nocturnal glucose infusion, diazoxide, and corticosteroid therapy. Glucose nocturnal infusion was stopped within 2 weeks after the start of everolimus treatment. Corticosteroid therapy was maintained. After 1 month of treatment, the patient experienced an acute respiratory distress syndrome, requiring reanimation. He died 1 day after the start of hospitalization. The diagnosis of

*Pneumocystis pneumonia* was confirmed by the PCR after lung fibroscopy. This infection was attributed to severe lymphopenia induced by corticosteroid and everolimus.

- Patient 9 was a 71-year-old male with a previous medical history of hypertension who was treated with everolimus for liver and bone metastatic insulinoma. Previous options for controlling hypoglycemia included transarterial liver chemoembolization, corticosteroid therapy, diazoxide, and continuous glucose infusion. This patient was able to stop receiving glucose infusion within a few days after the start of the treatment with everolimus, and diazoxide was maintained. After 1.5 months of treatment, the patient experienced respiratory distress, mixed cardiac failure, and noninfectious pneumonitis, leading to death. Cardiac failure was attributed to everolimus because left ventricular ejection fraction was determined to be normal (FEVG 70%) when measured before the treatment but had decreased to 40% after the treatment for 1.5 months.
- Patient 1 was a 42-year-old female who discontinued everolimus after 2 months of treatment because of a lack of clinical response coupled with pulmonary toxicity. After 2 months of treatment, this patient developed an ectopic Cushing's syndrome and dyspnea, requiring supplemental oxygen. At that time, and despite the Cushing's syndrome, she still had hypoglycemia, which required glucose infusion. Disease progression was noted at subsequent morphologic evaluations, along with a typical feature of noninfectious pneumonitis, which disappeared after drug withdrawal.
- Patient 11 was a 72-year-old female with a previous history of hypertension who had experienced a grade 3 mixed, noninfectious pneumonitis and cardiac

failure, which induced a temporary interruption of the drug; after regression of the toxicity, everolimus was restarted at a reduced dose (5 mg/day), which was well tolerated after a follow-up of 4 months. Cardiac failure was attributed to everolimus because left ventricular function measured before the treatment was normal (FEVG 60%) but had decreased to 45% after 4 months of treatment.

- Patient 8 was a 61-year-old male who had discontinued everolimus because of an asymptomatic noninfectious grade 1 pneumonitis. Pneumonitis regressed after everolimus withdrawal, but hypoglycemia recurred within a few days. In addition, the disease was noted to have progressed at morphologic evaluation after discontinuation of everolimus.
- Patient 6 was a 73-year-old male who was censored as previously mentioned after 3 months of everolimus treatment because he had started depot octreotide to control a pulmonary embolism thought to be hyperglucagonemia related, but congestive cardiac failure was later diagnosed. Cardiac failure was attributed to everolimus.

**Other toxicities** All the 12 patients experienced adverse events. The most common adverse events included the following: five patients reported asthenia (two grade 1 and three grade 2), three anorexia and/or weight loss (grade 2), five stomatitis (grade 2), two peripheral edema (one grade 1 and one grade 2), two diarrhea (one grade 1 and one grade 2), three neutropenia (two grade 1 and one grade 2), one hypertriglyceridemia (grade 2), three hepatic cytolysis (two grade 2 and one grade 3), one skin rash (grade 1), and one palmar-plantar erythrodysesthesia (grade 1). One patient experienced a biliary cyst rupture, requiring reanimation a few days after everolimus initiation, but it was not attributed to the treatment, which was continued at a reduced dose after hospitalization.

## Discussion

Control of hormone-related symptoms of NET is one of the critical goals in the therapeutic management of patients with NET. Indisputable progress has been made in this field as a result of the introduction of proton pump inhibitors in patients with gastrinoma, as well as somatostatin analog therapy in patients with the carcinoid syndrome (5). However, significant proportions of deaths are still due to hormone-related symptoms in patients with NET, as reported in malignant pheochromocytoma, in gastroenteropancreatic NET with heart carcinoid syndromes, and in malignant insulinoma (5, 29, 30). Our study, which analyzed the experience of a national network over a 4-year period, is the largest to date in patients with malignant insulinoma and clearly suggests that

everolimus should be considered a new medical option for these patients.

Medical therapy for insulinoma is considered only in inoperable patients or in patients with unresectable malignant insulinoma, as reported in our series (5). Recent recommendations suggest the use of everolimus as an alternative to chemotherapy as the first line of antitumor systemic therapy in the case of progressive malignant insulinomas (31). Diazoxide therapy is the oldest antisecretory medical option that is still largely prescribed, even if data are lacking regarding the duration of its benefit and tolerance in the long run in malignant insulinoma (32, 33). Somatostatin analog efficacy in the control of hypoglycemic symptoms has also been reported in malignant insulinoma, mainly in case reports. However, worsening of hypoglycemic symptoms has been reported in benign or malignant insulinomas treated with somatostatin analog, suggesting that this option could be introduced first with a short-acting drug (34, 35, 36). Other antitumor options, mainly transarterial liver chemoembolization, are frequently used with the expectation of combining antitumor and antisecretory early responses (5). Finally, beneficial effects with peptide receptor radionuclide therapy have been demonstrated in some patients with malignant insulinomas (37) as well as surgery including liver transplantation in anecdotal cases (5, 31, 37, 38). Although sunitinib has recently been approved in progressive advanced pNET, the decline in blood glucose reported with this agent makes its use in malignant insulinoma questionable (37, 39).

Data on everolimus in the control of hypoglycemic symptoms have been recently published (20, 21, 22, 23). Our study confirms these data, with the largest number of patients ever reported in the literature and a significant duration of follow-up. Indeed 11 of the 12 (91%) patients experienced a complete clinical response after everolimus initiation despite a median failure of four previous lines. In none of these patients was the combination of everolimus with another drug found to be superior to everolimus alone. This symptomatic effect was observed in the absence of significant morphologic response, suggesting that a reduction in tumor mass was not the leading cause of improvement. Two hypotheses can be raised to explain our results: first, chronic mTOR inhibition may affect insulin secretion by the tumor and the number of insulin receptors present on  $\beta$ -pancreatic cells, which can lead to a decrease in insulin production and release (15, 16); and, second, impaired Akt activation affects insulin sensitivity. Thus, long-term administration of everolimus may alter insulin secretion, as well as insulin-mediated peripheral glucose utilization and insulin-mediated suppression of hepatic glucose production (40), leading to hyperglycemia. In addition, insulin resistance may be worsened by ectopic triglyceride deposition (18).

Adverse events were similar to those described in previous reports, apart from the three heart failure reports. Pulmonary adverse events were found to be prevalent. Indeed, two deaths occurred at 1 and 1.5 months of treatment: one case of *Pneumocystis pneumonia* and one case of mixed cardiac failure associated with noninfectious pneumonitis. In both cases, pulmonary adverse effects were considered by local investigators to be related to everolimus. Indeed, the immunosuppressive properties of everolimus are well known and serve as the rationale for its use in renal and cardiac transplantation (41). Moreover, noninfectious pneumonitis is a class effect of rapamycin analogs such as everolimus and temsirolimus (13, 42). It should be noted that two patients received corticosteroid therapy and one systemic chemotherapy before or concomitant with everolimus, and this may have increased their risk for infection or cardiac dysfunction. Finally, three cases of cardiac insufficiency were reported, in which patients had chronic and treated arterial hypertension. Cardiac dysfunction could be considered everolimus related because cardiac function measured before the treatment was normal in two patients. To the best of our knowledge, this study is the first to report such adverse effects, and the mechanism that causes them needs to be further explored. In two of these three cases, cardiac function recovered after dose adjustment to 5 mg/day or everolimus withdrawal and diuretic treatment. However, we do not think that these major drawbacks should discourage clinicians from using everolimus in these patients. Indeed, the two fatal cases were among the first patients treated with everolimus in 2007, and at that time, pulmonary toxicity was still poorly anticipated. From that date forward, guidelines for close lung surveillance have been published (43). Baseline pre-treatment chest X-ray and CT scan are recommended. During the course of mTOR inhibitor treatment, patients should inform the clinician of any new symptoms such as cough, dyspnea, and fever. Prompt clinical examination and imaging are needed to make the diagnosis if symptoms should occur. A decrease in the dose of drug is recommended in cases of asymptomatic significant radiologic alterations, or withdrawal in cases of clinical alteration. In addition, the poor prognosis of metastatic insulinoma suggests that hormone-related symptoms still play a major role in the mortality of these patients, and this justifies the potential adverse events of medical intervention. However, one question that remains is whether one should consider patients with metastatic insulinoma at increased risk for severe adverse events when treated with everolimus. The combined use of corticosteroid therapy or systemic chemotherapy in these patients may increase the risk for secondary opportunistic infectious disease and/or cardiac dysfunction. We recommend that heart function should be cautiously analyzed when combined or sequential lines of treatment targeting heart function are given.

In conclusion, everolimus appears as a new major effective treatment modality for patients with metastatic insulinoma and refractory hypoglycemia. Cardiac and pulmonary tolerance should be carefully monitored in these patients.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

### Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

### Acknowledgements

We thank all participating centers of the French Group of Endocrine Tumors (INCA-RENATEN network). We thank Jean François Gauthier for reviewing and commenting on the manuscript.

### References

- 1 Soga J, Yakuwa Y & Osaka M. Insulinoma/hypoglycemic syndrome: a statistical evaluation of 1085 reported cases of a Japanese series. *Journal of Experimental and Clinical Cancer Research* 1998 **17** 379–388.
- 2 Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, Andrews JC, Lloyd RV & Service FJ. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1069–1073. (doi:10.1210/jc.2008-2031)
- 3 Queiroz Almeida M, Machado MCC, Correa-Giannella ML, Giannella-Neto D & Albergaria Pereira MA. Endogenous hyperinsulinemic hypoglycemia: diagnostic strategies, predictive features of malignancy and long-term survival. *Journal of Endocrinological Investigation* 2006 **29** 679–687.
- 4 Lepage C, Ciccolallo L, De Angelis R, Bouvier AM, Faivre J & Gatta G. European disparities in malignant digestive endocrine tumours survival. *International Journal of Cancer* 2010 **126** 2928–2934.
- 5 Jensen RT, Cadiot G, Brandi ML, De Herder WW, Kaltsas G, Komminoth P, Scoazec J-Y, Salazar R, Sauvanet A & Kianmanesh R. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology* 2012 **95** 98–119. (doi:10.1159/000335591)
- 6 Hay N & Sonenberg N. Upstream and downstream of mTOR. *Genes and Development* 2004 **18** 1926–1945. (doi:10.1101/gad.1212704)
- 7 Missiaglia E, Dalai I, Barbi S, Beghelli S, Falconi M, Della Peruta M, Piemonti L, Capurso G, Di Florio A, Delle Fave G *et al.* Pancreatic endocrine tumors: expression profiling evidences a role for AKT–mTOR pathway. *Journal of Clinical Oncology* 2010 **28** 245–255. (doi:10.1200/JCO.2008.21.5988)
- 8 Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, De Vries EGE *et al.* Everolimus for advanced pancreatic neuroendocrine tumors. *New England Journal of Medicine* 2011 **364** 514–523. (doi:10.1056/NEJMoa1009290)
- 9 Yao JC, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruzsniwski P, Hoosen S, St Peter J, Haas T, Lebwohl D *et al.* Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *Journal of Clinical Oncology* 2010 **28** 69–76. (doi:10.1200/JCO.2009.24.2669)



- 10 Sankhala K, Mita A, Kelly K, Mahalingam D, Giles F & Mita M. The emerging safety profile of mTOR inhibitors, a novel class of anticancer agents. *Targeted Oncology* 2009 **4** 135–142. (doi:10.1007/s11523-009-0107-z)
- 11 Bourcier ME, Sherrod A, DiGuardo M & Vinik AI. Successful control of intractable hypoglycemia using rapamycin in an 86-year-old man with a pancreatic insulin-secreting islet cell tumor and metastases. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 3157–3162. (doi:10.1210/jc.2009-0788)
- 12 Atkins MB, Hidalgo M, Stadler WM, Logan TF, Dutcher JP, Hudes GR, Park Y, Liou S-H, Marshall B, Boni JP *et al.* Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *Journal of Clinical Oncology* 2004 **22** 909–918. (doi:10.1200/JCO.2004.08.185)
- 13 Duran I, Siu LL, Oza AM, Chung T-B, Sturgeon J, Townsley CA, Pond GR, Seymour L & Niroumand M. Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *European Journal of Cancer* 2006 **42** 1875–1880. (doi:10.1016/j.ejca.2006.03.015)
- 14 Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, Sosman J, McDermott D, Bodrogi I *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *New England Journal of Medicine* 2007 **356** 2271–2281. (doi:10.1056/NEJMoa066838)
- 15 Aspinwall CA, Lakey JR & Kennedy RT. Insulin-stimulated insulin secretion in single pancreatic  $\beta$  cells. *Journal of Biological Chemistry* 1999 **274** 6360–6365. (doi:10.1074/jbc.274.10.6360)
- 16 Leibiger IB, Leibiger B, Moede T & Berggren PO. Exocytosis of insulin promotes insulin gene transcription via the insulin receptor/PI-3 kinase/p70 s6 kinase and CaM kinase pathways. *Molecular Cell* 1998 **1** 933–938. (doi:10.1016/S1097-2765(00)80093-3)
- 17 Fuhrer DK, Kobayashi M & Jiang H. Insulin release and suppression by tacrolimus, rapamycin and cyclosporin A are through regulation of the ATP-sensitive potassium channel. *Diabetes, Obesity & Metabolism* 2001 **3** 393–402. (doi:10.1046/j.1463-1326.2001.00150.x)
- 18 Di Paolo S, Teutonico A, Leogrande D, Capobianco C & Schena PF. Chronic inhibition of mammalian target of rapamycin signaling downregulates insulin receptor substrates 1 and 2 and AKT activation: a crossroad between cancer and diabetes? *Journal of the American Society of Nephrology* 2006 **17** 2236–2244. (doi:10.1681/ASN.2006030196)
- 19 Fraenkel M, Ketzinel-Gilad M, Ariav Y, Pappo O, Karaca M, Castel J, Berthault M-F, Magnan C, Cerasi E, Kaiser N *et al.* mTOR inhibition by rapamycin prevents  $\beta$ -cell adaptation to hyperglycemia and exacerbates the metabolic state in type 2 diabetes. *Diabetes* 2008 **57** 945–957. (doi:10.2337/db07-0922)
- 20 Kulke MH, Bergsland EK & Yao JC. Glycemic control in patients with insulinoma treated with everolimus. *New England Journal of Medicine* 2009 **360** 195–197. (doi:10.1056/NEJMc0806740)
- 21 Ong GSY, Henley DE, Hurley D, Turner JH, Claringbold PG & Fegan PG. Therapies for the medical management of persistent hypoglycaemia in two cases of inoperable malignant insulinoma. *European Journal of Endocrinology* 2010 **162** 1001–1008. (doi:10.1530/EJE-09-1010)
- 22 Ferrer-García JC, Tolosa-Torréns M, Hernando-Meliá C, Arribas-Palomar L & Sánchez-Juan C. Everolimus resolving hypoglycemia, producing hyperglycemia, and necessitating insulin use in a patient with diabetes and nonresectable malignant insulinoma. *Endocrine Practice* 2011 **17** e17–e20. (doi:10.4158/EP10282.CR)
- 23 Fiebrich H-B, Siemerink EJM, Brouwers AH, Links TP, Remkes WS, Hospers GAP & De Vries EGE. Everolimus induces rapid plasma glucose normalization in insulinoma patients by effects on tumor as well as normal tissues. *Oncologist* 2011 **16** 783–787. (doi:10.1634/theoncologist.2010-0222)
- 24 Chandra P, Yarandi SS, Khazai N, Jacobs S & Umpierrez GE. Management of intractable hypoglycemia with Yttirum-90 radioembolization in a patient with malignant insulinoma. *American Journal of the Medical Sciences* 2010 **340** 414–417. (doi:10.1097/MAJ.0b013e3181ee7be2)
- 25 Rindi G, Klimstra DS, Arnold R, Klöppel G, Bosman FT, Komminoth P, *et al.* Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In *WHO Classification of Tumours of the Digestive System*, pp 13–14. Eds FT Bosman, F Carneiro, RH Hruban & ND Theise. Lyon: IARC, 2010.
- 26 Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, De Herder WW, Eriksson B, Falchetti A, Falconi M, Komminoth P *et al.* TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Archiv* 2006 **449** 395–401. (doi:10.1007/s00428-006-0250-1)
- 27 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, Van Oosterom AT, Christian MC *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of the National Cancer Institute* 2000 **92** 205–216. (doi:10.1093/jnci/92.3.205)
- 28 Liu Y-J, Zhu G-P & Guan X-Y. Comparison of the NCI-CTCAE version 4.0 and version 3.0 in assessing chemoradiation-induced oral mucositis for locally advanced nasopharyngeal carcinoma. *Oral Oncology* 2012 **48** 554–559. (<http://www.ncbi.nlm.nih.gov/pubmed/22289637>)
- 29 Amar L, Baudin E, Burnichon N, Peyrard S, Silvera S, Bertherat J, Bertagna X, Schlumberger M, Jeunemaitre X, Gimenez-Roqueplo A-P *et al.* Succinate dehydrogenase B gene mutations predict survival in patients with malignant pheochromocytomas or paragangliomas. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 3822–3828. (doi:10.1210/jc.2007-0709)
- 30 Møller JE, Pellikka PA, Bernheim AM, Schaff HV, Rubin J & Connolly HM. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. *Circulation* 2005 **112** 3320–3327. (doi:10.1161/CIRCULATIONAHA.105.553750)
- 31 Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B & Salazar R. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2012 **95** 157–176. (doi:10.1159/000335597)
- 32 Gill GV, Rauf O & MacFarlane IA. Diazoxide treatment for insulinoma: a national UK survey. *Postgraduate Medical Journal* 1997 **73** 640–641. (doi:10.1136/pgmj.73.864.640)
- 33 Goode PN, Farndon JR, Anderson J, Johnston ID & Morte JA. Diazoxide in the management of patients with insulinoma. *World Journal of Surgery* 1986 **10** 586–592. (doi:10.1007/BF0165532)
- 34 Stehouwer CD, Lems WF, Fischer HR, Hackeng WH & Naafs MA. Aggravation of hypoglycemia in insulinoma patients by the long-acting somatostatin analogue octreotide (Sandostatina). *Acta Endocrinologica* 1989 **121** 34–40.
- 35 Gama R, Marks V, Wright J & Teale JD. Octreotide exacerbated fasting hypoglycaemia in a patient with a proinsulinoma; the glucostatic importance of pancreatic glucagon. *Clinical Endocrinology* 1995 **43** 117–120; discussion 120–122. (doi:10.1111/j.1365-2265.1995.tb01901.x)
- 36 Healy ML, Dawson SJ, Murray RML, Zalberg J & Jefford M. Severe hypoglycaemia after long-acting octreotide in a patient with an unrecognized malignant insulinoma. *Internal Medicine Journal* 2007 **37** 406–409. (doi:10.1111/j.1445-5994.2007.01371.x)
- 37 De Herder WW, Van Schaik E, Kwekkeboom D & Feelders RA. New therapeutic options for metastatic malignant insulinomas. *Clinical Endocrinology* 2011 **75** 277–284. (doi:10.1111/j.1365-2265.2011.04145.x)
- 38 Gedaly R, Daily MF, Davenport D, McHugh PP, Koch A, Angulo P & Hundley JC. Liver transplantation for the treatment of liver metastases from neuroendocrine tumors: an analysis of the UNOS database. *Archives Surgery* 2011 **146** 953–958. (doi:10.1001/archsurg.2011.186)

- 39 Agostino NM, Chinchilli VM, Lynch CJ, Koszyk-Szewczyk A, Gingrich R, Sivik J & Drabick JJ. Effect of the tyrosine kinase inhibitors (sunitinib, sorafenib, dasatinib, and imatinib) on blood glucose levels in diabetic and nondiabetic patients in general clinical practice. *Journal of Oncology Pharmacy Practice* 2011 **17** 197–202. (doi:10.1177/1078155210378913)
- 40 Johnston O, Rose CL, Webster AC & Gill JS. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. *Journal of the American Society of Nephrology* 2008 **19** 1411–1418. (doi:10.1681/ASN.2007111202)
- 41 Dunn C & Croom KF. Everolimus: a review of its use in renal and cardiac transplantation. *Drugs* 2006 **66** 547–570. (doi:10.2165/00003495-200666040-00009)
- 42 Vahid B & Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. *Chest* 2008 **133** 528–538. (doi:10.1378/chest.07-0851)
- 43 Albiges L, Chamming's F, Duclos B, Stern M, Motzer RJ, Ravaud A & Camus P. Incidence and management of mTOR inhibitor-associated pneumonitis in patients with metastatic renal cell carcinoma. *Annals of Oncology* 2012 **23** 1943–1953. (doi:10.1093/annonc/mds115)

---

Received 20 December 2012

Revised version received 31 January 2013

Accepted 7 February 2013