Management of hyperglycaemia in Cushing’s disease: Experts’ proposals on the use of pasireotide

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Abstract

Cushing’s disease causes considerable morbidity and mortality, including cardiovascular, metabolic, respiratory and psychiatric complications, bone demineralization and increased susceptibility to infections. Metabolic complications include a high prevalence of impaired glucose tolerance, fasting hyperglycaemia and diabetes. Although pituitary surgery is the gold-standard treatment, other treatment strategies such as radiotherapy and medical therapy to reduce cortisol synthesis may be proposed in the event of recurrence or failure, or when surgery is not an option. Bilateral adrenalectomy can also be considered. One of the medical treatments used in Cushing’s disease is the somatostatin analogue pasireotide, which acts on adrenocorticotropic hormone (ACTH) secretion by the pituitary. Its efficacy in reducing urinary free cortisol, plasma cortisol and ACTH, and in improving the clinical signs of the disease has been demonstrated. Its observed adverse effects are similar to the known effects of first-generation somatostatin analogues, although disturbances of carbohydrate metabolism are more frequent and more severe with pasireotide. The aim of the present review was to summarize the epidemiology and pathophysiology of the disturbances of glucose metabolism that arise in Cushing’s disease, and to propose recommendations for detecting and monitoring glucose abnormalities and for managing pasireotide-induced hyperglycaemia.

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Keywords: Review; Cushing’s disease; Glucose metabolism; Diabetes; Secondary diabetes; Pasireotide

Résumé

Prise en charge de l’hyperglycémie au cours de la maladie de Cushing : propositions d’experts pour l’utilisation de pasiréotide.

La maladie de Cushing entraîne une morbi-mortalité importante avec des complications cardiovasculaires, métaboliques, respiratoires et psychiatriques, une déminéralisation osseuse ainsi qu’une sensibilité accrue aux infections. Parmi les complications métaboliques, il est observé une forte prévalence d’intolérance au glucose, d’hyperglycémie à jeun et de diabète. Bien que la chirurgie hypophysaire soit le traitement de référence, en cas de récidive, d’échec ou d’inopérabilité, d’autres stratégies thérapeutiques telles que des médicaments agissant sur la synthèse du cortisol, la radiothérapie, peuvent être proposés. Enfin, en dernière intention, une surrénalectomie bilatérale peut être effectuée. Parmi les thérapies médicamenteuses utilisées dans la maladie de Cushing, le pasiréotide, analogue de la somatostatine qui agit sur la sécrétion hypophysaire d’ACTH, a fait la preuve de son efficacité en diminuant le cortisol libre urinaire, les concentrations plasmatiques de cortisol et d’ACTH et en améliorant les signes cliniques de la maladie. Les effets secondaires observés sont similaires à ceux connus avec les analogues de la somatostatine de

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1. Introduction

Cushing’s disease is due to pituitary adenoma with adrenocorticotropic hormone (ACTH) hypersecretion and is the most common cause (about 70% of cases) of Cushing’s syndrome, a set of clinical manifestations associated with chronic exposure to endogenous glucocorticoid excess [1,2].

Cushing’s disease is potentially serious because of the multiple complications associated with hypercortisolism, including: metabolic complications such as obesity, diabetes and dyslipidaemia; hypertension; cardiovascular and thromboembolic complications associated with hypercoagulability; increased susceptibility to infections; bone demineralization and the resulting fracture risk; psychiatric complications; and respiratory complications. The mortality rate is 1.7- to 3.7-fold higher in patients chronically exposed to glucocorticoid excess than in the general population [3]. This excess mortality is higher still in patients with persistent hypercortisolism (relative risk 3.8–4.4), but decreases after prolonged remission [4]. However, even after prolonged control of hypercortisolism, metabolic abnormalities such as impaired glucose tolerance can persist, as measured by a 75 g oral glucose tolerance test (OGTT) [5]. The main causes of excess mortality in Cushing’s disease are cardiovascular and cerebrovascular events, which alone account for around 45% of deaths. Quality of life is also impaired and not fully restored even after cure or long-term control [6].

Although transsphenoidal pituitary surgery is the gold-standard treatment for Cushing’s disease, its success rate is between 65% and 90%, depending on the size of the pituitary adenoma, the possibility of localizing it preoperatively and especially intraoperatively, the operating conditions and the surgeon’s expertise. The adenomas recur in about 20% of cases and very late relapses have been reported. Several alternative strategies are available after failure of transsphenoidal surgery: repeat surgery, effective in around 50% of cases; fractionated conformal radiotherapy or targeted radiosurgery, which has variable success (17–83% beyond 2 years) and often results in hypopituitarism (20–60% after 5 years); various pharmacological options to reduce cortisol secretion; and bilateral adrenalectomy, which is always effective but leads to delayed morbidity due to permanent adrenal insufficiency and the possibility of corticotrophic tumor progression.

Several pharmaceutical agents are available to control the harmful effects of chronic glucocorticoid excess. They act through a variety of mechanisms, including inhibition of steriodogenesis, chemical adrenalectomy targeting corticotroph adenoma (cabergoline) and peripheral suppression of the tissue effects of glucocorticoids (mifepristone) [1]. However, no large-scale, prospective, randomized clinical trials have been conducted to precisely evaluate the efficacy of these various treatments, none has been licensed for the treatment of Cushing’s disease and all of them have potentially severe adverse effects. They are offered as preparation prior to or after failure of surgery and sometimes while waiting for radiotherapy to take effect.

Pasireotide (SOM230) is a new treatment option for Cushing’s disease. It was recently evaluated in prospective trials and obtained marketing authorization for this indication in April 2012. Pasireotide is a somatostatin analogue with high affinity for the SSTR1, -2, -3 and -5 somatostatin receptor subtypes. Its affinity for SSTR5 is 40-fold greater than that of octreotide, a first-generation somatostatin analogue with a predominant affinity for SSTR2. Corticotroph adenomas predominantly express the SSTR5 subtype, hence the lack of efficacy of first-generation somatostatin analogues against these tumors [7].

A prospective multicentre, randomized, phase-III study of 162 patients with Cushing’s disease used pasireotide to suppress ACTH secretion, thereby acting directly on the underlying mechanism of the disease. Pasireotide was effective in reducing levels of urinary free cortisol, plasma cortisol and ACTH while improving clinical signs of the disease (excess body weight, hypertension), quality of life and certain metabolic parameters (plasma lipids). The adverse effects observed with pasireotide were the same as those observed with all somatostatin analogues except that glucose homoeostasis was also more frequently and more severely impaired [8].

2. Epidemiology of diabetes and impaired glucose tolerance in Cushing’s disease

Diabetes is twice as prevalent during long-term glucocorticoid therapy than in the general population. About 50% of patients with Cushing’s syndrome have a disorder of glucose metabolism: two-thirds have overt diabetes while the remainder exhibit impaired glucose tolerance or fasting hyperglycaemia [9]. The proportion with high fasting plasma glucose in the French registry of 437 patients with Cushing’s disease is 26% [10], while the European Cushing’s syndrome registry shows a prevalence of 35% in the 481 Cushing’s syndrome patients and 33% in the 294 patients with Cushing’s disease [11]. As these prevalence figures are based on measurement of fasting blood glucose, they are probably greatly underestimated, as fasting blood glucose levels are often normal in endogenous and exogenous hypercortisolism, and dysglycaemia is often more pronounced during the postprandial period and rarely analyzed. This means that the true prevalence of diabetes in
hypercortisolism could be up to 50% higher than these figures indicate [12]. In a study of 48 patients with active Cushing’s disease, over two-thirds of those with diabetes had been diagnosed by OGTT, thereby confirming the inadequacy of the fasting blood glucose test for assessing the prevalence of diabetes in hypercortisolism [13]. Thus, a true estimate of the prevalence of diabetes is essential to properly evaluate the impact of hypercortisolism, as diabetes is a risk factor for excess mortality in the disorder [3,14].

3. Pathophysiology of diabetes in Cushing’s syndrome

Glucocorticoids impair glucose regulation through several mechanisms that induce insulin resistance and impair pancreatic β-cells. Langerhans’ islet β-cells express the nuclear glucocorticoid receptor, and glucocorticoids interfere with β-cell glucose uptake and metabolism by decreasing the expression of the glucose transporter GLUT2 and glucokinase, leading to defective exocytosis of insulin granules when calcium enters the cytoplasm [15]. The effect of glucocorticoids on β-cell function depends on the dose and type of glucocorticoid, and duration of glucocorticoid exposure. Exogenous glucocorticoids also reduce the insulinotropic effect of incretin peptides, particularly glucagon-like peptide (GLP)-1 [16]. Recently, a study in healthy volunteers and one case report suggested that GLP-1 agonists could prevent this effect [17,18]. Glucocorticoids also have deleterious effects on the insulin sensitivity of target tissues (liver, adipose tissue and muscle). In muscle, glucocorticoids reduce glucose uptake and glycogen. In the liver, glucocorticoids induce the enzymes involved in gluconeogenesis and antagonize glycogen synthesis by inhibiting the action of insulin. Glucocorticoids also enhance the effect of glucagon on hepatic gluconeogenesis, thereby increasing hepatic glucose production. In addition, they promote the accumulation of visceral fat and the metabolic phenotype of central obesity characteristic of hypercortisolism. In adipose tissue, glucocorticoids promote lipolysis and the release of free fatty acids, which are substrates for gluconeogenesis. AMP kinase enzyme activity is inhibited at the level of visceral adipose tissue, resulting in an increase in the activity of the fatty acid synthase that promotes abdominal accretion of adipose tissue, a major determinant of insulin [19]. Furthermore, glucocorticoids induce synthesis of the adipokines involved in the process of insulin resistance.

Glucocorticoids also affect protein metabolism by reducing protein synthesis and accelerating protein degradation, leading to the release of amino acids that interfere with insulin signaling pathways. The generalized insulin resistance induced by glucocorticoids in Cushing’s disease affects the insulin signaling pathway through a post-receptor effect, notably by decreasing levels of insulin receptor substrate (IRS)-1, phosphatidylinositol 3 (PI3)-kinase and protein kinase B in muscle [20]. Evaluation of insulin sensitivity in Cushing’s disease in vivo using the hyperinsulinaemic–euglycaemic clamp technique has shown that glucose utilization (M value) was 50% lower than in normal subjects, so reflecting severe insulin resistance, and was improved by clinical control of hypercortisolism [21].

4. Glycaemic profiles in exogenous hypercortisolism and Cushing’s disease

Chronic exogenous glucocorticoid excess is a risk factor for postprandial hyperglycaemia [22]. A recent study using the continuous interstitial glucose monitoring technique with subcutaneous sensors showed the high prevalence of hyperglycaemia episodes in patients without known diabetes treated with exogenous glucocorticoid (prednisolone) for exacerbation of chronic obstructive pulmonary disease. Hyperglycaemia (blood glucose >2 g/L) was seen in 50% of the patients treated with the glucocorticoid vs. 8% in patients not receiving such therapy. The hyperglycaemic episodes occurred predominantly during postprandial periods in the afternoon and evening, whereas morning fasting blood glucose levels did not differ between the glucocorticoid-treated and -untreated groups and were close to normal. It should be borne in mind that these results reflect, in part, the pharmacokinetics of prednisolone and cannot be extrapolated to Cushing’s syndrome, where hypercortisolism shows no circadian variation [23]. Nevertheless, predominantly postprandial hyperglycaemia has also been observed in Cushing’s syndrome, while fasting blood glucose levels can remain within the normal range [12,24].

5. Impact of pasireotide on glucose metabolism

5.1. Preclinical studies

Somatostatin analogues affect glucose homoeostasis because of the expression of somatostatin receptor subtypes on the membranes of pancreatic islet-cells. Experiments in vitro conducted on cultured isolated pancreatic islets have clarified the mechanism through which somatostatin affects endocrine secretion of the pancreatic hormones that regulate glucose homoeostasis. In humans, somatostatin inhibits β-cell insulin secretion through the SSTR2 and SSTR5 receptor subtypes. Somatostatin also inhibits glucagon secretion by pancreatic α cells by activating and binding to the SSTR2 receptor subtype [25,26]. By acting predominantly on the SSTR2 subtype, the first-generation somatostatin analogues (octreotide, lanreotide) have less of a detrimental effect on insulin/glucagon balance than does pasireotide, which inhibits insulin secretion much more potently than glucagon due to its high affinity for SSTR5.

The effects of pasireotide and octreotide alone and in combination on blood glucose, insulin and glucagon have been evaluated in a rat model. Unlike in humans, the action of somatostatin on the endocrine pancreas in rodents is mediated by the sole SSTR5 for insulin secretion, whereas glucagon secretion is mediated by SSTR2. A single subcutaneous dose of pasireotide led to a rapid transient and dose-dependent increase in blood glucose, while subcutaneous octreotide had little or no effect. Continuous infusion of pasireotide resulted in small transient elevations of blood glucose. These findings suggest that the ratio of SSTR5/SSTR2 activation is a major factor in the hyperglycaemia observed with pasireotide therapy. However, co-administration of octreotide and pasireotide can prevent the hyperglycaemia observed with pasireotide alone. This result
suggests that enhanced SSTR2 activation can counteract the hyperglycaemic effect of SSTR5 activation [27].

5.2. Studies in healthy volunteers

The impact of pasireotide on human glucose homeostasis was investigated in the randomized double-blind B2216 study in which therapeutic doses of pasireotide (600 μg and 900 μg) were administered twice daily to healthy volunteers for 8 days [28]. Pasireotide’s hyperglycaemic effect was assessed using a 75 g OGTT, insulin secretion was evaluated by OGTT and a hyperglycaemic clamp with arginine stimulation, and peripheral and hepatic insulin sensitivity was evaluated by hyperinsulinaemic–euglycaemic clamp test. During the OGTT, hyperglycaemia was observed with pasireotide after 60 min (blood glucose > 8 mmol/L), reaching an average peak of 14 mmol/L, but at 3 h, levels were closer to 10 mmol/L. During the OGTT and hyperglycaemic clamp study, the insulin, GLP-1 and gastric inhibitory peptide (GIP) secretion responses were significantly reduced, while glucagon secretion was affected to a lesser degree. Pasireotide-induced hyperglycaemia is therefore mediated by a severe defect in the secretion of insulin and incretin hormones GLP-1 and GIP. Glucagon secretion, however, is moderately inhibited, while peripheral and hepatic insulin sensitivity was unaffected during hyperinsulinaemic–euglycaemic clamp in these insulin-sensitive healthy volunteers.

5.3. Results of phase-II and phase-III studies in patients with Cushing’s disease

The experimental findings and results of studies conducted in healthy volunteers highlight the issue of pasireotide metabolic safety and particularly its use in endocrine disorders — Cushing’s disease and acromegaly — in which glucose tolerance is impaired. This review only discusses the data obtained in Cushing’s disease.

In the phase-II study [29] evaluating the action of subcutaneous pasireotide 600 μg twice daily for 15 days in patients with Cushing’s disease, mean urinary free cortisol returned to normal in 5/29 patients (17.2%) and decreased in 22/29 patients (75.9%). A hyperglycaemia-related event was seen in 35.9% of patients. Twelve patients developed mild hyperglycaemia (grade 1) and two developed severe hyperglycaemia [1.6–2.5 g/L (8.9–13.9 mM)] that qualified as a serious adverse event (grade 2).

In the pivotal phase-III study conducted over 1 year [8] in 162 patients with Cushing’s disease, mean urinary free cortisol normalized after 6 months in 14.6% (95% CI: 7.0–22.3) of patients receiving pasireotide 600 μg twice daily and in 26.3% (95% CI: 16.6–35.9) of patients receiving pasireotide 900 μg twice daily, while 50 out of 103 patients showed substantial reductions (either normalization or ≥ 50% reduction from baseline) in urinary free cortisol levels at month 6. A hyperglycaemia-related adverse event was observed in 118 of the 162 patients (73%), 6% of which led to treatment discontinuation.

6. Recommendations for managing hyperglycaemia during pasireotide therapy for Cushing’s disease

The most frequently reported grade 3 or 4 adverse events were hyperglycaemia and diabetes in 38 patients (23.4%) and two patients (1.2%), respectively, with no severe complications (ketoacidosis, hyperosmolar coma) [grade 3 = blood glucose 2.5–5 g/L (13.9–27.8 mM), requiring hospitalization or prolongation of hospitalization; grade 4 = blood glucose > 5 g/L (>27.8 mM), life-threatening and requiring immediate intervention].

Fasting blood glucose and glycated haemoglobin (HbA1c) increased at the start of treatment and then stabilized after 2 months. In the whole study population (including diabetic patients), HbA1c increased from 5.8% at baseline to 7.2% and 7.4% after 6 months and to 7.3% and 7.2% after 12 months in the groups receiving pasireotide 600 μg and 900 μg twice daily, respectively. Hyperglycaemia was more common in the 900-μg twice-daily group and in patients with preexisting impairment of glucose metabolism: 55 patients (34%) with diabetes and 39 patients (24%) with impaired glucose tolerance. At the end of the study, 51/107 patients (48%) without diabetes at baseline had an HbA1c > 6.5%. Antidiabetic treatment was initiated in 74 of the 162 patients: 53/129 initially untreated patients (41%) received single-agent antidiabetic therapy; and the antidiabetic therapy of 21/33 previously treated patients (64%) was intensified. After initiation of antidiabetic therapy, blood glucose levels decreased from 1.66 to 1.21 g/L in the 600-μg twice-daily group, and from 1.59 to 1.34 g/L in the 900-μg twice-daily group [8].

6.1. Blood glucose tests and monitoring frequency

Patients with Cushing’s disease have a greater predisposition to hyperglycaemia. For this reason, it is recommended to monitor blood glucose and HbA1c levels in all patients with Cushing’s disease receiving pasireotide therapy, and to pay even more attention to those with overt diabetes or impaired glucose regulation, such as impaired glucose tolerance or fasting hyperglycaemia. Patients with risk factors for diabetes (such as previous gestational diabetes, android obesity, the metabolic syndrome or steroid-induced diabetes) are likely to develop more severe hyperglycaemia on introduction of pasireotide.
6.1.1. Blood glucose tests before introducing pasireotide

Fasting blood glucose and HbA1c should be measured in all patients before initiating pasireotide therapy (Fig. 1). Fasting blood glucose ≥ 1.26 g/L (7 mM) and/or HbA1c ≥ 6.5% confirm the diagnosis of diabetes, while fasting blood glucose between 1.05 and 1.25 g/L (6.1 and 7 mM) indicates fasting hyperglycaemia. A 75 g OGTT should be systematically performed if fasting blood glucose is less than 1.26 g/L (7 mM) and HbA1c is less than 6.5%. Blood glucose at 1.40–1.99 g/L (7.8–11 mM) 2 h after the oral glucose load indicates impaired glucose tolerance, while blood glucose ≥ 2 g/L (≥ 11.1 mM) 2 h after the oral glucose load indicates overt diabetes. The objective is to detect glucose abnormalities and to initiate and/or adapt antidiabetic treatments to control glucose levels as well as possible before introducing pasireotide.

6.1.2. Frequency of glycaemic monitoring during pasireotide therapy

For all patients receiving pasireotide and regardless of their glycaemic status, self-monitoring of capillary blood glucose is advisable at least once or twice a week in a fasting state as well as one or two postprandial tests per week (1.5 to 2 h after the start of a meal) after any of the three daily meals (Fig. 2). This will detect any drift towards hyperglycaemia, in which case antidiabetic therapy can be rapidly initiated or adjusted. Patients with glucose intolerance, fasting hyperglycaemia, or newly diagnosed or mild diabetes are advised to self-monitor their capillary blood glucose (SMBG) more frequently (3 to 7 times per week). Patients with overt diabetes should carry out SMBG according to the current American Diabetes Association (ADA) recommendations [30]. The exact frequency is individualized on a case-by-case basis.

Fasting plasma blood glucose should be systematically determined from a venous blood sample by a laboratory at 1, 2, 4, 8 and 12 weeks after initiating pasireotide. These intervals correspond to those recommended for liver-function testing (aspartate and alanine aminotransferases [ASAT, ALAT], and total bilirubin) during pasireotide therapy. After initiating pasireotide, HbA1c should be assessed after the first 6 weeks of treatment and every 3 months thereafter until discontinuation (Fig. 2).

In patients with no blood glucose abnormalities and whose HbA1c remains less than 6% after 3 months of pasireotide therapy, HbA1c can be measured every 3 months. Fasting blood glucose may also be determined from venous or capillary blood at regular intervals at the physician’s discretion, depending on the clinical context (such as degree of control of hypercortisolism, underlying conditions and age).

After discontinuation of pasireotide, fasting blood glucose should be monitored every 4 weeks and HbA1c every 3 months in patients exhibiting blood glucose abnormalities during pasireotide therapy to reevaluate any persistent diabetes.

In patients whose dose of pasireotide is increased, self-monitoring of capillary blood glucose is advised at least once or twice a week in a fasting state, as well as one or two postprandial tests per week (1.5–2 h after the start of a meal) after any of the three daily meals. Fasting plasma blood glucose should also be systematically determined by a laboratory from a venous
Fig. 2. Frequency of glycaemic monitoring during pasireotide therapy.

6.2. Treatment modalities for hyperglycaemia in Cushing’s disease before and during pasireotide therapy

6.2.1. Rationale

No glycaemic interventional studies have been conducted in the population of patients with hyperglycaemia secondary to the use of pasireotide to control hypercortisolism due to Cushing’s disease. The only data available concern the short-term effects of several oral or parenteral antidiabetic medications on pasireotide-induced hyperglycaemia in healthy volunteers. The B2124 study conducted in 90 healthy volunteers examined the blood glucose abnormalities observed with a glucose tolerance test after 7 days of daily pasireotide administration, and the impact of the main classes of antidiabetic drugs on blood glucose abnormalities observed during pasireotide therapy. The study included five treatment groups, all of which received pasireotide 600 μg twice daily but, in one group, without an oral antidiabetic, while the other four groups received pasireotide in combination with either metformin, nateglinide, vildagliptin or liraglutide. Glucose tolerance was evaluated in all five groups by OGTT performed before and after 7 days of pasireotide therapy. The addition of metformin had little effect on glycaemic excursions during the OGTT, but such excursions were improved — in the order of increasing effect — by nateglinide, the dipeptidyl peptidase (DPP)-4 inhibitor vildagliptin and the GLP analogue liraglutide [28].

6.2.2. Principles of pharmacological treatment for pasireotide-induced hyperglycaemia

The treatment strategy should always take into account the risk–benefit ratio. It should also be acknowledged that no treatment strategy for pasireotide-induced hyperglycaemia has been evaluated in randomized controlled trials. Given the insulin resistance observed in Cushing’s disease, metformin combined with lifestyle measures is the first-choice treatment based on a theoretical rationale in patients with Cushing’s disease who develop pasireotide-induced diabetes. Metformin should be systematically introduced with lifestyle measures before starting pasireotide therapy in all patients with impaired glucose tolerance, fasting hyperglycaemia or diabetes. Its use as a first-line therapy is in line with the recent European and North American guidelines for the management of type 2 diabetes [31].

In patients known to have diabetes before the introduction of pasireotide, their antidiabetic therapy should be intensified according to changes in blood glucose parameters (fasting blood glucose, postprandial blood glucose and HbA1c). Patients with poorly controlled hyperglycaemia (HbA1c > 8%) are potentially at increased risk of developing severe hyperglycaemia during pasireotide therapy, so particular care needs to be taken in these patients to achieve good glycaemic control before starting the treatment.

If metformin fails to control hyperglycaemic excursions during pasireotide therapy, all antidiabetic treatments should be considered in combination with metformin according to European association for the study of diabetes (EASD)/ADA consensus guidelines, but preferably, in this setting,
Fig. 3. Possible treatment strategies based on European association for the study of diabetes (EASD)/American diabetes association (ADA) consensus guidelines adapted for Cushing’s disease treated with pasireotide.

7. **Conclusion**

Cushing’s disease is a complex disorder that has to be managed in centres with expertise in adrenal diseases and diabetes. It frequently impairs glucose regulation and can cause diabetes, thereby requiring specific management in addition to treatment for the cause of the hypercortisolism. If pituitary surgery fails, one alternative is the somatostatin analogue pasireotide, the unquestionable value of which was demonstrated in a recent phase-III study. Physicians initiating pasireotide therapy should proactively monitor patients for the development or exacerbation of diabetes, and a blood glucose-monitoring schedule may be proposed (Fig. 2). More studies also need to be conducted so that scientifically validated recommendations for the management of hyperglycaemia during pasireotide therapy for Cushing’s disease can be proposed.

**Disclosure of interest**

Y. Reznik carried out clinical trials as co-investigator for Novartis, Medtronic, Eli Lilly and Novo Nordisk. He provided advisory services to Novartis, Medtronic, Abbott and Eli Lilly and attended conferences organized by Eli Lilly and Medtronic as a contributor.

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