

Pasireotide in an insulin-requiring diabetic acromegalic patient without worsening of hyperglycemia

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Summary

Long-acting pasireotide is an effective treatment option for acromegaly, but it is associated with hyperglycemia, which could impact its use in patients with diabetes. We present a case of a 53-year-old man with acromegaly and type 2 diabetes mellitus (glycated hemoglobin (HbA_{1c}): 7.5%), who refused surgery to remove a pituitary macroadenoma and enrolled in a Phase 3 clinical trial comparing long-acting pasireotide and long-acting octreotide in acromegalic patients. The patient initially received octreotide, but insulin-like growth factor 1 (IGF-1) levels remained elevated after 12 months (383.9 ng/mL; 193.0 ng/mL; reference range: 86.5–223.8 ng/mL), indicating uncontrolled acromegaly. He switched to pasireotide 40 mg and subsequently increased to 60 mg. Within 6 months, IGF-1 levels normalized (193.0 ng/mL), and they were mostly normal for the next 62 months of treatment with pasireotide (median IGF-1: 190.7 ng/mL). Additionally, HbA_{1c} levels remained similar to or lower than baseline levels (range, 6.7% to 7.8%) during treatment with pasireotide despite major changes to the patient's antidiabetic regimen, which included insulin and metformin. Uncontrolled acromegaly can result in hyperglycemia due to an increase in insulin resistance. Despite having insulin-requiring type 2 diabetes, the patient presented here did not experience a long-term increase in HbA_{1c} levels upon initiating pasireotide, likely because long-term control of acromegaly resulted in increased insulin sensitivity. This case highlights the utility of long-acting pasireotide to treat acromegaly in patients whose levels were uncontrolled after long-acting octreotide and who manage diabetes with insulin.

Learning points

- Long-acting pasireotide provided adequate, long-term biochemical control of acromegaly in a patient with insulin-requiring type 2 diabetes mellitus who was unresponsive to long-acting octreotide.
- Glycemic levels initially increased after starting treatment with pasireotide but quickly stabilized as acromegaly became controlled.
- Long-acting pasireotide, along with an appropriate antidiabetic regimen, may be a suitable therapy for patients with acromegaly who also have insulin-requiring type 2 diabetes mellitus.

Background

Acromegaly is a rare disease in which a benign somatotrophic adenoma causes excessive secretion of growth hormone (GH), resulting in the overproduction

of insulin-like growth factor 1 (IGF-1) (1). When GH or IGF-1 levels are not controlled, various symptoms and comorbidities can develop, including pronounced facial



features, increased perspiration, headaches, paresthesia, sexual dysfunction, skeletal growth and soft-tissue swelling. Goals of treatment include reducing clinical symptoms and achieving biochemical control of hormone levels. First-line treatment for acromegaly is removal of the pituitary adenoma by transsphenoidal surgery (1). Medical treatment options are available for patients with recurrent disease after surgery, who are poor candidates for surgery, or who refuse surgery, including somatostatin analogs (SSAs) that exert pharmacological activity via binding to somatostatin receptors (2, 3). There are 5 subclasses of somatostatin receptors (sst_{1-5}) that, when activated, inhibit the release of a variety of hormones, including GH and insulin (4).

Long-acting pasireotide is an SSA injection approved by the US Food and Drug Administration (FDA) for the treatment of patients with acromegaly who have had an inadequate response to surgery or for whom surgery is not an option (2). In a 12-month Phase 3 superiority study (C2305, ClinicalTrials.gov identifier, NCT00600886), pasireotide was more effective than long-acting octreotide in providing biochemical control (normalization of IGF-1 level and GH level <2.5 ng/mL) for medically naive patients with acromegaly (5). In the 12-month crossover extension phase of the C2305 trial, 17.3% of the patients whose acromegaly was inadequately controlled with octreotide achieved biochemical control with pasireotide (6). Pasireotide, however, was associated with more hyperglycemia-related adverse events compared to octreotide (5). After beginning pasireotide treatment, mean fasting plasma glucose (FPG) and glycated hemoglobin (HbA_{1c}) levels initially increased and then quickly stabilized for up to 26 months (7). Pasireotide has a higher affinity for sst_5 (4), a key regulator of insulin secretion in the pancreas (3), than other SSAs. A randomized, open-label study in healthy volunteers demonstrated that pasireotide-associated hyperglycemia was caused by a decrease in insulin secretion, not by a decrease in insulin sensitivity (8). It is recommended that patients be monitored for pasireotide-associated hyperglycemia during treatment and prescribed an antidiabetic regimen upon initial signs of hyperglycemia (2).

Currently, it is unclear whether pasireotide is a viable treatment option for insulin-requiring type 2 patients with diabetes and acromegaly. While pasireotide can cause hyperglycemia, the chronic elevation of GH in patients with acromegaly is associated with decreased insulin sensitivity and elevated glycemic levels (1). It has been reported that patients who initiate treatment with

pasireotide have an initial increase in glycemic levels that peaks within several months but stabilizes once acromegaly is controlled (7, 9).

Herein, we present a case study of a patient with acromegaly with insulin-requiring type 2 diabetes mellitus who refused surgery to remove a pituitary macroadenoma and participated in the C2305 trial. During the initial 12-month core phase, the patient did not achieve biochemical control while being treated with octreotide. The patient was enrolled in the extension phase and crossed over to pasireotide for an additional 68 months. Biochemical control was achieved within 6 months after initiation of treatment with pasireotide and generally remained controlled throughout the course of treatment. Moreover, while on long-term pasireotide, HbA_{1c} levels remained stable, indicating that pasireotide may be an effective treatment option for patients with acromegaly with insulin-requiring type 2 diabetes.

Case presentation

The patient was a 53-year-old man with a 15-year history of type 2 diabetes mellitus as well as vertigo, hypertension, obstructive sleep apnea, obesity, hyperlipidemia, bilateral carpal tunnel syndrome and arthralgia. While being evaluated for vertigo, an MRI revealed a 1.2-cm pituitary macroadenoma with remodeling of the sella floor and a deviation of the infundibulum to the right with no suprasellar extension.

Investigation

The patient's IGF-1 levels were uncontrolled (551.0 ng/mL (reference range: 86.5–223.8 ng/mL)) and GH levels were elevated (2-hour 5-point mean GH: 1.7 ng/mL), which led to the acromegaly diagnosis. The patient also had an elevated baseline level of FPG (140 mg/dL) and HbA_{1c} (7.5%) and was being treated with metformin 1000 mg twice daily (b.i.d.), pioglitazone 45 mg once daily (q.d.), glipizide extended release 10 mg q.d. and insulin detemir (rDNA origin) injection 30 units q.d.

Treatment

The patient refused surgical removal of the pituitary adenoma and was enrolled in the C2305 study in April 2009, and he was assigned to receive intramuscular injections of octreotide 20 mg every 28 days. Baseline IGF-1 and GH levels were 487.4 ng/mL and 1.7 ng/mL respectively.

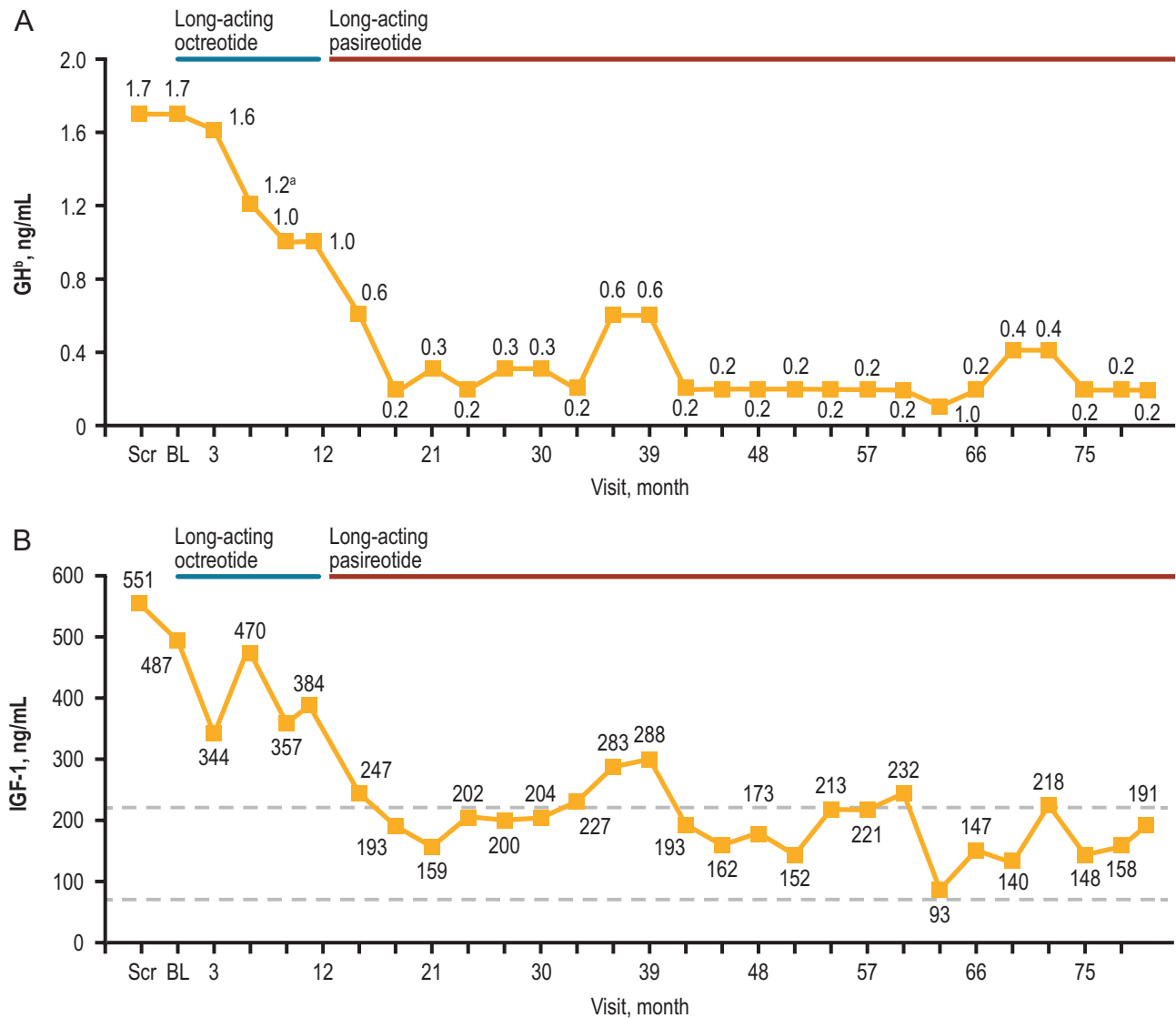


Figure 1 Levels of (A) 2-hour, 5-point mean GH and (B) IGF-1 measured during initial screening and throughout treatment with octreotide and pasireotide. The biochemical reference range of 86.5–223.8 ng/mL is indicated by the dotted gray lines. BL, baseline; GH, growth hormone; IGF-1, insulin-like growth factor 1; Scr, screening. ^aSample was hemolyzed. ^bGH levels are 2-hour 5-point mean GH levels.

After 3 months, IGF-1 (344.1 ng/mL) and GH (1.6 ng/mL) levels remained elevated (Fig. 1), resulting in a dose increase to 30 mg every 28 days. Insulin aspart 10 units at dinnertime was added to his antidiabetic regimen because his HbA_{1c} level remained elevated (8.5%). Treatment continued for 12 months, and IGF-1 levels remained uncontrolled (383.9 ng/mL), although GH levels decreased to 1.0 ng/mL. Glycemic levels continued to indicate uncontrolled type 2 diabetes mellitus (HbA_{1c}: 7.3%; FPG: 147 mg/dL; Fig. 2).

After 12 months of treatment with octreotide, the patient entered the extension phase of the study and

was crossed over to pasireotide 40 mg via intramuscular injection every 28 days.

Outcome and follow-up

After 3 months of treatment with pasireotide (month 15 from baseline), IGF-1 levels decreased to 246.7 ng/mL but remained slightly above the reference range (86.5–223.8 ng/mL; Fig. 1). GH levels continued to decrease to 0.6 ng/mL. The dose of pasireotide was then increased to 60 mg every 28 days. After 6 months of treatment with pasireotide (month 18 from baseline),

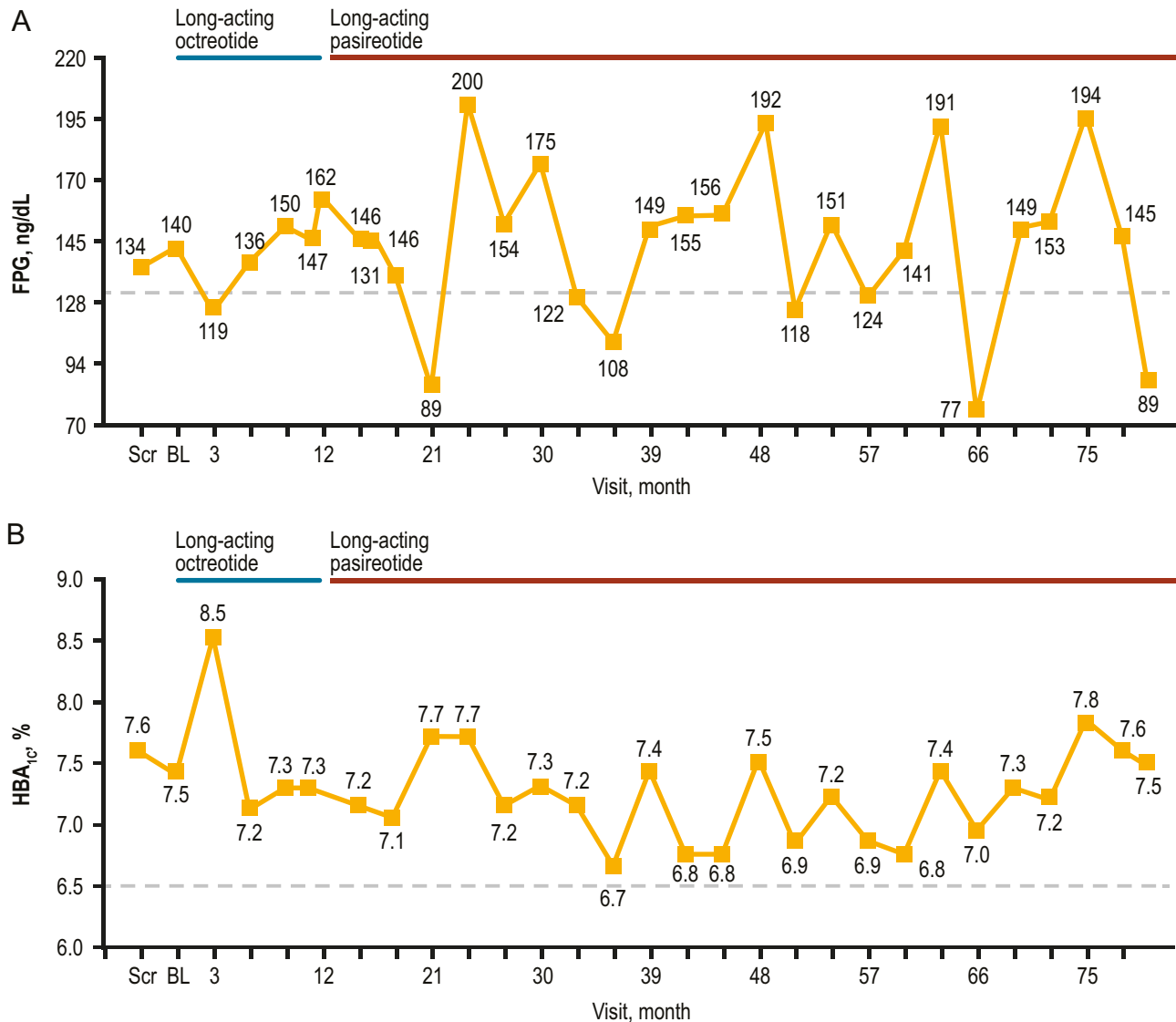


Figure 2

Levels of (A) fasting plasma glucose (values above the dashed line indicate type 2 diabetes mellitus) and (B) HbA_{1c} measured during initial screening and throughout treatment with octreotide and pasireotide (values $\geq 6.5\%$ indicate diabetes). Note: FPG levels were variable because the patient was not always compliant with diet and exercise. BL, baseline; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; Scr, screening.

IGF-1 levels normalized reaching 193.0ng/mL, and GH levels further decreased to 0.2ng/mL. For the next 62 months, IGF-1 levels generally remained within the reference range. At visits that occurred 33, 36, 39 and 60 months after baseline, IGF-1 levels were slightly above the upper limit of the reference range (226.8, 283.5, 288.4 and 231.8ng/mL respectively) but eventually normalized without changes to overall treatment. Additionally, GH levels remained ≤ 0.6 ng/mL and decreased weight (from 282 pounds to 258 pounds) was noted over the 68-month course of treatment with pasireotide.

During the first month of treatment with pasireotide, FPG levels initially increased from 147 to 162mg/dL

but decreased to 146mg/dL after 3 months of treatment with pasireotide (Fig. 2). After 6 months of treatment with pasireotide (month 18 from baseline), levels of FPG (131mg/dL) and HbA_{1c} (7.1%) were below baseline. FPG levels continued to be variable during the course of treatment with pasireotide, ranging from 77 to 200mg/dL. However, HbA_{1c} remained stable overall, with reported levels that were similar to or lower than baseline (range, 6.7% to 7.8%) throughout the 68-month course of treatment with pasireotide. FPG levels were variable throughout treatment, ranging from 77 to 100ng/dL, because the patient was not always compliant with diet and exercise. During this treatment period, the patient



Table 1 Changes to antidiabetic medications during the course of treatment.

Visit	Metformin	Insulin detemir	Insulin aspart	Other antidiabetic medications
Screening	1000 mg b.i.d.	25 units q.d.		Pioglitazone 45 mg q.d. Glipizide extended release 10 mg b.i.d.
Initiate treatment with octreotide long-acting ^a				
Baseline ^a	1000 mg b.i.d.	30 units q.d.		Pioglitazone 45 mg q.d. Glipizide extended release 10 mg b.i.d.
Month 3 ^b	1000 mg b.i.d.	30 units q.a.m. 45 units q.h.s.	10 units q.d. with dinner	Glipizide extended release 10 mg b.i.d.
Month 6	1000 mg b.i.d.	35 units q.a.m. 50 units q.h.s.	15, 15, 20 units with meals and sliding scale	Glipizide extended release 10 mg b.i.d.
Month 11 ^c	1000 mg b.i.d.	35 units q.a.m. 60 units q.h.s.	20, 20, 25 units with meals and sliding scale	Glipizide extended release 10 mg b.i.d.
Initiate treatment with pasireotide long-acting				
Month 12 ^d	1000 mg b.i.d.	50 units q.a.m. 60 units q.h.s.	20, 20, 25 units with meals and sliding scale	Glipizide extended release 10 mg b.i.d.
Month 15 ^e	1000 mg b.i.d.	45–60 units q.a.m. 40–70 units q.h.s.	20, 15, 25, 10 units with meals, at bedtime, and on a sliding scale	
Month 21	1000 mg b.i.d.	85 units b.i.d.	20 t.i.d. units with meals and on a sliding scale	
Month 30	1000 mg b.i.d.	36–85 units b.i.d.	8–24 t.i.d. units with meals and on a sliding scale	Sitagliptin 50–100 mg q.d.
Month 60	1000 mg b.i.d.	60 units q.h.s. 80 units q.a.m.	30 t.i.d. units with meals and on a sliding scale	Sitagliptin 100 mg q.d.
Month 63	1000 mg b.i.d.	60 units q.h.s. 80 units q.a.m.	35 t.i.d. units with meals and on a sliding scale	Liraglutide 0.6 mg q.d.
Month 66	1000 mg b.i.d.	70–90 units b.i.d.	10–35 t.i.d. units with meals and on a sliding scale	Liraglutide 1.2–1.8 mg q.d.

b.i.d., twice daily; q28d, every 28 days; q.a.m., every morning; q.d., once daily; q.h.s., every night at bedtime; t.i.d., three times daily.

^aOctreotide long-acting 20 mg intramuscularly (IM) q28d initiated. ^bDose of octreotide long-acting increased to 30 mg. ^cEnd of main trial/start of extension phase. ^dPasireotide long-acting 40 mg IM q28d initiated after 1 year main trial. ^eDose of pasireotide long-acting increased to 60 mg at month 16.

continued to take metformin 1000 mg b.i.d., while dosing of insulin varied due to changes in diet and exercise (Table 1). At month 28, sitagliptin was added to the antidiabetic regimen, which was replaced by liraglutide at month 63.

Discussion

Long-acting pasireotide is an FDA-approved SSA for the treatment of patients with acromegaly who have had an inadequate response to surgery or for whom surgery is not an option (2). In this case, we present a surgically naive patient with insulin-requiring type 2 diabetes mellitus who achieved adequate biochemical control of acromegaly with pasireotide after an inadequate response to 12 months of treatment with octreotide. Recent guidelines from the Endocrine Society suggest that biochemical goals of acromegaly treatment include IGF-1 levels that fall within an age-normalized range and GH levels <1.0 ng/mL (1). After 1 year of treatment with octreotide, levels of both GH (1.0 ng/mL) and IGF-1 (383.9 ng/mL [reference range, 86.5–223.8 ng/mL]) were outside of the range of biochemical control.

However, within 6 months of switching to treatment with pasireotide, biochemical control goals were achieved (GH, 0.2 ng/mL; IGF-1, 193.0 ng/mL) and remained relatively stable for 68 months. This case exemplifies that pasireotide can be an effective treatment for acromegaly in patients who do not respond adequately to octreotide. This is consistent with data from a previous Phase 3 clinical trial in which pasireotide was effective in 15% to 20% of patients with acromegaly that was inadequately controlled with octreotide or lanreotide (9). Although pasireotide, octreotide and lanreotide are all SSAs with a similar mechanism of action, their affinities for different somatostatin receptors vary. Notably, compared with other approved SSAs, pasireotide binds with greatest affinity to sst₅, which is expressed in 86% of the tumors (4).

While pasireotide use can cause an increase in glycemic levels, the chronic elevation of GH levels, as seen in patients with acromegaly, is also associated with hyperglycemia, mostly via a decrease in insulin sensitivity (1). Thus, patients who initiate treatment with pasireotide typically see initial increases in FPG and HbA_{1c} that peak within several months before stabilizing upon achieving control of acromegaly (7, 9). Despite having



insulin-requiring type 2 diabetes, the patient presented here did not experience a long-term increase in HbA_{1c} levels after initiating pasireotide, likely because a long-term stable reduction in GH levels resulted in an increase in insulin sensitivity. During the 68 months of treatment with pasireotide, HbA_{1c} levels were stable overall, suggesting that pasireotide may be an acceptable option in the treatment of acromegaly in patients managing type 2 diabetes with insulin.

An understanding of the pathophysiology of pasireotide-associated hyperglycemia is needed when determining the appropriate antidiabetic therapy to administer. Insulin secretion can be directly regulated by sst₅, which is present on insulin-secreting β cells in the pancreas (3). The greater binding affinity of pasireotide to sst₅ compared with octreotide or lanreotide suggests a mechanism for hyperglycemia that is associated only with pasireotide, resulting in decreased insulin secretion without decreased insulin sensitivity (8). Indeed, *post hoc* analyses of Phase 3 clinical trials have identified predictive risk factors for pasireotide-associated hyperglycemia in patients with acromegaly, including body mass index (≥ 25 kg/m²), increased FPG (≥ 126 mg/dL) and HbA_{1c} ($\geq 6.5\%$) at baseline and a history of dyslipidemia (10, 11). However, the observation that the patient in this case study experienced no long-term increase in HbA_{1c} levels while being treated with pasireotide and receiving insulin is not unexpected. Expert recommendations for the treatment of pasireotide-associated hyperglycemia indicate that metformin, which increases insulin sensitivity, is the optimal first-line antidiabetic medication (12). Metformin-based antidiabetic therapy can be intensified with the addition of a dipeptidyl peptidase-4 (DPP-4) inhibitor, such as sitagliptin. If necessary to achieve optimal glycemic control, the DPP-4 inhibitor can be replaced with a GLP-1 receptor agonist such as liraglutide. To characterize the optimal management of pasireotide-associated hyperglycemia, an ongoing Phase 4 study will compare glycemic control at 16 weeks in patients treated with pasireotide and either incretin-based therapy or insulin (ClinicalTrials.gov identifier: NCT02060383) (13).

Taken together, this information suggests that patients with insulin-requiring type 2 diabetes who have not achieved biochemical control of acromegaly using treatment with octreotide may be suitable candidates for treatment with pasireotide. Moreover, this case study demonstrates that improvements in or stabilization of hyperglycemia associated with acromegaly may be achieved upon obtaining and maintaining adequate biochemical control with long-term pasireotide. In cases

of pasireotide-associated hyperglycemia, these may be effectively managed if appropriate antidiabetic therapies are administered.

Declaration of interest

M B G has served as an investigator for and received grants from Novartis Pharmaceuticals Corporation, Novo Nordisk, OPKO, Chiasma, Teva and Pfizer, Inc. K L S has no potential conflict of interest to declare regarding the publication of this article.

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Patient consent

The C2305 trial was conducted in accordance with the Declaration of Helsinki (1964), with the subjects' understanding and consent and the ethics committees' approval. Written informed consent was obtained from the patient for the publication of this case report.

Authors contributions

M B G was the physician who diagnosed and treated the patient. K L S was the research coordinator who analyzed the data for the case. Both authors contributed to the concept, draft development and approval of the manuscript for submission.

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