CASE REPORT

Analgesic effect of long-acting somatostatin receptor agonist pasireotide in a patient with acromegaly and intractable headaches

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SUMMARY

A 22-year-old woman presented with worsening vision loss and headaches. A diagnosis of acromegaly was confirmed after detection of an invasive pituitary macroadenoma and biochemical testing. Despite two attempts of surgical debulking of the tumour and administration of long-acting octreotide and cabergoline, growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels were uncontrolled. The patient experienced persistent headaches despite surgery, gamma knife radiation and ventriculoperitoneal shunt placement; she was then enrolled in the ACCESS trial (ClinicalTrials.gov identifier, NCT01995734). Pasireotide (Signifor; Signifor LAR) was initiated, which led to reduced GH and IGF-1 levels and resolution of her intractable headaches. This highlights the use of monthly pasireotide in resolving headaches and improved biochemical control in a patient with acromegaly. We postulate that the headaches improved due to an analgesic and/or anti-inflammatory effect mediated by somatostatin receptors targeted by pasireotide. This may represent an additional benefit of pasireotide and requires further investigation.

BACKGROUND

Acromegaly is an endocrine disorder characterised by excess secretion of growth hormone (GH) from somatotroph cells in the anterior pituitary, typically due to a pituitary macroadenoma.^{1–3} Patients with acromegaly may present with symptoms that include headache, visual field deficits, joint pain, visceral enlargement, hypertension and new-onset type 2 diabetes mellitus.^{1–3} Persistent exposure to elevated levels of GH and its primary mediator, insulin-like growth factor 1 (IGF-1), is associated with worsened comorbidities and increased mortality.^{1,2}

Somatostatin analogues have been used to treat acromegaly in recent years. These analogues have varying affinity for the five somatostatin receptors. Binding studies using synthetic somatostatin analogues have shown that the somatostatin receptors can be divided into two subgroups: SRIF₁ (somatotropin release-inhibiting factor) and SRIF₂. The SRIF₁ group consists of sst₂, sst₃ and sst₄. Binding of somatostatin and analogues with affinity to these receptors exerts antihormonal and antimitotic actions.⁴ The SRIF₂ group consists

of sst₁ and sst₅. Studies using agonists that target these receptors suggest that this group of somatostatin receptors may exert anti-inflammatory and analgesic effects.^{4–8}

Pasireotide (Signifor; Signifor LAR) is a novel multireceptor-targeted somatostatin analogue approved for the treatment of acromegaly. It has demonstrated high binding affinity for four of the five human somatostatin receptors (sst₁, sst₂, sst₃ and sst₅), whereas first-generation somatostatin analogues, such as octreotide, bind mainly with high affinity to sst₂.^{9,10} Pasireotide has provided effective biochemical control in medically naive patients¹¹ and in some patients with inadequate biochemical control with other somatostatin analogues.¹² This may in part be due to its high binding affinity for sst₂ and sst₃, which have been shown to be expressed on GH-secreting adenomas.^{10–13} Improvements in symptoms of disease, which included fatigue, headache, osteoarthritis, paresthesia and perspiration, were also observed.¹¹

Here, we report a case study of a patient treated with long-acting pasireotide, who achieved biochemical control of acromegaly and had complete resolution of intractable headaches. The patient was enrolled in the ACCESS study (ClinicalTrials.gov identifier, NCT01995734), which was an open-label, uncontrolled, single-arm, multicentre, expanded-treatment protocol safety study designed to provide patients with acromegaly access to long-acting pasireotide while regulatory approval was being sought. To be included in the cohort, patients with acromegaly must have undergone surgery to remove the pituitary tumour (unless they were not eligible for surgery or refused surgery) and had uncontrolled acromegaly, as defined by IGF-1 levels greater than the upper limit of normal and random GH greater than 1 ng/mL within 30 days of screening. Patients were monitored every 3 months locally, as per the treatment plan indicated in the protocol, but data were not collected or evaluated by the study sponsor.

CASE PRESENTATION

A 22-year-old woman presented with worsening vision loss and reported debilitating headaches. An invasive pituitary macroadenoma, measuring 3.2×3.5 × 4.3 cm, was discovered using MRI of the pituitary in March 2011 (figure 1A). The patient exhibited signs of acromegaly, which

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Figure 1 MRI of pituitary tumour. (A) T1-FLAIR coronal post contrast from 3 March 2011 (at initial diagnosis). (B) T1 coronal post contrast from 4 October 2015.

included coarse facial features as well as large hands and feet. The diagnosis of acromegaly was confirmed with the detection of elevated GH and IGF-1 levels (274 ng/mL (reference range, 0–8 ng/mL) and 957 ng/mL (reference range, 117–329 ng/mL), respectively). In April 2011, endoscopic transsphenoidal surgery was performed to remove the central portion of the tumour, and long-acting octreotide 40 mg once monthly was initiated. However, there was still a significant amount of residual tumour (measuring 4×4×3.7 cm), and an additional pituitary tumour resection was performed via a transcranial approach in June 2011. After surgery, GH level was 7.45 ng/mL, and IGF-1 level was >1600 ng/mL. Even though a combination of octreotide 40 mg once monthly and cabergoline 0.5 mg twice weekly was initiated in June 2011, IGF-1 levels remained elevated and the patient continued to experience headaches.

The patient described the headaches as generalised with a pressure-like sensation of moderate to severe intensity and associated with nausea and vomiting. The headaches initially occurred a couple times a week and then later in her clinical course occurred daily. She experienced temporary relief after each surgery; however, the headaches would then recur. In September 2011, she experienced an acute worsening of headaches and was found to have ventriculomegaly on MRI. A ventriculoperitoneal (VP) shunt was placed to manage headaches in October 2011 with improvement of ventriculomegaly on CT scan of the head and temporary relief of the headaches. However, a month later, the patient began to again experience headaches and underwent gamma knife radiation for further management of the acromegaly. Additionally, the patient experienced substantial weight gain from 201 pounds in June 2011 to 331 pounds in August 2013.

Topiramate 100 mg twice daily (indicated to improve headaches and weight loss) was started in August 2013 as the patient continued to experience persistent headaches despite having had surgical debulking, gamma knife radiation and medical treatment of the acromegaly. After an initial improvement, headaches recurred in October 2013, and topiramate dosage was increased to 200 mg twice daily. The patient continued to experience debilitating headaches despite adjustments to the VP shunt and treatments with ibuprofen (800 mg three times a day, from 2011), acetaminophen with codeine (every 6 hours, from 2013) and topiramate from 2013. The patient's weight gain also remained unresolved by topiramate and was measured at 324 pounds in August 2014. Tumour size remained unchanged at approximately 3.0×2.0 cm from October 2013 until October 2014 (table 1).

Table 1 Change in tumour size

Date	Tumour size (cm)	Comments
March 2011	3.5×4.3 × 3.2	—
April 2011	4.0×4.1 × 3.7	Residual tumour after transsphenoidal surgery
June 2011	3.6×2.5 × 3.2	Resection of tumour after craniotomy
October 2012	3.2×2.2 × 1.3	Residual tumour surrounding right cavernous sinus
October 2013	3.3×2.1 × 1.8	Mass unchanged in size
October 2014	3.0×2.0 × 1.5	Mass unchanged in size
October 2015	3.0×1.9 × 1.5	Mass unchanged in size

In August 2014, the patient was enrolled in the ACCESS trial, and pasireotide 40 mg was initiated, after discontinuing long-acting octreotide and cabergoline in July 2014 to facilitate an adequate washout of the previous treatments. Baseline GH and IGF-1 levels were 9.03 ng/mL and 1090 ng/mL, respectively. Within a month after pasireotide initiation, the patient reported complete resolution of headaches, and the headaches remained resolved through the end of the trial, as summarised in figure 2. Pasireotide treatment led to biochemical control within ~9 months (GH and IGF-1 levels, 1.92 ng/mL and 291 ng/mL, respectively). Tumour size was unchanged 1 year after initiation of pasireotide as shown in figure 1B. The patient's weight was reduced from 324 pounds to 298 pounds after 9 months of pasireotide treatment. However, glycated haemoglobin levels increased from 5.2% to 6.3%, and fasting plasma glucose level increased from 88 mg/dL to 116 mg/dL. The patient was started on metformin for management of hyperglycaemia.

OUTCOME AND FOLLOW-UP

In this case study, pasireotide provided robust resolution of headaches in a patient with acromegaly who had inadequate response to surgical debulking, gamma knife therapy and other medical therapy, including octreotide. The resolution of headaches was likely mediated via somatostatin receptors that modulate analgesic and anti-inflammatory responses. This may provide an additional benefit of pasireotide in patients with acromegaly who have persistent headaches and requires further investigation. In addition to resolution of headaches, the patient also achieved sustained biochemical control and weight reduction, thereby highlighting the significance of controlling acromegaly to improve overall quality of life.

DISCUSSION

Acromegaly is associated with symptoms such as headache, diabetes mellitus, joint pain and visceral enlargement. Improvement in symptoms is considered to be an important goal of treatment and in some cases is independent of the achievement of biochemical control. A study of patient-reported outcomes found that 29.7% of patients perceived that the burden of acromegaly had a substantial impact on daily lives, and a few symptoms remained unresolved even after surgery.¹⁴ Headache is a common symptom reported in approximately 55% of patients with acromegaly and is a clinical marker of disease activity thought to be associated with several factors related to tumour growth and GH hypersecretion.^{2 15 16} In a study of patients with pituitary tumours who experienced incapacitating headaches, surgery resulted in improved headaches in 49% of patients, whereas 36% of patients experienced no improvement, and 15% had worsening of their headaches,¹⁷ suggesting that pituitary surgery does not always resolve headaches effectively.

Figure 2 Patient timeline: GH and IGF-1 levels through the course of treatment with long-acting pasireotide. GH, growth hormone; IGF-1, insulin-like growth factor 1; VP, ventriculoperitoneal.

For this patient, treatment with pasireotide was associated with resolution of intractable headaches within a month of first receiving treatment. This occurred before the patient achieved biochemical control and raises the possibility of an analgesic and/or anti-inflammatory effect, likely mediated via somatostatin receptors that have been shown to modulate inflammatory and nociceptive responses, in particular sst_1 and sst_4 .⁴⁻⁸ Somatostatin is a peptide that is released by various cells in the body, including neuroendocrine and inflammatory cells as well as neurons and exerts its effects throughout the body.⁴ The analgesic and anti-inflammatory effects of somatostatin are thought to be mediated via its actions in sensory and sympathetic neurons, which include downregulation of nociception and inhibition of cytokine release.^{4 18 19} These effects have been supported by acute and chronic pain animal models using somatostatin agonists that target the sst_4 receptor.^{5 6} Other studies have also demonstrated analgesic and/or anti-inflammatory effects via the sst_1 receptor. A study by Mulak *et al* on a mouse model of visceral pain demonstrated analgesic effects of somatostatin agonists via sst_1 .⁷ Furthermore, Imhof *et al* demonstrated the analgesic effects of pasireotide via the sst_1 receptor in a mouse model of immune-mediated arthritis.⁸ This study also showed that pasireotide and octreotide exerted analgesic and anti-inflammatory effects via the sst_2 receptor.⁸ These findings suggest that the sst_2 receptor mediates antihormonal and antimitotic actions and also exerts analgesic and anti-inflammatory effects.

Interestingly, our patient was initially treated with octreotide and failed to achieve biochemical control and alleviation of

headaches but had a significant response when therapy was changed to pasireotide. This was also observed by Marina *et al* in two patients with acromegaly and severe headache who responded to treatment with pasireotide after a lack of response to octreotide. The pituitary adenomas in these patients were found to not only express sst_2 and sst_5 receptors, but a truncated sst_5 variant which was thought to account for the poor response to treatment with octreotide.¹⁵ Expression of these variants of sst_5 on GH-secreting adenomas has been associated with more aggressive features and worse prognosis.²⁰ The alleviation of headaches and achievement of biochemical control in our patient were likely mediated via the effect of pasireotide on multiple receptors, including sst_1 , sst_2 and sst_5 . More studies are needed to further elucidate the effects of pasireotide in alleviation of pain and biochemical control, particularly in patients with persistently elevated GH levels and headaches, despite surgery and other interventions.

The results from this case study are also in alignment with several other studies in which treatment with pasireotide was associated with significant improvement of headaches.^{11 21 22} In patients with acromegaly treated with subcutaneous administration of pasireotide, biochemical control was achieved in approximately one-third of patients, and the percentage of headache-free patients was greater at the end of the study than at baseline.²¹ In a 6-month extension study, the number of headache-free patients approximately doubled.²² Thus, pasireotide exhibits marked biochemical control as well as amelioration of headaches in patients with acromegaly and presents a viable

treatment alternative for patients resistant to other somatostatin analogues.^{9 15}

Finally, pasireotide is generally well tolerated and has an adverse effect profile similar to other somatostatin analogues, with diarrhoea and cholelithiasis as the most commonly reported adverse effects.^{10–12 21–23} However, treatment with pasireotide has been associated with a significantly higher incidence of hyperglycaemia in clinical trials,^{11 12 22 23} as occurred in our patient. The hyperglycaemia is thought to be due to the inhibition of insulin secretion from the pancreas.^{4 10 24} Therefore, patients treated with pasireotide must be closely monitored for the occurrence of hyperglycaemia, particularly those patients with a history of pre-diabetes or diabetes.

Learning points

- Headaches may occur in patients with acromegaly, unrelated to tumour size or biochemical status, and may persist even despite multiple management modalities such as surgery, ventriculoperitoneal shunting and medical therapies such as octreotide.
- Pasireotide (Signifor; Signifor LAR) is a new somatostatin receptor analogue that not only effectively leads to biochemical normalisation of growth hormone and insulin-like growth factor 1, but may have analgesic and anti-inflammatory effects that could potentially alleviate headaches in this subset of patients who have persistent tumour burden.
- Pasireotide is generally well tolerated; however, patients should be closely monitored for the occurrence of hyperglycaemia while on the medication.

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