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CASE SERIES

Long-term pasireotide-LAR treatment in the personalized therapy of patients with complex acromegaly: a collection of clinical experiences

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Abstract

Pasireotide-LAR is recommended as a second-line treatment for patients with acromegaly. Although the effects of pasireotide-LAR have been well characterized in clinical studies, real-practice evidence is scant, especially in the long term and within the individualization of therapy in patients with comorbidities. To provide additional insight on the individualized approach to acromegaly management, six clinical cases of complex acromegaly treated with pasireotide-LAR for more than 5 years were reported. Pasireotide-LAR allowed the normalization of insulin-like growth factor 1 (IGF1) values in all patients and reduced tumour residue volume where present. A good safety profile and long-term tolerability were also reported.

Keywords: acromegaly, diabetes mellitus, growth hormone, IGF1, pasireotide-LAR, somatotropinoma.

Citation

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Introduction

Acromegaly is a rare endocrine disorder typically caused by a pituitary tumour and characterized by excessive secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF1), its target hormone.[1,2] In a recent review and meta-analysis, the pooled prevalence of acromegaly was estimated at around 59 cases per million people worldwide, with an incidence of 3.8 per million person-years and considerable regional variability.[3] However, estimates on prevalence and incidence may greatly vary according to regional differences, with prevalence estimates ranging from 28 to 137 cases per million population and incidence ranging from 2 to 12 cases per million person-years.[4]

Prolonged exposure to increased levels of GH and IGF1 leads to progressive systemic complications, including bone, cardiovascular, metabolic, cerebrovascular and respiratory diseases.[5,6] Up to 50% of patients with acromegaly have insulin resistance, which results from the direct anti-insulin effects of GH and leads to glucose intolerance and diabetes.[7] The prevalence of diabetes amongst patients with acromegaly has been variably estimated (16–56%), and a positive correlation between baseline IGF1 levels and diabetes has been reported.[7,8] Additional risk factors for diabetes in patients with acromegaly are age, BMI and a family history of diabetes, as in the general population.[7]

Treatment of acromegaly aims to excise the disease-causing adenoma and reduce GH and IGF1 levels to

normal values.[6] Accordingly, surgical tumour resection through transsphenoidal (TS) selective adenectomy is considered the first line of treatment, with reported biochemical cure rates varying between 32% and 85% depending on tumour size, cavernous sinus invasion and neurosurgical experience.[6,9]

In patients for whom first-line or second-line surgery is not feasible or fails, first-generation somatostatin receptor ligands (SRLs) with selectivity for somatostatin receptor sub-type 2 (SSTR2) receptors, namely, octreotide-LAR and lanreotide (LAN) autogel, are further treatment options.[10] However, their effectiveness is sub-optimal, with IGF1 normalization reported in about 30–50% of patients.[11–14]

Pasireotide-LAR is a second-generation long-acting somatostatin multi-receptor ligand with 106-fold higher binding affinity to somatostatin receptor sub-type 5 (SSTR5) as compared with octreotide-LAR and LAN autogel, respectively.[15,16] Pasireotide-LAR is recommended in Europe as a second-line treatment for uncontrolled acromegaly on first-generation SRLs and after surgical failure.[17] Starting pasireotide-LAR 40 mg every 4 weeks is recommended, with subsequent up-titration to 60 mg monthly in case of uncontrolled levels of GH or IGF1 after 3 months of treatment.[18]

The efficacy and safety of pasireotide-LAR were assessed in a phase III clinical trial in patients with acromegaly uncontrolled on first-generation SRLs. Patients in the pasireotide-LAR group achieved better biochemical disease control than those receiving octreotide-LAR, with a safety profile similar to other SRLs, except for a higher frequency and severity of hyperglycaemia and diabetes due to secondary pharmacological activity at SSTR5 receptors.[19]

Although the effects of treatment with pasireotide-LAR have been well characterized in clinical studies, real-practice evidence of the effectiveness and safety of this agent is still limited, especially in the long term.[9,20–22] Thus, sharing real-life experiences on representative individual cases helps to improve the use of pasireotide-LAR and disease management. To this aim, a group of experts in treating patients with acromegaly participated in an advisory board to share and compare their experience in clinical practice with pasireotide-LAR. Starting from the advisory board contents, this paper presents a collection of clinical experiences on the long-term use of pasireotide-LAR (>5 years of treatment) to provide additional insight into the personalized approach to acromegaly management. In particular, the collected clinical experiences addressed the use of pasireotide-LAR in case of contraindication to surgery, poor response or resistance to first-line treatments, presence of burdening symptoms and associated concomitant therapies.

Patients and methods

The authors retrospectively selected and reported clinical experiences related to patients with acromegaly treated with pasireotide-LAR as monotherapy or in addition to other concomitant therapeutic regimens. Selection criteria were age ≥18 years and an indication of treatment with pasireotide-LAR based on manufacturer's label, current guidelines and physician judgment. Due to the retrospective description of these clinical experiences, treatment regimens were not standardized. Data collection was conducted following the ethical principles of the revised version of the Declaration of Helsinki. The retrospective review of patient data was notified to the Ethics Committee of participating centres when required. In all cases, patients provided informed consent to treatment and anonymous publication of clinical data.

Clinical cases

Case 1: pasireotide-LAR in a patient with acromegaly not eligible for radical surgery

A 23-year-old man with acromegaly presented in March 2006 with an increased size of acral extremities, changes in face physiognomy and a recent diagnosis of carpal tunnel syndrome. IGF1 levels were high (952 ng/mL; upper limit of normal (ULN) 360 ng/mL); GH was also elevated (28.5 ng/mL). Contrast-enhanced MRI showed a hypointense focal area referable to a pituitary non-invasive adenoma (maximal diameter 10 mm). In April 2006, the patient underwent TS, and pathological examination showed a mixed GH/prolactin (PRL) pituitary tumour (Ki-67 proliferative index: 2–3%; p53: 8–10%). In 2008, MRI showed no evidence of residual disease, but IGF1 levels were again high (445 ng/mL) and GH nadir was 10.2 ng/mL after an oral glucose tolerance test. Octreotide-LAR 30 mg i.m. every 28 days was then initiated; after an initial biochemical response, it was necessary to increase the dose (40 mg every 28 days) until 2011, when the patient was switched to pegvisomant (20 mg/day) and IGF1 levels normalized. In 2013, MRI showed a hypodense formation of 4 mm residue of the known disease, which remained stable until 2016, when MRI showed a growth of the pituitary lesion (up to 1 cm). Because of an extension into the cavernous sinus preventing radical surgery, the patient was switched to LAN autogel (120 mg every 28 days for 2 years and then every 21 days for the subsequent 3 years). IGF1 was 313 ng/mL (ULN: 263 ng/mL), and MRI was unchanged (Figure 1A). A combination of a first-generation SRL with pegvisomant was proposed, but the patient refused this treatment due to the high number of injections; therefore, monotherapy with a second-generation long-acting

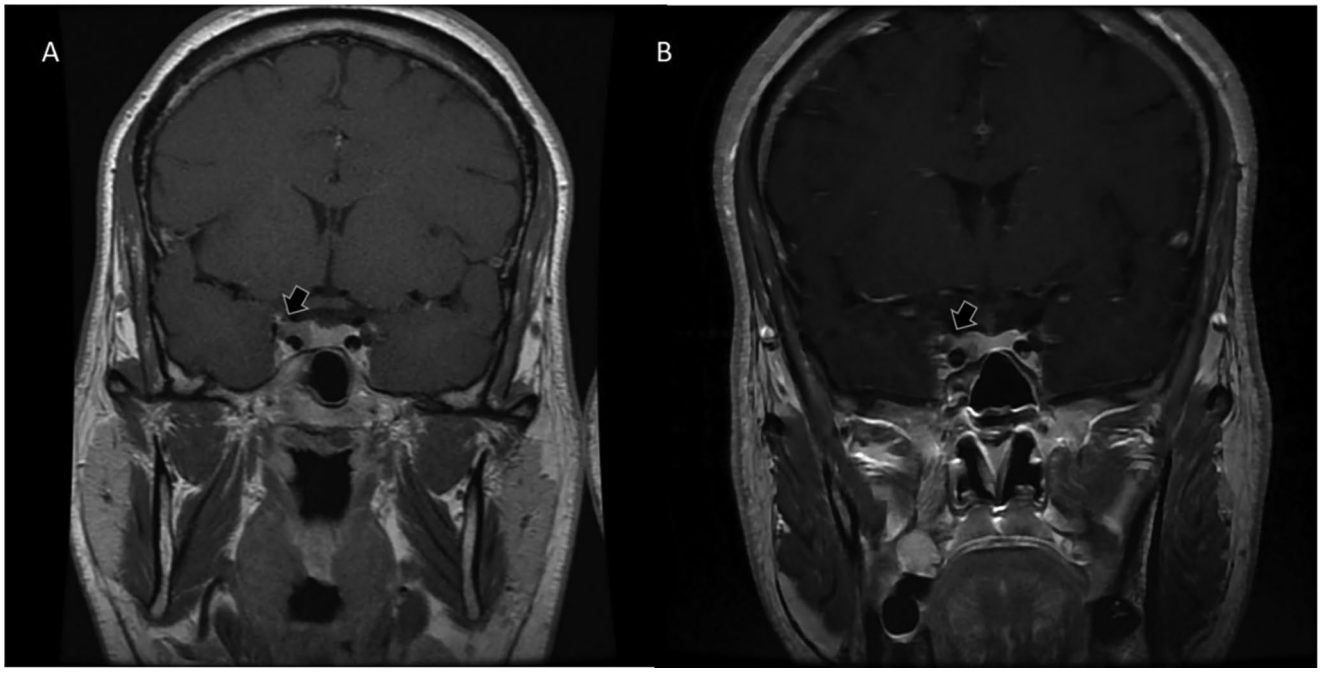
somatostatin multi-receptor ligand was suggested. Treatment was then switched to pasireotide-LAR (40 mg every 28 days and 60 mg every 28 days after 3 months to reach the biochemical control). After 6 months, the patient reported reduced IGF1 levels (174 ng/mL) and partial tumour shrinkage (Figure 1B). At the same time, the patient reported a worsening of glucose metabolism with iatrogenic diabetes (glycaemia 141 mg/dL at 6 months post-pasireotide *versus* 110 mg/dL pre-treatment; HbA1c 6.8% *versus* 6.1% pre-treatment) and slow-release metformin (1,000 mg per day) was added to manage this condition.

In this young patient, in whom a second surgery was not an option, treatment with pasireotide-LAR allowed the normalization of IGF1 values and reduced adenomatous residue volume (Figure 1). The patient has been treated with pasireotide-LAR for 3 years; the slight worsening of the glycometabolic picture is well controlled with metformin.

Case 2: pain-relieving effect of pasireotide-LAR in patient with acromegaly and migraine headache

A 40-year-old female patient presented in 2014 with a pituitary macroadenoma associated with increasing migraine, irregular menses, weight gain (+10 kg), labile hypertension (up to 140/100 mmHg) and moderate hyperprolactinaemia (PRL: 39 ng/mL; normal <23.3 ng/mL), in the context of a familial history of type 2 diabetes (mother). MRI showed a non-invasive suprasellar macroadenoma (maximal diameter 21 mm). Mild acromegalic features were noticed, and IGF1 was markedly elevated (858 ng/mL; ULN 360 ng/mL). Oral glucose tolerance test (75 g) confirmed unsuppressed GH levels (4.8–3.7 ng/mL), insulin resistance and glucose intolerance. The patient underwent TS with post-operative remission of acromegaly, blood pressure and glucose tolerance normalized. However, 6 months later, the migraine reappeared, and IGF1 levels started to rise (from 305 to 362 ng/mL). MRI confirmed the post-operative empty sella with no visible tumour remnant. The patient was first treated with cabergoline 1.5 mg/week but the headache worsened in the context of moderate recurrent GH/IGF1 hypersecretion (GH 4.1 ng/mL, IGF1 422 ng/mL). LAN autogel was started (120 mg every 28 days) with sub-optimal endocrine results (IGF1: 385 ng/mL) and control of migraine up to 7–10 days after administration, with the need for a daily analgesic therapy until the next injection. After a neurological consultation that confirmed the diagnosis of high-frequency migraine without aura, triptans were introduced without clinical benefit. Because of mild hypertension, the patient also started enalapril (5 mg daily) and beta-blockers (propranolol, 40 mg daily) with no effect on migraines.

Figure 1. Post-contrast coronal T1 MRI shows pituitary mass in the right and inferior portion of the pituitary with lateral extension into the cavernous sinus before starting pasireotide-LAR (A, arrow) and initial shrinkage after 6 months of treatment (B, arrow). Tumour tissue had hypointense signal after gadolinium enhancement whereas the normal hypophysis showed homogeneous enhancement on the left side.



A progressive escape to LAN autogel efficacy was also noticed (pre-injection values: GH 3.6 ng/mL, IGF1 461 ng/mL), and a particularly severe, invalidating, 72-h lasting migraine episode was reported. In May 2016, the patient was switched to pasireotide-LAR (40 mg every 28 days). Biochemical control was rapidly achieved (Figure 2), with a rapid relief in headache and a sustained remission of migraine after administration of the second dose. In this patient, pasireotide-LAR was preferred to other treatments despite a persisting empty sella in consideration of the clear pain-relieving effects of first-generation SRL injections. Currently, after 7 years, the patient is still on pasireotide-LAR treatment with very occasional and light episodes of migraine. At last control, GH was 0.19 ng/mL and IGF1 was 125 ng/mL (ULN: 90–360 ng/mL). Pasireotide-induced hyperglycaemia is controlled with diet, metformin 1,000 mg × 2 and empagliflozin 5 mg daily (HbA1c 48 mmol/mol at the last control).

Cases 3 and 4: combination therapy with pasireotide-LAR in patients with uncontrolled acromegaly

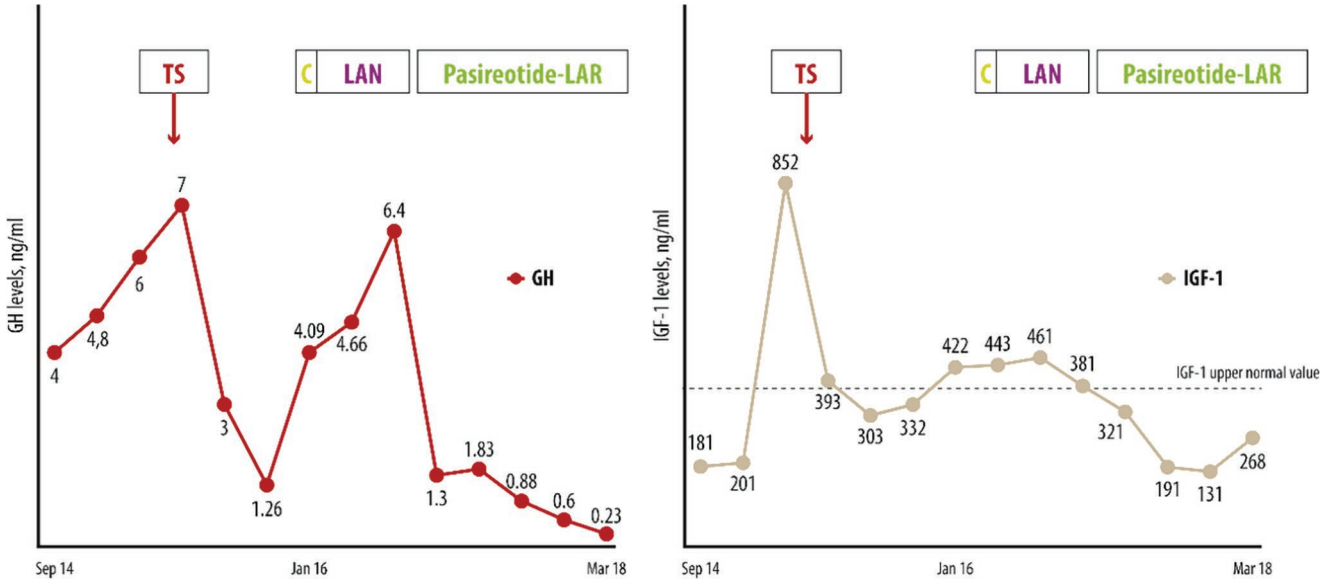
Case 3

A 48-year-old female patient with acromegaly presented in 2014 with hand swelling, pain, and growth of hands and feet. GH was 11.4 ng/mL and IGF1 was 1556 ng/mL (range 65–235 ng/mL). Pituitary contrast-enhanced MRI showed a large adenoma (36 mm) with optic chiasma compression and encasement of the carotid artery. Imbalance between the adenoma size and the symptoms suggested a recent and rapid disease evolution. The patient underwent surgery. Histology examination confirmed a sparsely granulated GH-secreting pituitary adenoma, with a Ki-67 index of 3%. The first surgery was not resolutive, and the patient was treated with LAN autogel without normalization of IGF1 and GH levels. A second surgery was conducted to further debulk the suprasellar portion of the pituitary tumour. The second histology analysis confirmed the diagnosis and proved an absent expression of the sub-type of the somatostatin receptor SSTR2A and a membranous expression of SSTR5 in over 50% of somatostatinoma cells (namely score 2–3 of Volante classification). According to the persistence of high GH and IGF1 and resistance to previous treatment with first-generation SRLs, pasireotide-LAR 60 mg/month was prescribed in 2015, which allowed for reduction of GH and IGF1, albeit to levels not consider normalized. Pegvisomant 15 mg/day, a GH receptor antagonist indicated for the treatment of acromegaly, was added after 1 year, allowing for achievement of biochemical control with levels of GH and IGF1 in the normal ranges for their respective assays. No adverse event or worsening of glucose metabolism occurred.

Case 4

A 54-year-old female patient presented with hypertension, amenorrhea for 6 months, headache and acral oedema. IGF1 levels were 648 ng/mL (ULN: 1.7 ng/mL), PRL was 104 ng/mL (normal <25 ng/mL), LH was 9.1 mU/L and FSH was 2.8 mU/L. MRI showed a macroadenoma (27×24×20 mm) with suprasellar involvement, imprint

Figure 2. Evolution of GH and IGF1 levels before and on pasireotide-LAR. GH and IGF1 levels are observable for the first 4 years of treatment but remained unchanged until the last visit (July 2023).



C, cabergoline; GH, growth hormone; IGF1, insulin-like growth factor 1; LAN, lanreotide (120 mg/28 days); TS, transsphenoidal surgery.

on the hypothalamus, compression of the optic chiasm and invasion of the left cavernous sinus, isointense on T1 and hyperintense on T2. The patient underwent TS surgery with an incomplete resection. Pathological examination showed a focal weak immunoreactivity for somatostatin receptors, low Ki-67 index (1%) and no p53 expression. After surgery, IGF1 decreased and then increased again. Neither LAN autogel (120 mg every 28 days) nor octreotide-LAR (30 mg every 28 days) normalized IGF1 levels, which remained between 377 and 429 ng/mL (ULN: 1.7 ng/mL). The patient was switched to pegvisomant (10 mg/day), which normalized IGF1 levels (330 ng/mL after 2 months, 177 ng/mL after 6 months). However, the residual tumour grew and IGF1 levels increased, and the patient underwent a second surgery. Pathological examination showed increased tumour aggressiveness with a Ki-67 index of up to 20% and diffuse p53 expression. Radiotherapy was added in February 2018 together with pasireotide-LAR (40 mg every 28 days) and pegvisomant (10 mg/day) to reduce IGF1 levels. IGF1 levels decreased progressively (296 ng/mL after 2 months of combined therapy), and pegvisomant administrations were reduced to three times a week (May 2023, IGF1 was 122 ng/mL; ULN: 44–210 ng/mL). Tumour tissue was stably reduced, and the combined therapy was well tolerated.

Cases 5 and 6: management of pasireotide-induced hyperglycaemia in patients with a history of diabetes

Case 5

A 65-year-old female patient was diagnosed with acromegaly in 1995. The patient reported a history of breast cancer, gallbladder stones and a family history of type 2 diabetes. After an incomplete tumour resection in 1996, the patient received stereotactic radiotherapy. Over the years, due to the lack of biochemical control of the disease, it became necessary to undertake pharmacological therapies with SSTR2 (octreotide and LAN autogel) without reaching the biochemical target of the disease (IGF1: 274 ng/mL, normal range: 72–167). In 2018, after 6 months of LAN autogel (120 mg every 28 days) with no results, the patient switched to pasireotide-LAR (40 mg every 28 days). To assess diabetes prior to initiation of pasireotide-LAR, continuous glucose monitoring for research purposes was started. Pre-treatment basal glucose metabolism was within normal limits (glycaemia: 101 mg/dL; HbA1c: 6.0%). Whereas IGF1 levels normalized rapidly within the first 2 months of treatment (100 ng/mL), fasting glucose and HbA1c increased (glycaemia: 142 mg/dL; HbA1c: 6.5%), and metformin was added but diabetes worsened (mean glycaemia: >300 mg/dL; HbA1c: 7.9%). It was decided to maintain the treatment with metformin alone and to reduce pasireotide-LAR to 20 mg with personalized administration every 6 weeks. After 5 years of treatment with pasireotide-LAR, control on IGF1 is well maintained (152 ng/mL after 2 years of treatment, 161 ng/mL at the last control) and glycaemic parameters normalized (basal glycaemia: 100 mg/dL; HbA1c: 6.5%).

Case 6

A 34-year-old patient presented with acromegaly diagnosed 17 years earlier after detecting a macroadenoma, headache episodes and acral enlargement. The patient did not report any family history of type 2 diabetes. In 2014, the patient underwent surgery with a postoperative tumour remnant. IGF1 was consistently off-target for age. The patient did not achieve biochemical control with LAN autogel and octreotide-LAR and was prescribed pasireotide-LAR (40 mg every 28 days) in 2015. IGF1 normalized quickly (130 ng/mL after 1 month). The patient was monitored by continuous glucose monitoring to evaluate the glycaemic trend at baseline and post-therapy. After 1 year of therapy with pasireotide-LAR, metabolic parameters remained controlled (basal glycaemia: 87 mg/dL; HbA1c: 4.5%) and are still maintained in the normal range after 8 years of therapy.

Discussion

Due to complexity and frequent comorbidities, the definition of therapeutic strategies for acromegaly often requires a careful analysis of the clinical history of a patient and the implementation of a multidisciplinary approach as well as evolving personalized medicine approaches based on the tumour profile across imaging, histology and, where applicable, genetics, in particular for long-term management, which is often required.[14,17,23]

Current medical options for acromegaly include SRLs, dopamine agonists and the GH receptor antagonist pegvisomant. Octreotide-LAR and LAN autogel, first-generation SRLs that predominantly act on SSTR2 receptors, are well tolerated but their effectiveness in terms of normalization of IGF1 levels is sub-optimal.[11,14] In the case of treatment failure, pasireotide-LAR, a broad-spectrum SRL that binds four out of five SSTRS, including SSTR2 and SSTR5, represents another option, considering its effectiveness in cases where acromegaly remains uncontrolled on first-generation SRL therapy, as reported in numerous clinical studies.[5,19,24,25] However, only a limited amount of relevant real-world evidence is currently available for pasireotide-LAR, especially in the long term and in patients with complex disease.[9,20–22]

We report a collection of clinical experiences including patients with complex acromegaly in treatment with

pasireotide-LAR for more than 5 years. Clinical experiences presented in this series report the feasibility of long-term pasireotide-LAR treatment in patients not eligible for surgery, with resistance to previous treatments, and/or with comorbidities and on concomitant therapies. In particular, the single or combined use of pasireotide-LAR in patients with more severe disease allowed the complete normalization of IGF1 values in all patients and showed a reduction in tumour residue volume where present. Good safety profile and long-term tolerability were reported for all patients. These observations are in agreement with previous evidence on long-term treatment with pasireotide-LAR[21,22] and with data showing that pasireotide-LAR monotherapy is more cost-effective compared with combination treatment and has the advantage when there are concerns of tumour growth.[26]

The risk of developing new-onset or worsening of pre-existing diabetes is one of the most important considerations when using pasireotide-LAR as reported in clinical trials and post-marketing studies, with occasional ketoacidosis.[19,20] Therefore, glycaemic status should be carefully assessed before starting treatment, patients with uncontrolled hyperglycaemia (HbA1c >8%) should not be placed on pasireotide-LAR until acceptable glycaemic control is obtained and diabetes monitoring should be intensified during treatment to optimize the use of antidiabetic drugs where necessary.[18] In this series of clinical experiences, some patients presented a modest worsening of their glycometabolic status, which was well controlled with antidiabetic therapy in all cases, as previously observed.[27] Nevertheless, the importance of careful glycaemic surveillance should be emphasized before starting and during therapy with pasireotide-LAR, and continuous glycaemia monitoring should be performed. For instance, recent real-world studies showed that, when there is an increase in blood glucose levels, a dose reduction of pasireotide-LAR over time and addition of hypoglycaemic agents allowed the maintenance of the biochemical response along with improved glycaemic control.[22,28] Consequently, dose reductions, when indicated according to patient needs, can sustain control of acromegaly as part of a personalized approach over long-term therapy and allow patients to maintain long-term biochemical control whilst minimizing adverse drug effects.

The pain-relieving effect, an observed benefit of pasireotide, was also observed, as previously reported in other studies and real-world experiences.[9,20,26,29] Headache is a frequent and sometimes invalidating symptom of acromegaly. In a recent study, most patients were reported to have the characteristic symptoms of migraine as defined by the International Headache Society diagnostic criteria.[30] This is typically associated with disease activity, which acts as a trigger, and SRL is known to exert a time-dependent and dose-dependent analgesic effect in patients with acromegaly. Headache may persist in the presence of biochemical control of acromegaly, especially after incomplete tumour resection, and is often ipsilateral to tumour remnant and, as a general rule, patients with pituitary tumours without acromegaly may also experience headache.[31] Better control of headache with pasireotide-LAR as compared with octreotide has been reported in some patients, sometimes preceding disease control, and it was proposed that this effect can be due to the action of the drug on multiple receptors, including SSTR1, SSTR2 and SSTR5.[30,32] In Case 2, migraine recurred early in the presence of an empty sella as soon as IGF1 started to increase after surgery, and the improved response to pasireotide-LAR appeared to be mainly related to the biochemical control of acromegaly. However, we cannot exclude additional analgesic effects of the drug as mentioned earlier. To further support this hypothesis, it has to be reported that octreotide has been used with some success in the treatment of primary migraine and cluster headache, supporting a role for SSTRs regardless of GH/IGF1 hypersecretion, in particular SSTR2, which may also exert anti-inflammatory effects.[29,33]

As observed for Cases 3 and 4, pasireotide-LAR and pegvisomant could be proposed as a third-line combination therapy in very severe cases (characterized by elevated IGF1 expression, tumour dimension and invasiveness, and high proliferative index Ki-67 expression), when surgery is not an option or if radiotherapy is contraindicated or not available, or whilst awaiting tumour-shrinking effects of radiation in more aggressive tumours.[23,34]

Conclusions

This collection of clinical experiences supports the clinical evidence from trials and reports on the effectiveness and versatility of long-term pasireotide-LAR treatment. Reported experiences also support the importance of tailored treatment in the management of acromegaly in daily clinical practice and the baseline clinical evaluations, including the presence of important comorbidities and resistance to previous therapy that could drive the therapeutic strategy with pasireotide-LAR.

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Availability of data: All data generated or analyzed in this case series are included in this article. Further inquiries can be directed to the corresponding author or the reference author for each clinical experience.

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