Pasireotide in Acromegaly: An Overview of Current Mechanistic and Clinical Data

Susan L. Samson

The Pituitary Center at Baylor St. Luke's Medical Center, Division of Endocrinology, Department of Medicine, Baylor College of Medicine, Houston, Tex., USA

Key Words

Acromegaly · Somatostatin analog · SOM230 · Pasireotide · Medical therapy · Somatostatin receptor ligand

Abstract

Background: Acromegaly is an insidious neuroendocrine disorder caused by hypersecretion of growth hormone (GH) by a somatotroph adenoma. Somatostatin receptor ligands (SRLs) are recommended as first-line medical therapy in patients for whom surgery has failed or is contraindicated. There are 5 known somatostatin receptor subtypes (SSTRs), 2 of which, i.e. SSTR2 and SSTR5, are expressed by a majority of somatotroph adenomas. The currently available SRLs, i.e. octreotide and lanreotide, primarily bind to SSTR2. Pasireotide (SOM230) is a new multireceptor-targeted SRL which has a broader binding profile and an increased affinity for SSTR1, 2, 3, and 5. **Methods:** PubMed searches were performed to identify all of the available published English language data on pasireotide with regard to the mechanism of action, in vitro effects, and clinical data. **Results:** Preclinical studies have demonstrated that pasireotide has a broader range of functional activity than octreotide. Recently, the efficacy of pasireotide in attenuating GH and insulin-like growth factor 1 (IGF-1) levels in patients with acromegaly has been evaluated in phase III clinical trials. Pasireotide demonstrated superiority over octreotide in achieving biochemical control (i.e. GH ≤ 2.5 $\mu\text{g/l}$ and age- and sex-matched

IGF-1 normalization) in patients with acromegaly, as well as significant efficacy in treating patients who were previously inadequately controlled on the maximum allowed doses of octreotide and lanreotide. Pasireotide-induced hyperglycemia was the most concerning adverse event but was reversible upon discontinuation of pasireotide. **Conclusion:** The clinical data support pasireotide as a promising new therapy for the treatment of acromegaly, and the long-acting formulation was recently approved in the US and Europe for the treatment of acromegaly.

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Introduction

Acromegaly is a chronic neuroendocrine disorder caused by excessive levels of growth hormone (GH) that drive the overproduction of insulin-like growth factor 1 (IGF-1). In over 90% of cases, the origin of GH hypersecretion is a benign pituitary somatotroph adenoma [1]. Each year, between 3 and 4 per million people are diagnosed with acromegaly [2], with an overall reported prevalence of 86–294 per million [3, 4]. The disease onset is insidious and symptoms can develop over the course of several years, leading to a delay in diagnosis of at least 5 years [5]. Clinical manifestations of the disease range from subtle acral enlargement to more serious consequences, such as diabetes mellitus (DM), hypertension,

sleep apnea, and respiratory and cardiac failure [6]. Furthermore, the rate of mortality among patients with acromegaly with elevated GH and IGF-1 is between 2.6 and 3.5 times greater than in the general population [7]. However, reducing GH levels to <2.5 µg/l (as determined by radioimmunoassay data, more likely <1 µg/l by more sensitive immunometric assays) or normalizing IGF-1 for age and sex restores the standardized mortality ratio in patients with acromegaly to that of the population [8]. Thus, the principal goals of treatment are to lower GH and normalize IGF-1 levels, and to prevent further tumor growth or even induce tumor shrinkage [9].

For most patients with acromegaly, transsphenoidal surgery is the first-line therapy. Use of medical treatment as the first-line approach may be appropriate in selected patients, such as those without compressive symptoms but with large and/or invasive tumors that are unlikely to be cured by surgery [10]. In some instances, medical therapy is administered for several months prior to surgery as a means to either reduce the tumor size [11] or alleviate other symptoms, like obstructive sleep apnea, in order to improve the patient's surgical candidacy [12]. Secondary reasons for opting for pharmacotherapy include the presence of residual tumor after transsphenoidal surgery or after radiation bridge therapy while awaiting remission, failed radiation treatment, or disease recurrence.

Medical therapies either target GH secretion from the pituitary adenoma or block peripheral GH action. Somatostatin receptor ligands (SRLs) and dopamine agonists suppress GH release via interaction with the respective receptors on the surface of the tumor. The approved SRLs octreotide and lanreotide are the recommended first-line postsurgery therapies for acromegaly [9]. Pegvisomant inhibits GH action at the GH receptors in the peripheral tissues, especially the liver, to reduce IGF-1 levels. Even with these therapies, however, a substantial proportion of patients (28–72%) still do not achieve biochemical control [13–16], raising the need for an alternative drug for the treatment of acromegaly. Recently, pasireotide, a multireceptor-targeted SRL, has been under investigation for the treatment of acromegaly. The long-acting formulation of pasireotide (long-acting release; LAR) was approved in late 2014 by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of acromegaly. This review summarizes the current data on the differentiating somatostatin receptor binding profile, and pre-clinical and clinical data that demonstrate the mechanism of action and clinical efficacy of pasireotide for the treatment of acromegaly.

Table 1. Binding affinities of somatostatin receptor ligands for SSTR1–5

SRL	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Octreotide	280	0.38	7.1	>1,000	6.3
Lanreotide	180	0.54	14	230	17
Pasireotide	9.3	1.0	1.5	100	0.16

Data are mean IC₅₀ values expressed as nmol/l. Adapted from Bruns et al. [18].

Differentiating Characteristics of Pasireotide Compared to Available Somatostatin Analogs

Binding Properties

Somatostatin, an inhibitory peptide, binds to its G protein-coupled receptors (GPCRs) to downregulate the secretion of various hormones from the pituitary, including GH. There are 5 known somatostatin receptor subtypes (SSTRs). For somatotroph tumors, the most prevalent SSTRs are 2 and 5, expressed in 96 and 86% of tumors, respectively, while SSTRs 1 and 3 are expressed by a smaller percentage of tumors [17]. The original somatostatin analog, octreotide, has the highest affinity for SSTR2 and a much lower affinity for SSTR3 and 5, with no appreciable binding to SSTR1 or 4. Lanreotide has a similar binding affinity for SSTR2 to octreotide, with a somewhat higher affinity for SSTR1 and a lower affinity for SSTR3 and 5 [18]. Pasireotide is distinguished from these other SRLs by its binding profile. It has a broader binding spectrum, with high-affinity binding to receptors SSTR2, 3, and 5 and moderate affinity for SSTR1 (table 1). Compared with octreotide, pasireotide affinity at receptors SSTR1, 3, and 5 is predicted to be 30-, 5-, and 39-fold higher, respectively, but 3-fold lower at SSTR2, based on EC₅₀ values [19]. The broadened selectivity of pasireotide, especially with regard to SSTR5, supports its clinical utility for somatotroph and corticotroph (adrenocorticotrophic hormone secreting) pituitary tumors, along with other neuroendocrine tumors that express multiple SSTRs [20].

Since nearly all somatotroph adenomas express SSTR2, they are vulnerable to the SSTR2-selective SRL octreotide. However, SSTR2 is susceptible to downregulation after even minimal administration of octreotide [21], making it a potentially suboptimal therapeutic target. Since most somatotroph adenomas also express SSTR5, with smaller percentages of tumors expressing SSTR1 and/or SSTR3,

the ability of pasireotide to bind with multiple receptor subtypes has the potential to provide a therapeutic advantage over octreotide [22].

Functional Assays

Receptor binding affinities do not necessarily predict functional effects, due to the fact that GPCRs frequently stimulate multiple effector systems [23]. One physiological effect of somatostatin is intracellular inhibition of adenylate cyclase, which occurs at all 5 SSTR subtypes. In vitro assays using cells expressing the various SSTR subtypes have shown that pasireotide binding at SSTR1, SSTR3, and SSTR5 causes functional responses, i.e. adenylate cyclase inhibition, that are >30-, 11-, and 158-fold higher, respectively, than those caused by octreotide, but with a 3-fold lower response compared to octreotide at SSTR2 [19]. These findings support that pasireotide has a broad range of functional activity which may result in a more optimal therapeutic option for targeting adenomas that express a variety of SSTRs.

Despite the increased functional activity of pasireotide compared to octreotide using the adenylate cyclase assay, a growing body of evidence suggests that other functional activities of SSTRs (such as ERK phosphorylation, stimulation of intracellular calcium accumulation, receptor internalization, and β -arrestin mobilization) may not be adequately predicted by the adenylate cyclase inhibition model [23–27], making the exact physiological responses to each drug difficult to predict. These functional differences between somatostatin and the SRLs may also underlie some of the benefits of treatment. For example, unlike somatostatin and octreotide, pasireotide binding does not produce SSTR2 internalization. This phenomenon has also been proposed as a mechanism underlying the lack of desensitization to pasireotide treatment [25] and implies that a longer-term response can be maintained with pasireotide than octreotide.

Preclinical Studies: Control of GH and IGF-1

A primary goal of SRL treatment in patients with acromegaly is the suppression of GH secretion, which consequently decreases the synthesis of IGF-1 in peripheral tissues, mainly the liver [28]. In primary cultures of rat pituitary cells, pasireotide has been shown to inhibit the GH-releasing hormone-stimulated release of GH with a 3- to 4-fold higher potency than somatostatin or octreotide (IC_{50} of 0.4, 1.5, and 1.3 nM, respectively) [18]. In rats, single-dose pasireotide administered subcutaneously

(s.c.) inhibited GH to a similar extent as a similar dose of octreotide at 1 h but was 4 times more potent after 6 h due to a prolonged duration of action [18, 29].

Pasireotide administered to rats continuously using osmotic minipump infusion (10 μ g/kg/h) also inhibited IGF-1 plasma levels to a greater extent than the same dose of octreotide after 2 days (90 vs. 51% inhibition) and after 2 weeks of treatment (60 vs. 20% inhibition) [29]. After 8 weeks of treatment, IGF-1 levels were inhibited by 74 and 18% for pasireotide and octreotide, respectively [29]. Similar results were observed in another study in which rats received the same concentration of pasireotide or octreotide for 18 weeks (75 vs. 27% inhibition of IGF-1, respectively) [18]. The effects of pasireotide in LAR form have also been investigated in rats. After a single s.c. injection of pasireotide LAR at 8 mg/kg, IGF-1 was still reduced by 49% after 35 days versus a 9% reduction in IGF-1 after the same concentration of octreotide LAR [22].

Similar studies have also been performed in other species. In rhesus monkeys, single-dose pasireotide and octreotide produced GH inhibition with similar ID_{50} values (0.5 vs. 0.4 g/kg, respectively), but a rapid rebound of GH to higher than baseline levels occurred within 3–4 h with octreotide but not pasireotide [29]. After multiple-dose administration over 30 h, plasma IGF-1 levels were also lowered by pasireotide (53%) but not octreotide [29]. In cynomolgus monkeys, 2 weeks of pasireotide infusion produced significantly greater inhibition of plasma GH levels than octreotide, and the inhibition lasted longer after cessation of pasireotide compared to octreotide. In both cynomolgus monkeys and beagle dogs, a significant inhibition of IGF-1 was observed with pasireotide but not octreotide [29].

In addition to inhibiting IGF-1 production through the reduction of GH secretion from the pituitary, pasireotide may also act peripherally to directly inhibit IGF-1 in some cells through the stimulation of IGF-binding protein 5 [30]. IGF-1 inhibition in mammary cells has been investigated in hypophysectomized rats, and it appears to be largely dependent upon SSTR3 and possibly SSTR5. In accordance with their respective binding properties, the effects of pasireotide are significantly stronger than the effects of octreotide for this mechanism of IGF-1 inhibition [30]. It has been hypothesized that pasireotide has a stronger effect than octreotide in tissues where multiple types of receptors are expressed, while octreotide may have a stronger effect in tissues that primarily express SSTR2 [31].

Preclinical Studies: Antiproliferative Effects

In addition to controlling GH and IGF-1 levels, SRLs also have antiproliferative effects, both directly through receptor binding and indirectly through mechanisms such as angiogenesis inhibition, suppression of tumor-stimulating growth factors (including IGF-1), and enhancement of immune components with antitumor effects [32–34]. Multiple SSTRs are expressed in a wide variety of both endocrine-related and nonneuroendocrine tumors [33]. The stimulation of somatostatin receptors produces antiproliferative effects by inducing G₀-G₁ cell cycle arrest (typically through SSTR2 and SSTR5) or G₂-M apoptosis (through SSTR2, SSTR3, and inhibition of IGF-1) [32, 33, 35]. In human lymphocytes, apoptosis induced by octreotide appears to be at least partially mediated through SSTR2, whereas pasireotide-induced apoptosis is primarily mediated through SSTR3, although an apoptotic effect caused by the heterodimerization of SSTR2/SSTR3 cannot be ruled out with either SRL [35]. Consequently, SRLs that target multiple receptor types may have stronger antiproliferative effects [22]. In a study of transgenic mice with GH- and prolactin-secreting pituitary adenomas, continuous injection of pasireotide (50 µg/kg/h) was associated with significantly superior antitumor effects compared to octreotide (50 µg/kg/h); octreotide slowed the tumor progression, while pasireotide induced tumor shrinkage [36].

Octreotide and pasireotide also inhibit vascular endothelial growth factor, which is involved in tumor growth and vascularization [33, 37]. Notably, SSTR2 expression on endothelial cells occurs only as they proliferate to form new blood vessels, providing a unique opportunity for SSTR2-targeted therapy during tumor outgrowth [33]. Additional SSTR subtypes may also be involved in antiangiogenesis. In a study of human endothelial vein cells stimulated with vascular endothelial growth factor, pasireotide significantly inhibited endothelial cell proliferation (up to 46%), whereas octreotide failed to inhibit proliferation across a wide range of concentrations, which may be related to more potent pasireotide activity at other SSTRs, such as SSTR1 and 5 [38].

Clinical Studies

Findings from preclinical studies have provided the impetus for evaluating pasireotide in patients with acromegaly. Clinical trial data which support the efficacy and safety of pasireotide in patients with acromegaly have recently been emerging and are summarized below.

Phase II: B2201 and B2201E

In a randomized, open-label, multicenter, phase II, crossover trial, 58 patients with acromegaly initially self-administered octreotide s.c. at 100 µg 3 times a day for 28 days to characterize the response to standard treatment [39]. Biochemical control was defined as GH ≤2.5 µg/dl and IGF-1 levels normalized for age- and sex-matched controls. Following octreotide treatment, each patient was crossed over to receive 200, 400, or 600 µg of pasireotide s.c. b.i.d. in randomized order for 28 days. At the end of the initial octreotide treatment, 9% of the patients achieved biochemical control. At the end of 4 weeks of pasireotide treatment, 11/58 patients (19%) achieved biochemical control and the response rate increased to 27% after 3 months. The tumor size was reduced by ≥20% in 39% of patients. In the extension phase of the study, 26 patients from the core study received either the lowest dose of pasireotide at which they had achieved biochemical control in the core phase or 600 µg b.i.d. Six patients (23%) attained full biochemical control at the end of 6 months [40]. The results from this small study illustrated that a greater number of patients with acromegaly could achieve control of GH and IGF-1 levels with pasireotide than with octreotide.

Phase III: C2305

Based on the outcome from the smaller phase II study, and the need to clearly delineate the effects of pasireotide from that of any lingering effects of octreotide treatment, a larger crossover study was designed to test the superiority of pasireotide LAR compared to octreotide LAR in medically naive patients with acromegaly. In this double-blind, multicenter, phase III trial, 358 patients were randomized to receive 40 mg of pasireotide LAR or 20 mg of octreotide LAR every 28 days [41]. At the end of 12 months of treatment, biochemical control, defined as GH ≤2.5 µg/l and age- and sex-matched normalization of IGF-1, was achieved by a significantly greater proportion of patients in the pasireotide LAR group compared to the octreotide LAR group (31.3 and 19.2%, respectively; *p* = 0.007; fig. 1). Among patients who had previous surgery, 39.4% of the pasireotide LAR group achieved biochemical control compared to 21.8% of the octreotide LAR group. Similarly, among de novo patients, a greater proportion of patients in the pasireotide LAR group achieved biochemical control compared to patients in the octreotide LAR group (25.7 vs. 17.3%, respectively). The mean tumor volume was reduced by 40 and 38% from baseline to month 12 in the pasireotide LAR and octreotide LAR groups, respectively. Both treatments also similarly im-

Fig. 1. Response rates at 12 months from the C2305 superiority trial. Proportion of patients in the overall population, the postsurgery subgroup, and the de novo subgroup with GH <2.5 µg/l and normal IGF-1 after 12 months of treatment with pasireotide LAR or octreotide LAR. In the overall population, biochemical control was achieved by a significantly greater proportion of patients treated with pasireotide LAR compared to octreotide LAR ($p = 0.007$). The study was not powered to detect treatment response differences within subgroups. Reproduced with permission from the Endocrine Society® [41].

proved the quality of life and other acromegaly-related symptoms such as perspiration, fatigue, osteoarthralgias, paresthesias, and headache.

In the extension phase of that same study, patients who did not fully benefit from their randomized treatment during the core phase could choose to cross over to the other therapy. Of the 81 patients who were inadequately controlled with octreotide LAR and switched to pasireotide LAR, 17.3% then achieved biochemical control 12 months after the crossover. On the other hand, none of the 38 patients who switched from pasireotide LAR to octreotide LAR experienced biochemical control 12 months after the crossover [42]. Tumor volume was reduced from the extension baseline by 24.7 and 17.9% in the patient populations crossed over to pasireotide LAR and octreotide LAR, respectively.

Phase III: C2402 (PAOLA)

In addition to the head-to-head trial described above (C2305), a distinct phase III trial was designed to test the superiority of pasireotide LAR in treating patients who are inadequately controlled (i.e. GH >2.5 µg/l, IGF-1 >1.3 times the upper limit of normal) on the maximum approved dose of octreotide LAR or lanreotide Autogel® (ATG). In total, 198 patients were randomized to receive

Fig. 2. Biochemical responses from the C2402 clinical trial. Changes in IGF-1 (a) and GH (b) levels in the groups on pasireotide LAR 40 and 60 mg and the active control group. Treatment with pasireotide LAR 40 and 60 mg resulted in greater reduction in IGF-1 and GH compared to the active control group. Reproduced with permission from Elsevier® [43].

either double-blinded pasireotide LAR at 40 mg ($n = 65$) or 60 mg ($n = 65$) or continued on their treatment with open-label octreotide LAR or lanreotide ATG ($n = 68$) [43]. At the end of 24 weeks, biochemical control was achieved by 15% of patients on pasireotide LAR 40 mg ($p = 0.0006$ vs. active control), 20% of patients on pasireotide LAR 60 mg ($p < 0.0001$ vs. active control), and none of the patients in the nonpasireotide active control treatment arm. The mean normalized IGF-1 declined from baseline to week 12 and remained stable up to week 24 in both pasireotide LAR groups, but the levels for the active control group remained close to baseline. At 24 weeks, the percentage decreases in IGF-1 levels were –28 and –39% for the groups on pasireotide LAR 40 and 60 mg, and –7% for the active control group (fig. 2). Similarly, GH levels

declined from baseline to week 12 and remained stable until week 24 in both pasireotide LAR groups. Percentage changes from baseline at 24 weeks were −23 and −51% for pasireotide 40 and 60 mg, respectively. The active control group experienced a small decrease in GH values, with a −3.2% change from baseline (fig. 2). These results provide strong evidence that pasireotide LAR is a viable alternative medical therapeutic option for patients with inadequate biochemical control on SSTR2-preferential SRL therapies (octreotide or lanreotide).

Tumor volume reductions >25% were observed in 18.5 and 10.8% of the groups on pasireotide LAR 40 and 60 mg, compared to 1.5% in the active control group. This observation is encouraging in that it suggests that, beyond biochemical control, pasireotide can induce further tumor shrinkage even in patients who have been previously treated with maximal octreotide. Whether tumor shrinkage is dependent or independent of a full biochemical response to pasireotide will require further subanalysis of the data.

Adverse Events

For the phase III CSOM C2305, common adverse events (AEs) reported in ≥10% of patients in the pasireotide LAR arm versus the octreotide LAR arm were generally mild to moderate diarrhea (39.3 vs. 45.0%), cholelithiasis (25.8 vs. 35.6%), and headache (18.5 vs. 25.6%) [41].

Notably, hyperglycemic events occurred in 28.7% of C2305 participants on pasireotide versus 8.3% of patients on octreotide and, included in these numbers, new-onset diabetes mellitus (DM) was diagnosed in 19.1 versus 3.9% of cases. Six of the 14 AE-related patient discontinuations in the pasireotide group were due to elevations in blood glucose. Similarly, in PAOLA (CSOM 2402), hyperglycemia (HG) and DM were more frequently reported in the groups on pasireotide 40 and 60 mg [33% had HG and 21% had DM (n = 63), and 31% had HG and 26% had DM (n = 62), respectively] compared to the active control group [14% had HG and 8% had DM (n = 66)] [43]. Importantly, in the C2305 study, HG resolved within 3 months to near-normal levels in patients who crossed over from pasireotide to octreotide LAR [44], suggesting that pasireotide-induced HG may be reversible.

Pasireotide-Induced HG: Healthy-Volunteer Studies

Despite the potential therapeutic benefits of pasireotide, HG is a common and concerning AE that, to date, has not been investigated in patients with acromegaly. In order to understand the underlying pathophysiology of

pasireotide-induced HG, the effects of short-acting pasireotide on glucose metabolism were investigated in normal-weight male volunteers. Subjects received therapeutic doses of pasireotide (600 or 900 µg) s.c. twice a day for 7 days [45]. Hyperglycemic clamps revealed decreases in insulin and C-peptide levels in the presence of intravenously administered glucose. Oral glucose tolerance testing showed a delayed time-to-peak glucose (120 vs. 30 min), possibly due to slowed gastric emptying. Additionally, there was a markedly blunted insulin secretory response even at the time of the glucose peak. Glucagon levels were mildly suppressed with pasireotide treatment, arguing against a significant contribution by hyperglucagonemia to HG. Data from euglycemic-hyperinsulinemic clamps did not support any changes in hepatic or peripheral insulin resistance. However, there was an absence of an incretin response. In pasireotide-treated subjects, administration of oral glucose did not lead to increases in either glucagon-like peptide 1 (GLP-1) or glucose-dependent insulinotropic polypeptide (GIP), indicative of pasireotide-induced inhibition of incretin secretion [46]. This finding is aligned with previously reported data that suggested that somatostatin could dampen GLP-1 secretion, most likely mediated through SSTR5 [47, 48].

The outcomes from human studies echo the results of animal experiments. In free-feeding rats, a single injection of pasireotide caused a rise in plasma glucose within 15 min of the injection without a compensatory increase in insulin [49]. However, with continuation of injections over 12 days, glucose levels declined to that of control rats. Similarly, continuous s.c. infusion of pasireotide caused a transient increase in glucose that waned by 14 days. These observations could point toward an unknown compensatory response, such as downregulation of SSTRs. Ludvigsen et al. [50] directly examined islet function in vitro outside of the influence of incretins. Rat islets were cultured with somatostatin, octreotide, and pasireotide for 48 h. All 3 treatments inhibited insulin release into the media, while the insulin content of the islet cells was increased. Only pasireotide attenuated acute insulin release in the presence of high glucose (16.7 mM). This effect was reversible as islet function recovered within 6 h of the removal of pasireotide. The reversal of the blunted insulin release observed in islet cells may underlie the aforementioned reversal of HG observed in patients who crossed over from pasireotide to octreotide in the C2305 clinical trial [44].

Although there are no clinical trial data supporting improvement of pasireotide-induced HG with long-term treatment, there is a report of 2 patients with Cushing's

disease, a neuroendocrine disorder resulting in hypercortisolism, who were treated with pasireotide for over 4 years. In each case, pasireotide-induced HG was spontaneously improved by month 45 while disease control was maintained. However, in one patient's case, the dose of pasireotide had been downtitrated in response to improvements in biochemical and clinical features [51]. Clinical trials are needed to support these findings in a larger patient population.

Another study in healthy males evaluated various strategies for managing pasireotide-induced HG [52]. Ninety volunteers were randomized to receive either 600 µg pasireotide s.c. alone or administered with metformin (biguanide) at 500 mg b.i.d., nateglinide (meglitinide) at 60 mg t.i.d., vildagliptin [dipeptidyl peptidase-4 (DPP-4) inhibitor] at 50 mg b.i.d., or liraglutide (GLP-1 agonist) s.c. at 0.6 mg q.d. for 7 days. On day 7, the glucose area under the curve increased by 69% from baseline in the pasireotide-only group. The increases from baseline were substantially lower in the groups that were concomitantly treated with metformin (60%), nateglinide (49%), vildagliptin (38%), and liraglutide (19%), indicating that the antidiabetic agents played a role in mitigating the effects of pasireotide on HG. Insulin levels were also examined in each treatment group. On day 1, the insulin level following pasireotide administration but preceding administration of antidiabetic agents was decreased in all groups by 66–71% from baseline. By day 7, the decrease in insulin was counteracted by vildagliptin and liraglutide (levels were 71 and 34% higher than day 1 levels, respectively). Metformin and nateglinide also attenuated the decrease in serum insulin, although to a considerably lower degree (levels were 6 and 3% higher than day 1 levels, respectively). From these data, it may be inferred that GLP-1 agonists and DPP-4 inhibitors might be the most viable antidiabetic agents to coadminister with pasireotide in order to manage pasireotide-induced HG. This possibility was also suggested in a recent publication of expert opinion for the management of pasireotide-induced HG in Cushing's disease [53], and further studies will need to be conducted to determine the best management for HG in acromegaly patients treated with pasireotide.

Discussion

From the current expert consensus, first-line medical treatments for patients with acromegaly are the two SSTR2-preferential SRLs octreotide LAR and lanreotide ATG [9]. However, a troubling proportion of patients do

not achieve biochemical control even with long-term treatment. Accordingly, there is an unmet need for an alternative option for patients who are either unresponsive to or inadequately controlled on octreotide or lanreotide. Pegvisomant, a GH receptor antagonist, has been shown to decrease IGF-1 levels [54]. However, it does not target the source of GH excess and does not suppress tumor growth, thus warranting the need for long-term tumor monitoring. In addition, GH levels cannot be used to monitor treatment efficacy or disease status with pegvisomant treatment. The dopamine agonist cabergoline, which is centrally targeted, is most effective only in patients with mild elevations in GH and IGF-1 [55]. The advantages of cabergoline include oral administration and a low cost. The role of cabergoline in increasing the risk of clinically significant cardiac valvulopathy in hyperprolactinemia patients remains unclear as some studies have reported no significant increase in patients with prolactinomas [56–58] while a meta-analysis revealed an OR around 2-fold for mild to moderate tricuspid regurgitation [59]. Regular monitoring of cardiac function is, however, recommended by the FDA and EMA.

Pasireotide, a multireceptor-targeted SRL with a high binding affinity for SSTR5 and a slightly lower affinity for SSTR2, has been evaluated in patients with acromegaly. Results from clinical trials assessing the efficacy of pasireotide compared to octreotide LAR and lanreotide ATG provide support for the long-term benefit of pasireotide LAR therapy in patients with acromegaly. The definition of biochemical control, i.e. a composite endpoint of GH <2.5 µg/l and normalized IGF-1, was chosen in order to be consistent with the most current definition of biochemical control available during the trial [10, 60] and provides a more pragmatic depiction of the overall effects of the drug than considering GH or IGF-1 alone. The most recent expert consensus, however, sets the goal for GH levels to <1 µg/l based on the availability of more sensitive assays [9] and, as such, data will need to be interpreted with this consideration in mind.

As the results of pasireotide LAR efficacy in treating acromegaly are still emerging and the overall efficacy of SRLs in controlling GH and IGF-1 levels remains incomplete, the current expert consensus recommends that the first step to address partial response to maximal doses of octreotide or lanreotide is to increase the dosage [9]. If the dose increase fails to achieve the biochemical goals, combination therapy may be implemented. SRLs can be combined with pegvisomant to concurrently activate SSTRs to suppress GH and block the GH receptor to inhibit its downstream effects. SRLs can also be combined with cab-

ergoline to simultaneously target two distinct classes of receptors involved in regulating pituitary GH secretion. Pasireotide is now added to our armamentarium for the treatment of acromegaly. In late 2014, pasireotide LAR was approved by the EMA and the FDA for patients with acromegaly for whom surgical resection was not curative or is not an option. However, mostly due to concerns regarding HG, the EMA limited the indication for pasireotide use to patients having failed treatment with another SRL.

In both acromegaly and Cushing's disease, most AEs reported with pasireotide treatment were mild to moderate gastrointestinal disturbances. However, pasireotide can elicit HG-related AEs in up to 73% of patients [61] and remains a serious concern. Based on the clinical experience with pasireotide-related HG in patients with Cushing's disease, combined with the mechanistic and management modalities elucidated by studies done in healthy males [45, 52], experts have recommended an HG management protocol for patients with Cushing's disease who are treated with pasireotide [53, 62]. A clinical trial to evaluate the efficacy of managing pasireotide-induced HG in patients with acromegaly and Cushing's disease is currently underway (clinicaltrials.gov identifier: NCT02060383).

As with any treatment, the clinical benefit of long-term treatment with pasireotide must be weighed against the

risk of AEs. The emergent results to date indicate that pasireotide LAR can benefit a proportion of patients who are currently inadequately controlled by octreotide or lanreotide. The addition of pasireotide as a medical option to treat acromegaly would enhance the therapeutic paradigms available to patients. Additional ongoing clinical trials will continue to augment efficacy and safety information for the utility of pasireotide in treating acromegaly, further defining its role in the scheme of medical treatment options for the disease.

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