Medical Treatment of Cushing’s Disease: Somatostatin Analogues and Pasireotide

Alberto M. Pedroncelli
Novartis Pharma AG, Basle, Switzerland

Key Words
Pasireotide · Somatostatin analogue · Cushing’s disease

Abstract
Cushing’s disease is Cushing’s syndrome caused by an adrenocorticotropic hormone-secreting pituitary adenoma and, in the absence of adequate treatment, can be fatal. Cushing’s disease represents an unmet medical need, with no approved medical therapies. Pasireotide is a novel multi-receptor-targeted somatostatin analogue with high affinity for sst1,2,3 and sst5. Compared with octreotide, pasireotide has an in vitro binding affinity 40-, 30- and 5-fold higher for sst5, sst1 and sst3, respectively, and 2-fold lower for sst2. Adrenocorticotropic hormone-secreting pituitary adenomas predominantly express sst5, followed by sst2 and sst1, suggesting that pasireotide may be effective in the treatment of Cushing’s disease. In a 15-day phase II trial of pasireotide 600 μg s.c. b.i.d. in patients with de novo or persistent/recurrent Cushing’s disease, 22 of 29 patients (76%) achieved reduced urinary free cortisol (UFC) levels, 5 of whom (17%) achieved normalized UFC. Patients who achieved normalized UFC had a significantly greater reduction in serum cortisol than those who did not (p = 0.04), and minimum pasireotide plasma concentrations appeared to be higher in responders. Based on these results, a randomized, double-blind phase III study comparing pasireotide 600 μg b.i.d. and 900 μg b.i.d. was initiated and is ongoing. This is the largest ever phase III study in patients with Cushing’s disease. The primary end point of this study is normalization of UFC after 6 months of treatment. Finally, preliminary results from a study on 17 patients with Cushing’s disease suggest that the combined use of pasireotide, cabergoline and low-dose ketoconazole may have additive beneficial effects in the medical treatment of Cushing’s disease.

Introduction
Endogenous Cushing’s syndrome can be caused by tumors of the adrenal glands that produce excess cortisol, known as autonomous adrenal hypercortisolism, secretion of adrenocorticotropic hormone (ACTH) or corticotropin-releasing hormone (CRH) from non-pituitary tumors, known as ectopic ACTH or CRH secretion or, most frequently, by an ACTH-secreting pituitary adenoma, which is known as Cushing’s disease [1]. Excessive secretion of ACTH by a pituitary corticotropic adenoma results in excessive cortisol secretion from the adrenal glands, which can result in weight gain, high blood pressure, depression, cognitive impairment, severe fatigue and muscle weakness, purplish skin striae, hyperpigmentation, loss of libido, impaired glucose metabolism, hirsutism, acne and menstrual disorders [2, 3]. Chronic hypercortisolism is associated with an increased incidence of systemic arterial hypertension, diabetes mellitus, central obesity, hyperlipidemia and hypercoagulability [2]. In the absence of adequate treatment, Cushing’s disease can be a fatal condition [4]; patients with Cushing’s dis-
ese have a mortality rate four times higher than age- and sex-matched controls [2].

Treatment goals in Cushing’s disease include the reversal of clinical features, the normalization of biochemical changes with minimal morbidity, and long-term control without recurrence [1]. First-line treatment for Cushing’s disease is pituitary surgery. Second-line options include repeat surgery, radiotherapy, bilateral adrenalectomy and medical therapy. Currently, there are no approved medications for the treatment of Cushing’s disease. The most commonly used medical therapies, such as ketoconazole, metyrapone and mitotane, target the adrenal glands and, therefore, do not treat the underlying cause of the disease or restore normal function of the hypothalamo-pituitary-adrenal axis [5]. The commercially available somatostatin analogue octreotide is mostly ineffective in treating Cushing’s disease [6–8].

**Pasireotide, a Multi-Receptor Targeted Somatostatin Analogue**

Pasireotide is a novel multi-receptor-targeted somatostatin analogue with high binding affinity to somatostatin receptor subtypes sst1,2,3 and sst5. Octreotide has high affinity for somatostatin receptor subtype sst2 and marginal affinity for sst5, which accounts for its efficacy in treating patients with acromegaly and symptomatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs), and can partly explain its lack of efficacy in Cushing’s disease [9]. Compared with octreotide, pasireotide has an in vitro binding affinity 40-, 30- and 5-fold higher for sst5, sst2 and sst3, respectively, and 2-fold lower for sst2 [10]. Because of these differences in binding affinity, it can be speculated that in cells and tissues that express somatostatin receptors other than sst2, pasireotide will have a stronger inhibitory effect on hormone secretion than octreotide. ACTH-secreting pituitary adenomas predominantly express sst3, followed by sst2 and sst1 [11, 12]. Therefore, by targeting multiple somatostatin receptor subtypes, pasireotide may prove to be effective not only in patients with acromegaly or GEP-NETs, but also in patients with Cushing’s disease.

**Preclinical Evidence**

In vitro evaluation of a mouse corticotrophic adenoma cell line (AtT-20 cells) showed high mRNA expression of sst3 receptors but few sst2 receptors, reflecting the expression profile of human corticotrophic adenomas [13]. Furthermore, in vitro studies in human ACTH-secreting pituitary adenomas and AtT-20 murine corticotrophic tumor cells showed that pasireotide inhibits basal and stimulated ACTH release. A 72-hour incubation with pasireotide 10 nM in human corticotrophic adenoma cells resulted in inhibition of ACTH release in three of five cultures (~30% to ~40%), whereas octreotide 10 nM inhibited ACTH release in only one culture (~28%) [14]. Importantly, the suppression of CRH-induced ACTH release exhibited by pasireotide in AtT-20 cells was unaffected by a 48-hour pretreatment with dexamethasone. By contrast, the suppressive effects of octreotide were almost completely blocked by dexamethasone [14, 15], suggesting that sst2 may be downregulated by glucocorticoid treatment (or by elevated endogenous cortisol levels), and that sst3 is more resistant to downregulation. This also suggested that by inhibiting ACTH release and subsequent cortisol levels via sst5, the expression of sst3 may be restored, thus further enhancing ACTH inhibition by an sst2/sst5 receptor ligand such as pasireotide.

**Clinical Evidence**

**Pasireotide as Monotherapy**

In order to assess the effects of pasireotide in patients with Cushing’s disease, a 15-day phase II, open-label, single-arm, multicenter, proof-of-concept trial was initiated [16]. Patients were aged ≥18 years and had clinically and biochemically confirmed Cushing’s disease, which was established by the mean of two consecutive 24-hour urinary free cortisol (UFC) levels ≥2 times the upper limit of normal, morning plasma ACTH levels within or above the normal range, and either MRI confirmation of a pituitary macroadenoma (adenoma ≥1 cm) or an inferior petrosal sinus gradient >3 after CRH stimulation. The primary efficacy outcome was normalization of mean UFC levels after 15 days of treatment. Secondary end points included changes in plasma ACTH and serum cortisol, pharmacokinetic evaluation and safety.

Thirty-nine patients self-administered pasireotide s.c. 600 µg twice daily for 15 days. Of the 29 patients in the primary efficacy analysis, 22 (76%) showed a reduction in UFC levels, of whom 5 (17%) had normal UFC levels (UFC responders), after 15 days of treatment with pasireotide (fig. 1). Overall, the mean UFC level decreased from baseline by 44.5% (p = 0.021). The mean ± SD UFC level decreased from 1,231 ± 1,141 nmol/24 h [446 ± 413
 Patients who achieved normalized UFC levels had a significantly greater reduction in serum cortisol than patients who did not. The mean baseline area under the plasma concentration-time curve from 0–8 h (AUC 0–8 h) of serum cortisol was 5,046 nmol·h/l. A significant difference in serum cortisol reduction from day –1 to day 15 was observed in UFC responders compared with UFC nonresponders (serum cortisol reduction of 1,248 vs. 420 nmol·h/l, p = 0.04) [16].

Steady-state levels of pasireotide were achieved within 5 days of treatment initiation, and the minimum plasma concentration (C min) of pasireotide on day 15 was above the theoretical C min (>1 μg/l) required to demonstrate efficacy (table 1). Furthermore, C min and AUC0–8 h values of pasireotide appeared to be higher in responders than nonresponders. The mean ± SD C min in responders (n = 5) was 7.8 ± 4.1 μg/l, which was ~1.8 times higher than that in nonresponders (4.3 ± 2.4 μg/l; n = 22), and the mean ± SD AUC0–8 h in responders was 119 ± 32.5 μg·h/l, which was ~1.3 times higher than that in nonresponders, 93.3 ± 38.3 μg·h/l [16].

Pasireotide was generally well tolerated, with 87% of patients experiencing an adverse event considered to be drug related, the majority of which were mild and gastrointestinal in origin. The most common adverse events were diarrhea (44%), nausea (23%) and abdominal pain (18%). Hyperglycemia occurred in 14 patients (36%), most of whom (n = 12) experienced mild hyperglycemia. Of the 14 patients, three had a documented medical history of diabetes mellitus and two of impaired fasting glucose at baseline [16].

Based on these encouraging phase II results, a large, randomized, double-blind phase III trial comparing pasireotide 600 μg s.c. b.i.d. and 900 μg s.c. b.i.d. in patients with de novo or persistent/recurrent Cushing’s disease was initiated and is ongoing. This is the largest ever phase III study in patients with Cushing’s disease. The primary end point of this study is normalization of UFC after 6

Table 1. Pharmacokinetic parameters of pasireotide 600 μg s.c. b.i.d. on days 1, 5, 12 and 15 in patients with Cushing’s disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1 (n = 36)</th>
<th>Day 5 (n = 38)</th>
<th>Day 12 (n = 38)</th>
<th>Day 15 (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C min, μg/l</td>
<td>0</td>
<td>3.9 ± 2.2</td>
<td>5.1 ± 4.2</td>
<td>4.9 ± 2.7</td>
</tr>
<tr>
<td>C max, μg/l</td>
<td>13.8 ± 4.5</td>
<td>20.8 ± 11.7</td>
<td>20.5 ± 6.9</td>
<td>21.1 ± 6.9</td>
</tr>
<tr>
<td>T max, h</td>
<td>2 (2–4)</td>
<td>2 (2–4)</td>
<td>2 (2–2)</td>
<td>2 (2–2)</td>
</tr>
<tr>
<td>AUC 0–8 h</td>
<td>51.7 ± 16.0</td>
<td>87.0 ± 34.2</td>
<td>94.5 ± 37.4</td>
<td>98.9 ± 33.9</td>
</tr>
<tr>
<td>μg·h/l</td>
<td>0</td>
<td>3.9 ± 2.2</td>
<td>5.1 ± 4.2</td>
<td>4.9 ± 2.7</td>
</tr>
</tbody>
</table>
| C min, C max and AUC0–8 h values are expressed as mean ± SD. T max values are expressed as median (range). C min = Minimum plasma concentration; C max = maximum plasma concentration; T max = time to C max; AUC0–8 h = area under the plasma concentration-time curve from 0 to 8 h. © 2009 The Endocrine Society. Reproduced with permission.
months of treatment. Key secondary end points include the proportion of responders at months 3 and 12, mean change in 24-hour UFC, plasma ACTH and serum cortisol, changes in QoL, and changes in signs and symptoms of Cushing’s disease.

**Combination Medical Therapy with Pasireotide**

In Cushing’s disease, medical therapy with adrenal-blocking agents is often used as pretreatment before surgery and after unsuccessful surgery and radiotherapy, although there is limited robust evidence for their efficacy [1]. Adrenal-blocking agents include metyrapone, mitotane, aminogluthethamide, etomidate and ketoconazole. Ketoconazole is the most often used adrenolytic agent and works by inhibiting cytochrome P450-dependent enzymes of steroidogenesis.

There have also been recent studies evaluating the use of the dopamine agonist cabergoline as a treatment for Cushing’s disease, either alone [17] or in combination with ketoconazole [18]. These studies showed that up to 2-years’ monotherapy with cabergoline results in UFC normalization in approximately one third of patients, whereas adding ketoconazole to cabergoline therapy can increase the proportion of patients with normalized UFC to approximately two thirds of patients [17, 18].

More recently, an 80-day clinical trial in 17 patients with Cushing’s disease was initiated to examine the efficacy of a stepwise approach to medical therapy, with pasireotide as the basal treatment modality, sequentially extended with cabergoline and ketoconazole [19]. Patients started treatment with pasireotide 100 μg s.c. t.i.d. If UFC had not normalized at day 15, the pasireotide dose was increased to 250 μg s.c. t.i.d. At day 32, patients with elevated UFC added cabergoline 1.5 mg q.i.d. At day 60, those patients who still had elevated UFC added ketoconazole 200 mg t.i.d.

Preliminary results suggest that the combined use of pasireotide, cabergoline and low-dose ketoconazole may have additive beneficial effects in the medical treatment of Cushing’s disease [19].

**Conclusion**

Pasireotide is a promising new pituitary-targeted treatment for patients with Cushing’s disease. Results from the large, randomized, double-blind, phase III trial will help to determine the role pasireotide will play in the treatment of Cushing’s disease. Furthermore, the combination of partially independent medical therapies which act through differential mechanisms is a rational approach to the treatment of Cushing’s disease.

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**Disclosure Statement**

Alberto M. Pedroncelli is an employee of Novartis Pharma AG, Basel, Switzerland.

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