Medical Treatment of Cushing's Disease with Pasireotide

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Abstract

Cushing's disease is the most common form of endogenous Cushing's syndrome and results from excess adrenocorticotropic hormone (ACTH) production by a corticotroph pituitary adenoma. Transsphenoidal surgical removal of the corticotroph adenoma is the treatment of choice for patients with Cushing's disease. However, despite advances in surgery, complete tumour removal is sometimes impossible and eventual disease recurrence occurs later even in patients who achieved an initial remission. Medical therapy is one of the second-line options, which can provide a primary or adjunctive role if the patient cannot safely undergo pituitary surgery, if surgery fails, or if the tumour recurs. However, until recently, few effective therapeutic options existed. Somatostatin receptors in the corticotroph tumours have been identified as potential therapeutic targets for Cushing's disease. Pasireotide is a novel somatostatin analogue which has high affinity for these receptors. In a recent Phase III clinical trial, pasireotide treatment was demonstrated to significantly reduce elevated cortisol levels in patients with Cushing's disease achieving normalisation of urinary free cortisol (UFC) levels in subset of patients and close to 50 % mean reduction in UFC levels were seen in the patients. Initial data also suggest that pasireotide could be highly effective as part of combined therapy for Cushing's disease.

Keywords

Cushing's disease, pasireotide, somatostatin receptors, ACTH, corticotroph tumour

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Cushing's disease is caused by a pituitary adenoma that secretes elevated levels of adrenocorticotropic hormone (ACTH), which stimulates the adrenal glands to produce excess cortisol.[1] The tumours are most frequently microadenomas (≤1 cm in diameter) while corticotroph macroadenomas are responsible for approximately 10 % of cases. Cushing's disease is the most common form of endogenous Cushing's syndrome accounting for about 70 % of patients with this condition and has an estimated annual incidence of 0.1–2.0 new cases per 100,000 worldwide.[2–4] Chronic stimulation by ACTH produces diffuse bilateral hyperplasia of the adrenal cortex which can sometimes become nodular and enlarged. The primary clinical symptoms of Cushing's disease are due to hypercortisolism. Symptoms and signs develop gradually and include weight gain (particularly on the trunk and face), fatigue, proximal muscle weakness, oedema, diabetes, hypertension, sleep disturbances, cognitive impairment, depression, osteoporosis, infections, skin atrophy, ecchymosis, hirsutism and menstrual irregularities in women and decreased libido and erectile dysfunction in men. If Cushing's disease is left untreated or uncontrolled, this can result in severe complications including ischaemic and thromboembolic cardiovascular events.[5] Individuals with such progression have a mortality rate four to five times higher than an age- and sex-matched population.[4,6,7]

Surgical Therapy of Cushing's Disease

The treatment goals in Cushing's disease include elective removal of corticotroph tumour while preserving pituitary function, reversal of clinical features, normalisation of biochemical changes and long-term control without recurrence. Surgical removal of the tumour is the first-line treatment; however, the risk of initial surgical failure in microadenoma is 10–35 % and recurrence of Cushing's disease may reach 20 % in the subsequent ten years. In the case of macroadenoma, surgery is unsuccessful in achieving remission in >45 % of cases, remission rates are lower (12–45 %) and recurrence occurs sooner than in microadenoma (mean 16 versus 49 months).[8] The reported rates of remission vary as a result of differing criteria of cortisol values and endpoints used to determine remission, and differences in the timeframe of patient monitoring (see *Table 1*). Patil et al. found that although surgical remission was achieved in 85.6 % of 215 patients with Cushing's disease who underwent first line transsphenoidal surgery for resection of a pituitary microadenoma, disease recurrence was found in a quarter of these (25.5 %) at five-year follow up.[9] Another study reported a remission rate of 56 % of 63 patients at 9.6 years post-transsphenoidal surgery.[10] Treatment options for patients with persistent or recurrent disease include repeat transsphenoidal surgery, pituitary radiotherapy, medical therapy and bilateral adrenalectomy. Repeat pituitary surgery is associated with an

Table 1: Reported Remission and Relapse Rates in Patients with Cushing's Disease Following Transsphenoidal Surgery

Immediate Post-operative Remission (%)	Later Relapse Rate (%)	Follow-up Time (Months)	Reference
71.4* (45/63)	22.2 (10/45)	115	Atkinson et al.[10]
77 (41/53)	5 (2/41)	72	Rees et al.[39]
82 (236/289)	9 (13/150)	11.1 years	Hammer et al.[40]
76.3 (510/668)	12.7 (65/510)	46	Bochicchio et al.[41]
85.6 (184/215)	17.4** (32/184)	6	Patil et al.[9]
68.5 (61/89)	11.5 (7/61)	92	Yap et al.[42]
78.7 (48/61)	14.6 (7/48)	88	Chee et al.[43]
58.6 (17/29)	17.6 (3/17)	35	van Aken et al.[44]

**A remission rate of 56 % was reported for the 63 patients at 9.6 years post-transsphenoidal surgery. **This figure increased to 25 % five years post-surgery.*

overall lower rate of success than that seen after the first operation.[11] These findings suggest a need for new therapies to treat patients with Cushing's disease who fail to achieve remission following surgical intervention.

Second-line Therapy When Pituitary Surgery Fails

Unlike other hormone secreting pituitary tumours, medical therapy is generally not considered as a first-line treatment option for patients with Cushing's disease.[8] The role of medical therapy has until recently only been administered short-term or while awaiting effectiveness of other therapeutic approaches: it is sometimes performed before surgery to minimise complications and to reduce the effects of severe hypercortisolism. In patients for whom surgery has failed, medical therapy is necessary to reduce elevated levels of cortisol and should be attempted before considering bilateral adrenalectomy. Medical therapy can also be useful in patients waiting for pituitary radiotherapy to take effect, which can take up to 2–3 years or more.[8,12] Effective medical treatment of Cushing's disease that targets directly the corticotroph tumour therefore represents an unmet clinical need.

Medical Therapies Targeted to Adrenal Glands and Glucocorticoids Receptors

Adrenal-directed therapy using the steroidogenesis inhibitors ketoconazole, metyrapone, mitotane and etomidate have been effective as palliative treatment in a significant proportion of patients; however, they all target the adrenal glands and do not treat the underlying cause of the disease.[8] Each of the medical therapies utilised in the treatment of Cushing's disease have their specific drawbacks and are not equally accessible in all countries (see *Table 2*). Monitoring of systemic levels of liver enzymes is needed during ketoconazole treatment because of the potential of hepatotoxicity;[13] in addition ketoconazole suppresses testosterone levels and is thus not the first choice in male patients with Cushing's disease. Metyrapone inhibits 11-hydroxylase to decrease cortisol levels producing an increase of ACTH levels and accumulation of precursor steroids including adrenal androgens and mineralocorticoid precursors; this can result in hypertension, hypokalaemia and hirsutism in women.[1] LCI699 is a new potent inhibitor of 11-beta-hydroxylase, the enzyme responsible for the last step of cortisol synthesis. The safety and efficacy of this drug are currently being evaluated,[14] however preliminary data has demonstrated efficacy with a satisfactory safety profile in a short-term proof-of-concept study.[15]

Mitotane has been used in few centres probably in view of dose-related gastrointestinal and neurological adverse effects (AEs).[16] Furthermore, it cannot be used in women contemplating pregnancy in the next five years.[17] Mifepristone is a type 2 glucocorticoid receptor and progesterone receptor antagonist that is approved in the US as a therapy to control hyperglycaemia in patients with Cushing's disease. A recent Phase III clinical trial demonstrated significant improvements in the clinical status of patients treated with mifepristone.[18] The open label study treated 43 Cushing's disease patients, who were either glucose intolerant or hypertensive, with mifepristone for six months. During the study, 60 % of glucose intolerant and 43 % of hypertensive patients had a significant improvement in glucose tolerance (≥25 %) or blood pressure (≥5 mm Hg), respectively, and a total of 87 % ($p<0.0001$) had significant improvement in clinical and metabolic status. While mifepristone is effective in treating Cushing's syndrome symptoms, due to the lack of adequate biochemical monitoring and potential for AEs, the use of this medication requires careful monitoring of dosing and drug–drug interactions by endocrinologists with expertise in its use.

Medical Therapies Targeting the Corticotroph Tumours

Recent advances in understanding of the pathogenesis of corticotroph tumours have led to the investigation of pituitary tumour-directed drugs in the treatment of Cushing's disease. Cabergoline is a D2 dopamine receptor agonist that is approved by the US Food and Drug Administration (FDA) as a therapy for hyperprolactinaemia.[19] As dopamine receptors are expressed in a subset of pituitary corticotroph tumours of patients with Cushing's disease, cabergoline has been evaluated as a potential therapy.[20] It has been found that cabergoline is able to normalise urinary free cortisol in 25–40 % of patients with Cushing's disease over 2–5 year follow-up, but the studies are limited to few single-centre prospective studies[21–23] and a retrospective study from two centres,[24] where each study included only 12–30 patients. Furthermore, the doses used varied between 1 to 7 mg/week, raising the need to monitor for long-tem potential cardiac valvulopathy and eventual escape phenomenon.[22] A recent pilot study using retinoic acid (up to 80 mg daily orally) shows some potential efficacy over 12 months but was effective in only three of seven patients during one year.[25]

The somatostatin analogue pasireotide is the first drug to be approved in the European Union (EU) targeting Cushing's disease and was recently recommended by the FDA advisory committee for approval to treat patients with Cushing's disease in the US. Somatostatin is a peptide hormone that regulates the endocrine system via interaction with 5 somatostatin receptors (sstr), which are G protein-coupled transmembrane receptors and are involved in the regulation of the release of numerous hormones. These receptors have variable tissue, organ and cytospecific distribution; human endocrine tumours often express the five subtypes with different intensity. Human pituitary corticotroph adenomas express receptor subtypes sst_1, sst_2 and sst_5,

Table 2: Current Medical Management of Cushing's Disease

Drug	Mechanism of Action	Comments	Reference
Ketoconazole	Inhibition of several steroidogenic enzymes	May be preferred in women. Monitoring of systemic levels of liver enzymes is needed during ketoconazole treatment due to hepatotoxicity Absorption inhibited by lowering stomach acidity	13
Metapyrone	Inhibits 11β hydroxylase	Most commonly used in pregnancy. AEs from increases in ACTH and resulting androgen and mineralocorticoid precursors, causing hypertension, hypokalaemia, acne and hirsutism	45,46
Mitotane	Inhibition of several steroidogenic enzymes and adrenolytic activity	Use limited by adverse gastrointestinal and neurological effects. Persists in the circulation long after discontinuation. Potential teratogen and can cause abortion; contraindicated in women contemplating pregnancy in the next 5 years	16,17
Etomidate	Inhibits 11β hydroxylase	Use is limited by the requirement for intravenous administration. Causes excess sedation and anaesthesia. Useful in cases with significant biochemical disturbance, sepsis and other serious complications such as severe psychosis, as well as in pre-operative instability	47
Mifepristone	Type II glucocorticoid receptor antagonist	Clinical improvement is associated with hypokalaemia, hypertension and adrenal insufficiency	18,48,49
Cabergoline	Dopamine D2 receptor agonist	Good short-term efficacy with 30–40 % of patients with sustained response over 2 years Potential nausea and hypotension and need for surveillance of potential cardiac valve insufficiency	22,24,50
Pasireotide	Somatostatin receptor agonist	Normalisation of UFC in 20–25 % of cases with potential long-term efficacy; overall 50 % decrease in UFC with clinical benefit. Frequent hyperglycaemia-related AEs and risk of cholelithiasis. Long-term effect on IGF-1 levels to be determined	27,30,36

ACTH = adrenocorticotropic hormone; AEs = adverse events; IGF-1 = insulin-like growth factor-1; UFC = urinary-free cortisol.

although expression of $sstr_5$ predominates.[26] The different ssts play different physiological roles. Activation of sst_5 inhibits ACTH secretion and therefore presents a potential therapeutic target for Cushing's disease. The somatostatin analogues octreotide and lanreotide are predominantly $sstr_2$-selective ligands and are mostly ineffective in treating Cushing's disease. The expression of sst_2 is relatively low in corticotroph adenomas and this subtype may be downregulated when circulating cortisol levels are high.[26]

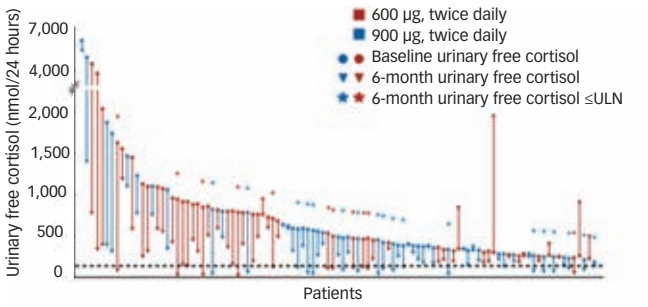
Pasireotide is a novel somatostatin analogue which has high affinity for four of the five sst subtypes. Compared with octreotide, pasireotide has an *in vitro* binding affinity 40-, 30- and five-fold higher for sst_5, sst_1, and sst_3, respectively and therefore in cells that express these receptors, pasireotide should have a stronger inhibitory effect.[27,28] *In vitro* studies with human ACTH-secreting pituitary adenomas and AtT-20 murine corticotrophic tumour cells demonstrated that pasireotide inhibited both basal and stimulated ACTH release.[26] Suppression of CRH-induced ACTH release by pasireotide was not affected by a 48-hour pre-treatment with dexamethasone, suggesting that the expression of sst_5 is relatively resistant to glucocorticoids.[26]

Following these findings, clinical trials investigating the use of pasireotide as a therapy for Cushing's disease were initiated. The primary efficacy endpoint was the normalisation of urinary-free cortisol (UFC), while serum cortisol and plasma ACTH were secondary endpoints. Although the primary target of pasireotide is inhibition of ACTH secretion, the measurement of this hormone is difficult owing to its pulsatile secretory pattern, short half-life and rapid degradation in plasma. In patients with Cushing's disease UFC is a surrogate measure for integrated ACTH activity and is accepted as a follow-up test in the assessment of therapy of Cushing's disease. In a 15-day Phase II, open-label, single-arm clinical trial of patients with *de novo* or persistent/recurrent Cushing's disease, 76 % achieved a reduction in UFC levels, with 17 % achieving a normalised UFC.[27] On the basis of these data, pasireotide was granted orphan drug status for Cushing's disease by the European Medicines Agency (EMA) in 2009.[29]

The Phase III B2305 clinical trial (NCT00434148) is the largest ever Phase III clinical study in patients with Cushing's disease.[30] The primary target patient population was those with persistent or recurrent Cushing's disease and treatment naive patients could only be enrolled provided they were not candidates for surgery. For patients on medical treatment for Cushing's disease, a washout period was completed before baseline efficacy assessments were performed. The double-blind study randomised 162 patients to twice daily subcutaneous pasireotide 600 µg (n=82) or 900 µg (n=80). Patients with UFC not exceeding two times the upper limit of the normal (ULN) range and less than the baseline at month three continued receiving double-blind randomised doses until month six. Patients with UFC exceeding twice the ULN at month three were unblinded and their dose escalated by 300 µg. At month six all patients were unblinded and open-label treatment continued from month six to month 12. During this phase, if the UFC level exceeded the ULN range, the dose could be increased by 300 µg twice daily (maximum, 1,200 µg twice daily) at any time. The dose could be reduced in steps of 300 µg twice daily if required due to AEs at any time during the study. After month 12, patients were able to enter an open-label extension of the trial.

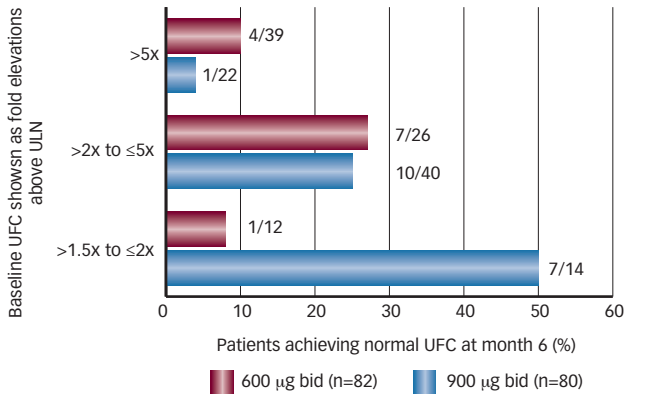
In the B2305 trial, the primary endpoint of UFC level at or below the ULN range at month six without up titration of the dose was achieved in 14.6 % of patients receiving the 600 µg dose (95 % confidence interval [CI], 7 to 22) and 26.3 % (95 % CI, 17 to 36) of those on the 900 µg dose. The 900 µg treatment arm met its primary endpoint (i.e. the lower bound of the 95 % CI for a dose group was greater than 15 %), however, the 600 µg treatment arm failed to meet this criterion. There was a rapid decrease in UFC, with a median 50 % reduction in UFC level in both dosage groups by month two and this remained stable up to month 12. In the majority of patients evaluable at month six, a decrease in UFC was seen from baseline to month six and almost half (48.5 %) achieved a substantial reduction (≥ 50 %) in UFC (see *Figure 1*). In general, patients allocated to receive 900 µg of pasireotide had lower UFC levels than those randomised to the 600 µg dose. It is important to note that the population of patients enrolled in this study was composed of patients with moderate to severe

Figure 1: Absolute Change in Urinary Free Cortisol from Baseline to Month Six in the 103 Individual Patients with Baseline and Month-six Urinary Free Cortisol Collections



Urinary free cortisol was available at baseline and at month six in a total of 103 patients; 50 patients had either a normalisation or greater than or equal to 50 % reduction from baseline in urinary free cortisol levels at month six. The black dashed line represents the upper limit of the normal range (ULN) (145 nmol per 24 hours [52.5 µg per 24 hours]). Source: Colao et al., 2012.[30]

Figure 2: Percentage of Patients in Whom Urinary Free Cortisol Levels were At or Below the Upper Limits of Normal Range Following Treatment with Pasireotide for Six Months



The percentage of patients in whom the urinary free cortisol (UFC) level was at or below the upper limit of the normal range (ULN) at month six of pasireotide treatment, categorised according to whether hypercortisolism at baseline was mild (UFC >1.5 to 2 times the ULN), moderate (>2 to 5 times the ULN), or severe or very severe (>5 times the ULN). bid = twice daily. Source: Colao et al., 2012.[30]

hypercortisolism (78 % of patients) with mean baseline UFC of 6.5 times ULN. Higher baseline UFC are associated with a lower normalisation rate of UFC. In patients with mild hypercortisolism at baseline (UFC 1.5 to 2 x ULN), the efficacy was as high as 50 % in the 900 µg bid group (see *Figure 2*).[30]

The biochemical response in UFC was also supported by reductions in serum cortisol, plasma ACTH and pituitary tumour size. Significant improvements in the signs and symptoms of Cushing's disease were also seen, including reductions in body weight, reductions in systolic and diastolic blood pressure and decreases in low-density lipoprotein (LDL) cholesterol levels (see *Figure 3*). Scores for health-related quality of life also improved. These improvements were seen regardless of whether a normal UFC was achieved, suggesting that a reduction in cortisol level may be associated with long-term clinical benefits. The most common AEs noted were transient gastrointestinal discomfort (diarrhoea, nausea, abdominal pain), hyperglycaemia-related AEs and increased risk of cholelithiasis and elevation of liver enzymes.

Compared with other somatostatin analogues, in the B2305 trial, pasireotide was associated with a higher rate of hyperglycaemia-related AEs (occurring in 72.8 % of patients). Glucose and glycated haemoglobin levels increased soon after treatment with pasireotide, necessitating the administration of glucose-lowering medications in almost half (45.6 %) of the patients. In patients with Cushing's disease, changes in insulin sensitivity associated with hypercortisolism can result in hyperglycaemia and/or diabetes. However, studies with healthy volunteers indicate that hyperglycaemia associated with pasireotide is related to decreases in insulin and incretins (glucagon-like peptide-1 [GLP-1] and gastric inhibitory polypeptide [GIP]) secretion, with no changes in insulin sensitivity.[31] Furthermore, the incretin-based antihyperglycaemic agents liraglutide and vildagliptin significantly reduced pasireotide-induced hyperglycaemia in healthy volunteers. Glycaemic status therefore, should be assessed prior to initiating pasireotide therapy and glycaemic regulation optimised. Patients should be monitored for hyperglycaemia throughout the treatment and appropriate intervention employed promptly on evidence of hyperglycaemia, following established treatment guidelines. Liver function monitoring is also recommended. Pasireotide was found to increase QT interval in normal subjects and can decrease heart rate in patients with Cushing's disease; careful monitoring of electrocardiogram is thus recommended prior and during its use and combinations with drugs which can also increase QT interval should be avoided. Pasireotide can also induce adrenal insufficiency, however this is rapidly corrected by stopping medication transiently and reducing the dose.[30]

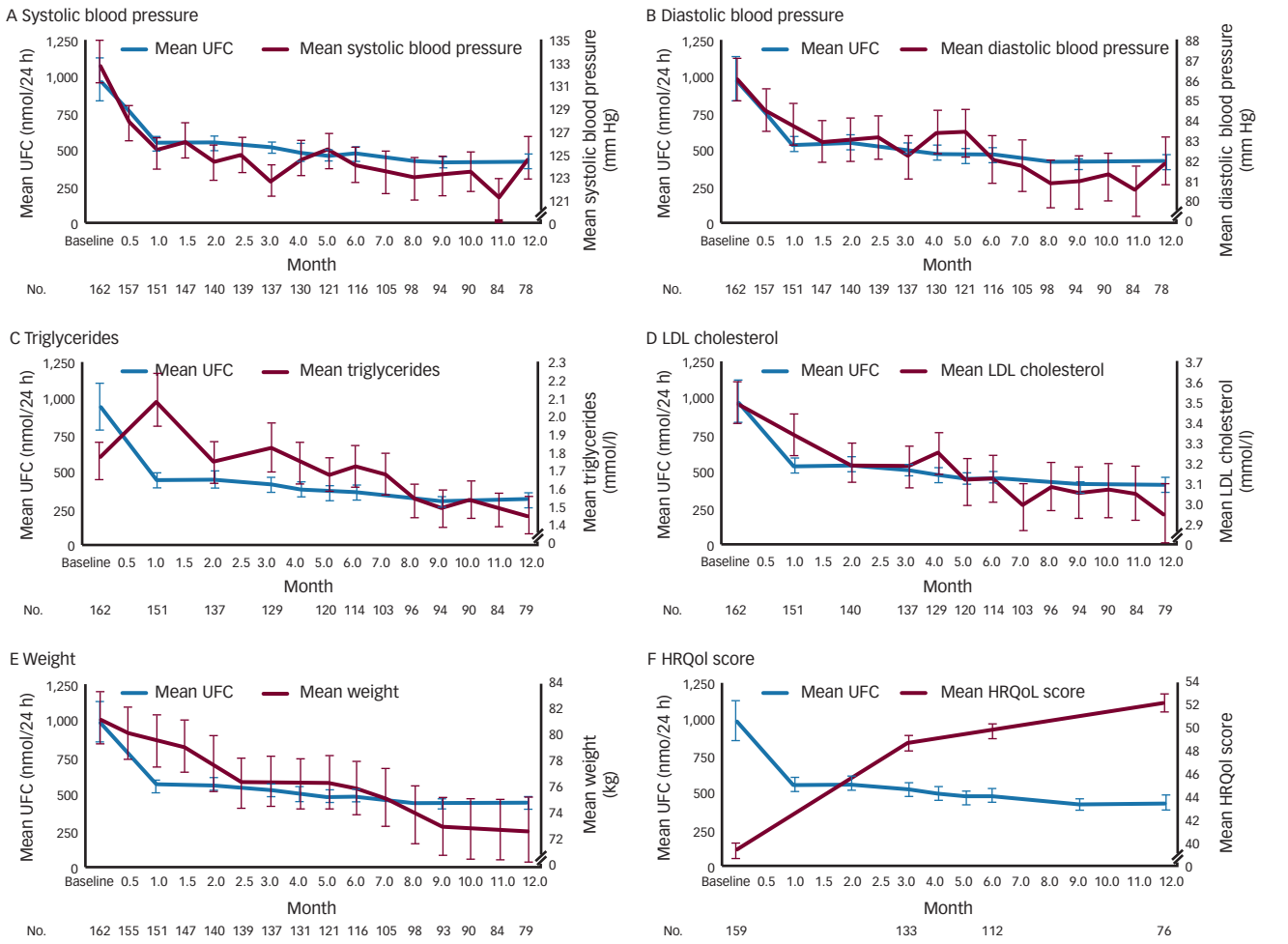
On the basis of these trial data, regulatory submissions for pasireotide in the treatment of Cushing's disease are underway worldwide. In April 2012, the EMA Committee for Medicinal Products for Human Use recommended approval of pasireotide for the treatment of Cushing's disease in territories throughout Europe.

Future Directions for the Use of Pasireotide as a Therapy for Cushing's Disease

Long-term use of pasireotide appears safe and effective. A presentation of 24-month pasireotide safety data, following a 12-month extension of the original pasireotide Phase III clinical trial, reported a similar safety profile to that of other somatostatin analogues.[32] Additionally, 24-month pasireotide treatment resulted in sustained reductions in UFC, plasma ACTH and serum cortisol.[33] A case has recently been reported of a 43-year-old woman with Cushing's disease who had received seven years of pasireotide treatment that was administered as part of a Phase II study. The patient's UFC remained in the normal range at most monthly assessments. Basal and desmopressin-stimulated ACTH levels also decreased as a result of treatment with pasireotide. To date, she has not had any serious adverse events.[34]

In the B2305 trial, patients unlikely to have a biochemical response to pasireotide treatment could be identified within the first few months of treatment; of the patients who were uncontrolled at both month one and two, (who did not have at least a 50 % reduction in UFC from baseline and their UFC was above ULN), 91.7 % were uncontrolled at month six.[30] Analyses of the prediction value of early response to pasireotide have shown that in general most patients who have an early response to pasireotide continue to respond, while the majority of patients who fail to respond biochemically to pasireotide within the first two months do not respond at a later time point.[35] The patient factors involved in

Figure 3: Changes in Signs and Symptoms of Cushing's Disease and Urinary Free Cortisol Level Over Time in the Overall Population



h = hours; HRQoL = health-related quality of life; LDL = low-density lipoprotein; UFC = urinary free cortisol. Source: Colao et al., 2012.[30]

responsiveness to pasireotide are currently unknown, however future studies on correlations between levels of expression of sst_5 in corticotroph tumours and response to pasireotide may aid in appropriate treatment decisions.

Since human corticotroph adenomas express both sst and dopamine receptors, combined therapy involving somatostatin analogues and dopamine agonists (pasireotide + cabergoline) may be a promising approach for patients who fail to achieve normal UFC levels when given cabergoline or pasireotide alone. In a recent study 17 patients with Cushing's disease were treated with 100 µg of pasireotide three times daily; this dose was increased to 250 µg subcutaneously three times daily at day 15 if the level of UFC had not normalised. At day 28, cabergoline was added to pasireotide at a dose of 0.5 mg every other day (this dose was increased to 1.0 mg every other day after five days and 1.5 mg every other day after 10 days) if the level of UFC remained elevated. If the level of UFC had not normalised at day 60, ketoconazole was added at a dose of 200 mg three times daily. Pasireotide monotherapy induced sustained normalisation of the UFC in 29 % of patients at day 80.[36] UFC normalisation occurred by day 28 and was sustained throughout the observation period. The addition of cabergoline normalised UFC in a further 24 %. At day 60, a total of 47 % still had elevated UFC levels with pasireotide–cabergoline combination therapy, although a trend toward normalisation of UFC was observed in all but one patient. The addition of ketoconazole increased the number of patients with a complete response to 88 %. The clinical features of Cushing's disease also improved. Although Feelders et al., suggested that stepwise medical therapy may be beneficial in the biochemical control of Cushing's disease,[36] pasireotide should not be administered in combination with other products that prolong the QT interval.[37] Additionally, in this study, decreases in insulin-like growth factor-1 (IGF-1) levels were found following pasireotide combination therapies,[36] and the potential consequences of suppression of growth hormone (GH) with long-term therapy should be further examined in future studies. Clearly longer studies examining the capacity of these new medical therapies to normalise cortisol diurnal rhythm, to restore normal hypothalamic-pituitary-adrenal (HPA) response to acute stress and decrease long-term increased morbidities of residual Cushing's disease will be important.

Study NCT01374906 is an ongoing Phase III clinical trial which will investigate two doses of pasireotide long-acting release (LAR) (10 mg and 30 mg; dosing period seven months), a monthly depot formulation in patients with persistent or recurrent disease or *de novo* mild to moderate Cushing's disease who are nonsurgical candidates. The planned recruitment is 148 participants and the estimated primary completion date is December 2015.[38]

Summary and Concluding Remarks

Cushing's disease is a serious endocrine disease for which currently surgery remains the first-line treatment, but unfortunately the rate of remission at long-term follow-up is suboptimal and recurrences are frequent. Moreover, no treatment has been proven as fully satisfactory when surgery fails. The results from the Phase III B2305 trial demonstrate that pasireotide significantly reduces elevated cortisol levels; there was a significant reduction in UFC in many patients and normalisation of UFC in a subset of patients. Thus pasireotide should have a significant role as a medical monotherapeutic option in the treatment of patients with persistent or recurrent Cushing's disease. It will also be pertinent to evaluate further the benefits of its combined use with other pituitary targeted therapies such as cabergoline in order to increase the optimal control of Cushing's disease. ■

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