

# Recent advancements in the drug treatment of endocrine diseases

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**ABSTRACT** – Recent years have seen several advances in the management of endocrine diseases. These include novel drugs developed as a consequence of better understanding of the pathophysiology of endocrine conditions, as well as improved delivery methods for existing drugs. In this article, we summarise recent studies evaluating several drugs used in the treatment of endocrine disorders.

**KEY WORDS:** endocrine diseases, pharmacotherapy

## Introduction

Control of hormone hypersecretion and replacement of hormone deficiencies are the mainstay of treatment in endocrinology. The ultimate goal of treatment is to reduce the long-term morbidity and mortality associated with hormone hypo- or hypersecretion and to improve the quality of life. Here, we review the evidence for the efficacy and safety of some of the recent drugs used in the pharmacotherapy of several endocrine diseases.

## Cushing's disease

The primary treatment for Cushing's disease is surgical removal of the adrenocorticotrophic hormone (ACTH)-secreting pituitary tumour. Medical control of hypercortisolism is required when surgery is contraindicated, in preparation for surgery and in cases of persistence or recurrence of hypercortisolism following surgery. Medication commonly used includes ketoconazole and metyrapone. Ketoconazole blocks the first step (side-chain cleavage) and, to a lesser extent, the last step in cortisol biosynthesis (ie conversion of 11-deoxycortisol to cortisol) by inhibiting 11 beta-hydroxylase. Metyrapone inhibits the last step in cortisol biosynthesis. Two medical treatments targeting the pituitary corticotroph adenoma have recently shown potential benefit in the treatment of Cushing's disease.

## Cabergoline

Dopamine (D)<sub>2</sub> receptors have been identified in corticotroph tumours. Treatment with cabergoline (a D<sub>2</sub> agonist) is associated with a reduction in 24-h urinary free cortisol (UFC) in patients with Cushing's disease.<sup>1,2</sup> In one study, cabergoline normalised 24-h UFC after six months in 25% of patients with Cushing's disease unsuccessfully treated by surgery at doses ranging from

2 to 3 mg/week.<sup>1</sup> In another study, normalisation of UFC was achieved in approximately 37% of patients with Cushing's disease within 3–6 months. In this study, 30% of patients had sustained normalisation of UFC after a mean of 37 months, with a mean dose of 2.1 mg/week of cabergoline.<sup>2</sup> Close follow-up is necessary for dose adjustments. However, UFC is not a good marker of cortisol dynamics and normalisation of UFC does not mean that the patient is necessarily in remission. Plasma cortisol concentrations more accurately reflect cortisol exposure and cortisol day curves showing a normal diurnal rhythm would give a better indication of disease response to cabergoline.

## Pasireotide

Pasireotide is a somatostatin analogue that binds to four of the five somatostatin receptors (1, 2, 3 and 5) and has highest affinity for subtype 5. In a recent randomised double-blind trial, patients with either newly diagnosed Cushing's disease who were not eligible for surgery or those with persistent and/or recurrent Cushing's disease after surgery received pasireotide subcutaneously at 2 doses, 600 µg or 900 µg, twice daily.<sup>3</sup> Approximately 26% of patients receiving the higher dose in the study achieved normalisation of UFC level at 6 months without dose uptitration. Serum and salivary cortisol and plasma ACTH levels decreased in both dose groups, and clinical signs and symptoms of Cushing's disease improved.<sup>3</sup> Pasireotide was associated with hyperglycaemia-related adverse events in approximately 73% of patients. Treatment with a glucose-lowering medication was started in 46% of patients.<sup>3</sup> In a report of 17 patients with Cushing's disease, a combination of cabergoline and pasireotide normalised UFC in four out of 12 patients (33%) not responding to pasireotide monotherapy.<sup>4</sup> Therefore, these drugs might offer some improvement in cortisol levels when other treatments have failed, but they should not be used as first-line therapy.

## Acromegaly

The first-line treatment of patients with acromegaly is surgery. Trans-sphenoidal surgery by a dedicated experienced pituitary surgeon should be offered to all patients with a microadenoma or a macroadenoma that appears to be fully resectable, or is causing visual impairment. Remission rates for acromegaly surgery improve with establishment of a specialist surgical service, with a reduction in surgeon numbers.<sup>5</sup> Primary medical treatment can be offered to patients who are unfit for surgery, refuse surgery or who are not amenable to surgical cure.<sup>6,7</sup> Several drugs are now available for the treatment of acromegaly. Medical therapy is often used when surgery alone has not been successful in achieving disease control. The updated consensus guidelines

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of 2010 define disease control as a growth hormone (GH) nadir of  $<0.4 \mu\text{g/l}$  on oral glucose tolerance test (with ultrasensitive assays), in conjunction with a normal age- and sex-adjusted insulin growth factor (IGF)-1.<sup>8</sup> A random post-treatment serum GH of  $<2.5 \mu\text{g/l}$ , or normalisation of serum IGF-I for age and sex is associated with mortality indistinguishable from the general population.<sup>9</sup> In a study from New Zealand, a serum GH of  $<1 \mu\text{g/l}$  was associated with a mortality rate indistinguishable from that expected for the age-matched general community.<sup>10</sup> There is no evidence that a nadir GH of  $<0.4 \mu\text{g/l}$  is any better in terms of survival than a random GH of  $1.0 \mu\text{g/l}$ . In addition, even if there were such evidence, it is not clear whether advantages of trying to achieve such tight control outweigh the potential disadvantages, including risks of further surgery, GH deficiency and adverse effects, and prohibitive costs of medical treatment.

### Somatostatin analogues

Somatostatin analogues, such as octreotide and lanreotide, bind to somatostatin receptors 2 and 5 on somatotrophs and inhibit GH secretion. The long-acting form of octreotide (octreotide LAR) is given intramuscularly at an initial dose of 20 mg monthly. The dose can be increased to 30 mg and then to 40 mg monthly if the serum IGF-1 is not normalised within two months. Lanreotide is available as an intramuscular form (lanreotide LA, 30 mg given every 1–2 weeks) and a deep subcutaneous form (lanreotide autogel, 60–120 mg given every 4–6 weeks). Somatostatin analogues lead to clinical and biochemical improvements in acromegaly, with normalisation of IGF-1 levels in 40–75% of patients. There does not appear to be a significant difference between the two 1-monthly preparations (octreotide LAR and lanreotide autogel) for control of biochemical markers and symptoms.<sup>11</sup>

Somatostatin analogues can also cause a significant reduction in adenoma size. In a systematic review of patients with acromegaly receiving primary medical treatment with somatostatin analogues, approximately 37% had a significant decrease in tumour size.<sup>12</sup> In a subsequent study, 75.5% of patients with acromegaly had a tumour shrinkage of 25% or greater after 12 months of primary therapy with a somatostatin analogue.<sup>13</sup> Five-year therapy with octreotide LAR or lanreotide as first-line therapy in patients with severe comorbidities and those who refused surgery induced a 'notable' ( $>75\%$ ) tumour shrinkage in 67% of patients and a 'moderate' (50–75%) tumour shrinkage in a further 24%.<sup>14</sup> The mechanism of the reduction in tumour size is not fully understood. Octreotide has antiproliferative effects on GH-secreting pituitary adenomas.<sup>15,16</sup> The adverse effects associated with somatostatin analogues include nausea, diarrhoea and gallstones. Although octreotide and lanreotide transiently inhibit insulin release, their overall clinical impact on glucose homeostasis is minimal.<sup>17</sup>

### Cabergoline

A recent meta-analysis of trials of cabergoline (a dopamine agonist) in acromegaly has shown that, when control is not achieved

with a somatostatin analogue, addition of cabergoline normalises IGF-1 levels in approximately 50% of cases.<sup>18</sup> Cabergoline alone normalised IGF-1 levels in one-third of patients with acromegaly.<sup>18</sup> Cabergoline is started at a dose of 250  $\mu\text{g}$  twice weekly. The dose can be increased, if needed, to 1 mg twice weekly.

### Pegvisomant

Pegvisomant is the pegylated form of mutant GH with prolonged half-life, which acts as a GH receptor antagonist. Pegvisomant treatment results in a reduction in serum IGF-1 concentrations as well as clinical improvement in fatigue, sweating, soft-tissue swelling and ring size.<sup>19</sup> In ACROSTUDY, an international surveillance registry study of patients with acromegaly, approximately 57% of patients had normal IGF-1 levels after one year of treatment with pegvisomant.<sup>20</sup> It is given as a daily subcutaneous injection at 10 mg/day. The dose is titrated every 4–6 weeks in 5 mg increments, to a maximum of 30 mg/day, with the aim of maintaining IGF-1 in the normal range. Alternate-day dosing can also be effective in some patients with acromegaly.<sup>21</sup> Gender, body weight, previous radiotherapy and baseline IGF-1 influence the dose of pegvisomant. Women might need higher doses and those who have had radiotherapy require lower doses.<sup>22</sup>

Pegvisomant therapy is associated with an increase in the serum GH concentration. Tumour size might continue to increase during treatment with pegvisomant. The ACROSTUDY, with a mean follow-up of 2.1 years, reported an increase in adenoma size in 3.2% of patients for whom magnetic resonance imaging (MRI) data were available.<sup>20</sup> Although an increase in adenoma size appears to be uncommon with pegvisomant, assessment of adenoma size by MRI should be performed at least annually. The adverse effects of pegvisomant include liver enzyme elevations and lipodystrophy at the injection site.<sup>20</sup> Liver function tests should be monitored during treatment with pegvisomant.

The combination of pegvisomant and a long-acting somatostatin analogue has been shown to normalise IGF-1 levels in most patients.<sup>23–25</sup> However, co-treatment with pegvisomant and somatostatin analogues has not been shown to be clearly better than pegvisomant alone.

### Graves' ophthalmopathy

#### Mild ophthalmopathy

A recent randomised trial showed selenium administration (100  $\mu\text{g}$  twice daily) to improve symptoms and quality of life, and to slow progression of the disease in patients with mild Graves' ophthalmopathy.<sup>26</sup> Patients had at least one sign of mild ophthalmopathy and disease duration of less than 18 months. All patients were euthyroid while receiving antithyroid drugs or, less commonly, following radioiodine treatment or thyroidectomy. Eyelid aperture and soft-tissue signs significantly improved

in patients receiving selenium after six months. Assessment at 12 months confirmed the findings at six months.<sup>26</sup> The exact mechanism of action of selenium is unclear. Oxygen free radicals might be involved in the pathogenesis of Graves' ophthalmopathy. Selenium is a component of selenoproteins, such as the four forms of glutathione peroxidase, which play an important role in antioxidant defence. Selenium treatment has not been shown to cause any adverse effects in the studies reported to date. However, more studies are required before selenium can be routinely recommended for patients with mild Graves' ophthalmopathy.

### Severe ophthalmopathy

Glucocorticoids are the primary treatment for severe Graves' ophthalmopathy. In a randomised, single-blind trial, intravenous glucocorticoids (once weekly methylprednisolone, 500 mg for six weeks, followed by 250 mg for six weeks) were shown to be more effective and better tolerated compared with oral prednisolone.<sup>27</sup> The advantage of intravenous over oral glucocorticoids has also been demonstrated in a meta-analysis that showed intravenous glucocorticoids were better in reducing clinical activity scores and had fewer adverse effects.<sup>28</sup>

## Adrenal insufficiency

### Hydrocortisone replacement

The daily cortisol production rate is 5.7–7.4 mg/m<sup>2</sup>/day or 9.5–9.9 mg/day, which is lower than previous estimates.<sup>29</sup> The traditional hydrocortisone replacement dose of 30 mg/day in patients with adrenal insufficiency is likely to result in over-replacement and increased risk for cardiovascular disease and bone loss. For example, it has been shown that bone mineral density (BMD) at the femoral neck and lumbar spine is reduced in patients with Addison's disease, indicating undesirable effects of the replacement therapy.<sup>30</sup> A recent study of patients with nonfunctioning pituitary adenoma and hypothalamic–pituitary–adrenal insufficiency suggests that higher glucocorticoid replacement doses are associated with increased overall mortality. The hazard ratio for mortality increased from 1.00 in patients on replacement doses of up to 19 mg to a hazard ratio of 2.03 in those receiving 20–29 mg.<sup>31</sup> Therefore, the total daily dose of hydrocortisone should not exceed 20 mg in most cases (except at times of intercurrent illness).

Three-times daily administration of hydrocortisone mimics the cortisol day curve observed in healthy subjects.<sup>32</sup> A typical three-times daily regimen comprises 10 mg in the morning, 5 mg in the early afternoon, and 2.5 mg in the late afternoon. Hydrocortisone dose recommendations are similar for patients with primary and secondary adrenal insufficiency. The hydrocortisone dose might need to be adjusted in patients taking concurrent medications that affect cytochrome P450 3A4 (CYP3A4) metabolism of glucocorticoids.<sup>33,34</sup> Most patients with primary adrenal insufficiency also require mineralocorticoid replacement to prevent volume depletion, hyponatraemia and hyperkalaemia.

A major difficulty for hydrocortisone replacement regimens is the inability to replicate truly the normal diurnal rhythm of cortisol. A novel once-daily dual-release oral hydrocortisone formulation with an immediate-release coating and an extended-release core has been developed to provide a more physiological serum cortisol profile. In a recent open randomised trial, patients taking the once-daily formulation had a lower body weight, blood pressure and glycated haemoglobin at 12 weeks compared with those taking hydrocortisone three times daily,<sup>35</sup> although the patients on the once-daily regimen were exposed to less hydrocortisone, as evidenced by the area under the curve. There is currently no evidence that this drug is any better than prednisolone.

## Osteoporosis

### Denosumab

Denosumab is a novel drug added to the armamentarium of agents used in the treatment of osteoporosis. However, the exact place of denosumab among the other medication used for osteoporosis is unclear. It is a human monoclonal antibody, which binds receptor activator of nuclear factor kappaB ligand (RANKL) and blocks the binding of RANKL to a receptor (RANK) on osteoclast precursors and osteoclasts. Thus, denosumab reduces the formation and function of osteoclasts, resulting in reduced bone resorption.

Denosumab has been shown to improve BMD and reduces the risk of fracture in postmenopausal women with osteoporosis.<sup>36,37</sup> In the FREEDOM trial, subcutaneous administration of denosumab (60 mg every six months) in postmenopausal women with osteoporosis improved BMD of lumbar spine and total hip after three years. Denosumab is also effective for the prevention of osteoporosis. In a two-year randomised controlled trial, denosumab improved the BMD of the lumbar spine, total hip and radius in postmenopausal women, with lumbar spine T-scores between –1.0 and –2.5.<sup>38</sup>

Oral bisphosphonates are the preferred option as initial treatment for postmenopausal women with uncomplicated osteoporosis owing to their efficacy, long-term safety data and favourable cost. National Institute for Health and Clinical Excellence (NICE) guidelines in the UK recommend denosumab as a treatment option for primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women at increased risk of fractures (depending on their age, independent clinical risk factors for fracture and T-score) who are unable to comply with the special instructions for administration of oral bisphosphonates, or have an intolerance of, or a contraindication to, bisphosphonates. The independent clinical risk factors in these guidelines include parental history of hip fracture, alcohol intake of four or more units daily and rheumatoid arthritis.<sup>39</sup>

The adverse events associated with denosumab include eczema, cellulitis and flatulence.<sup>36</sup> Hypocalcaemia and vitamin D deficiency should be corrected before starting denosumab and all

patients should be adequately supplemented with calcium and vitamin D. Patients with chronic kidney disease are at higher risk for hypocalcaemia and serum calcium should be monitored in these patients.

### *Transdermal parathyroid hormone*

Parathyroid hormone (PTH) is an effective anabolic treatment for osteoporosis. However, daily subcutaneous administration limits its use. A novel transdermal teriparatide (human PTH 1-34) patch used for six months has been reported to be safe and effective in increasing lumbar spine and total hip BMD in postmenopausal women with osteoporosis.<sup>40</sup> The transdermal system used in this study was an adhesive patch with teriparatide-coated microneedles. Transient hypercalcaemia was seen in up to 24% of patients treated with teriparatide compared with 3% in the placebo group.<sup>40</sup> Transdermal PTH might be an appealing alternative to daily injections.

### **Primary hyperparathyroidism**

Parathyroidectomy should be offered to patients with primary hyperparathyroidism who are symptomatic or meet any of the criteria in the Third International Workshop on Asymptomatic Primary Hyperparathyroidism guidelines (ie age less than 50 years, low BMD (T-score <−2.5 at any site or previous fragility fracture), creatinine clearance <60 ml/min or serum calcium of 0.25 mmol/l or more above the upper limit of normal).<sup>41</sup> Patients with symptoms or severe hypercalcaemia owing to primary hyperparathyroidism who are unable to undergo parathyroidectomy can be treated with cinacalcet.

### *Cinacalcet*

Cinacalcet activates the calcium-sensing receptor in the parathyroid gland and inhibits PTH secretion. Cinacalcet is taken orally and can be started at a dose of 30 mg twice daily. The dose is adjusted every 2–4 weeks to a maximum of 90 mg four times daily. Cinacalcet reduces serum calcium in most patients with primary hyperparathyroidism.<sup>42–44</sup> However, it is not a substitute for parathyroidectomy. Cinacalcet does not have a significant effect on bone mineral density<sup>43,45</sup> and its effects are not permanent. The adverse events most commonly reported include nausea, diarrhoea, arthralgia, myalgia and paraesthesia.

### **Neuroendocrine tumours**

Surgery is the only curative treatment for neuroendocrine tumours (NETs). For patients with unresectable tumours and metastatic disease who are not eligible for surgery, the aim of treatment is to improve and maintain an optimal quality of life. Patients who are symptomatic with carcinoid syndrome and pancreatic NETs associated with hormone hypersecretion are managed with somatostatin analogues, such as octreotide and other medication as appropriate for the specific syndrome. More

recently, it has been reported that, in addition to symptomatic improvement, octreotide therapy might also be associated with disease stabilisation in patients with midgut NETs. In the PROMID trial, octreotide LAR significantly lengthened time to tumour progression in patients with metastatic midgut NETs.<sup>46</sup>

Two recent trials have reported promising results with everolimus and sunitinib in patients with progressive advanced pancreatic NET.<sup>47,48</sup> However, there are currently no comparative trials to help choose between these agents in the initial treatment of advanced pancreatic NETs.

### *Everolimus*

Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has recently been reported to prolong progression-free survival among patients with progressive advanced pancreatic NETs.<sup>47</sup> The median progression-free survival with everolimus was 11.0 months compared with 4.6 months with placebo.<sup>47</sup> mTOR is a threonine kinase that is involved in several signalling pathways implicated in NET growth. Furthermore, it also controls the production of hypoxia inducible factor and regulates angiogenesis. The adverse events associated with everolimus include stomatitis, rash, diarrhoea, fatigue, infections (mainly of the upper respiratory tract), anaemia and hyperglycaemia.

### *Sunitinib*

Sunitinib, a multitargeted tyrosine kinase inhibitor, has also been reported to improve progression-free survival in patients with advanced pancreatic NETs.<sup>48</sup> Median progression-free survival with sunitinib was 11.4 months compared with 5.5 months with placebo.<sup>48</sup> Sunitinib inhibits a range of growth factor receptors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors. The most frequent adverse events associated with sunitinib are diarrhoea, nausea, vomiting and fatigue.

### **Polycystic ovary syndrome**

Polycystic ovary syndrome (PCOS) is a common cause of female infertility. Metformin can promote ovulation and improve metabolic risk factors in patients with PCOS. However, clomiphene has been shown to be superior to metformin in achieving live birth in women with PCOS.<sup>49</sup>

### *Clomiphene*

Clomiphene binds to hypothalamic oestrogen receptors and inhibits the negative feedback effect of oestradiol. This stimulates gonadotropin-releasing hormone (GnRH) and subsequently gonadotropin secretion, resulting in growth of the ovarian follicle. In a large randomised trial, the live-birth rate was approximately 23% in the clomiphene group and 7% in the metformin group.<sup>49</sup> The addition of metformin to clomiphene did not provide further benefit. The rate of multiple pregnancies



was 6% in the clomiphene group compared with 0% in the metformin group.<sup>49</sup>

Clomiphene is started on the fifth day of a cycle (after either spontaneous menses or withdrawal bleeding induced by a progesterone challenge). It is initially given at a dose of 50 mg daily for five days. The dose can be increased to 100 mg if ovulation does not occur in the first cycle. Most conceptions initiated by clomiphene occur within the first six cycles.

### Syndrome of inappropriate antidiuretic hormone secretion

Hyponatraemia resulting from the syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) is a common clinical problem encountered by endocrinologists. Vasopressin (ADH) antagonists are a new class of drugs for the treatment of patients with hyponatraemia and SIADH.<sup>50–53</sup> The vasopressin receptor antagonists cause a selective water diuresis ('aquaresis') without having an effect on sodium excretion. The loss of electrolyte-free water increases serum sodium concentration in patients with SIADH. The antidiuretic response to vasopressin is mediated by the V<sub>2</sub> receptors.<sup>54,55</sup>

#### Tolvaptan

Tolvaptan, a selective V<sub>2</sub> receptor antagonist, effectively increases the serum sodium concentration in patients with SIADH as shown in the Study of Ascending Levels of Tolvaptan in Hyponatraemia (SALT) trials.<sup>51</sup> Tolvaptan was also associated with an improvement in mental status scores in patients with a serum sodium < 130 mmol/l at baseline.<sup>51</sup> Adverse effects associated with tolvaptan include dry mouth and increased thirst and urination.

However, there are several limitations to the use of tolvaptan. First, the increase in thirst might limit the rise in serum sodium concentration.<sup>51</sup> In addition, there is a risk of overly rapid correction of hyponatraemia, which can lead to irreversible neurological deficits. In the SALT trials, approximately 2% of patients exceeded the daily correction limit of 12 mmol/l.<sup>51</sup> Therefore, more than 2% of treated patients will exceed the currently recommended daily correction limit of 10 mmol/l with tolvaptan, with potential disastrous consequences of osmotic demyelination. For this reason, hospitalisation is needed for starting tolvaptan. Furthermore, the high cost of tolvaptan also prohibits its use. Fluid restriction remains the mainstay of treatment of SIADH. A serum sodium of 130 mmol/l or higher can be achieved with fluid restriction in most patients with SIADH. Furthermore, there is no evidence that tolvaptan is any better than demeclocycline, if an oral agent is required in addition to fluid restriction.

### Conclusion

Industry-sponsored clinical trials have provided information about novel treatments for endocrine disease as well as optimising the use of existing drugs. Physicians should be aware of the risks and benefits of new medication to help patients make informed decisions about their management.

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