New drugs

Pasireotide diaspartate

Approved indication: Cushing's disease
Signifor (Novartis)
ampoules containing 900 microgram/mL
Australian Medicines Handbook section 10.6.6

Cushing's disease is caused by pituitary adenomas which secrete adrenocorticotrophic hormone (ACTH). Surgical treatment helps most patients, but some do not enter remission and others relapse. Pasireotide is an option for these patients and is also indicated for those who cannot have surgery.

The pituitary adenomas contain receptors for somatostatin (growth hormone release inhibiting factor). Pasireotide is an analogue of somatostatin which binds to these receptors. This inhibits the secretion of ACTH.

To test the hypothesis that pasireotide would work in Cushing's disease the drug was injected twice a day by patients who had 24-hour urinary free cortisol at least twice the upper limit of normal. After 15 days, 22 of 29 patients had reduced cortisol. In five of them, the urinary cortisol returned to normal. Average concentrations of plasma ACTH and serum cortisol also reduced.[1]

A phase III trial studied 162 patients with Cushing's disease who had levels of 24-hour urinary free cortisol at least 1.5 times the upper limit of normal. They were randomised to receive twice-daily injections of pasireotide 600 microgram or 900 microgram. If the urinary cortisol level was more than twice the upper limit of normal after three months, the dose was increased by 300 microgram twice daily for a further three months. The primary end point of the double-blind trial was at six months, but the trial continued with an open-label phase for a further six months. The mean duration of treatment was 10.8 months.[2,3]

Urinary free cortisol declined rapidly. By six months 15% of the patients given 600 microgram and 26% of those given 900 microgram had levels within the normal range. After 12 months the corresponding figures were 13% and 25%. Clinical changes at 12 months included an average weight loss of 6.7 kg and decreased mean blood pressure (–6.1 mmHg systolic, –3.7 mmHg diastolic). There were also improvements in triglycerides and low density lipoprotein cholesterol.[2]

Glucose intolerance is common in Cushing's disease, but this did not improve with treatment. By the end of the study 51 of the 107 patients who did not have diabetes at the start of the study had become diabetic (glycated haemoglobin of more than 48 mmol/mol or 6.5%). A new hypoglycaemic drug had to be started in 74 of the 162 patients in the phase III trial.[2]

Pasireotide is given by subcutaneous injection preferably into the abdomen or top of the thigh. Approximately 17% of patients will have injection-site reactions. Although pasireotide is not metabolised it is eliminated in the bile so liver disease will increase exposure to the drug. Approximately 30% of patients develop cholelithiasis,[2] so ultrasound scans of the gall bladder are recommended before and during treatment. Liver enzymes can increase so liver function tests are recommended before treatment, after one or two weeks and then monthly for the first three months of treatment. Sustained changes in liver function are an indication for stopping pasireotide permanently. Severe liver disease is a contraindication.

The most frequent adverse effects of pasireotide are nausea and diarrhoea. Abdominal pain and headache are also common. In some patients the reduction in cortisol in response to pasireotide caused symptoms of hypocortisolism. Hypopituitarism can also occur. The drug can prolong the QT interval on the ECG and cause bradycardia. There is therefore a risk of interaction with drugs such as beta blockers and antiarrhythmic drugs. There have been no clinical studies of drug interactions. There were also no studies in children, pregnant or lactating women.

Only a minority of patients have a complete response to pasireotide. In the phase III trial only 48% of the patients continued the drug for 12 months.[2] The main cause of discontinuation was lack of efficacy. Increasing the dose may not increase efficacy. The drug should probably be stopped if there has been no response after two months of treatment. The combination and comparison of pasireotide with other treatments requires further research.

T T manufacturer provided additional useful information

REFERENCES *†

1. Boscaro M, Ludlam WH, Atkinson B, Glusman JE, Petersenn S, Reincke M, et al. Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. J Clin Endocrinol Metab 2009;94:115-22.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

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2. Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, et al. A 12-month phase 3 study of pasireotide in Cushing's disease. N Engl J Med 2012;366:914-24.
3. Pivonello R, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, et al. Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study. Clin Endocrinol (Oxf). 2014 Feb 17. doi: 10.1111/cen.12431. [Epub ahead of print]

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).