Somatuline Autogel: an extended release lanreotide formulation

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Somatuline Autogel provides effective control of growth hormone levels and is at least as effective as intramuscular Somatuline LA. Somatuline Autogel has a first order kinetic profile providing at least 28 days' efficacy with reduced burst release and a more consistent drug release over the dose period. The product is presented in a pre-filled syringe and is given deep subcutaneously.

Somatostatin analogues are indicated for the treatment of acromegaly when the circulating levels of growth hormone (GH) remain abnormal after surgery and/or radiotherapy. They are also indicated for the symptomatic relief of neuroendocrine tumours (particularly carcinoid). In clinical trials, a novel formulation of lanreotide (Somatuline® Autogel®, Ipsen Ltd, Slough) has shown to be at least as efficacious as Somatuline® LA, the original microparticle formulation of lanreotide. Somatuline Autogel is an extended release preparation which is supplied in a pre-filled syringe ready for use as a deep subcutaneous injection. This has advantages for both the clinician and for the patient.

PHARMACOLOGY OF SOMATULINE AUTOGEL

Like natural somatostatin, lanreotide is a peptide inhibitor of numerous endocrine, neuroendocrine and exocrine mechanisms. It exhibits high affinity for both the somatostatin type 2 (SSTR2) and type 5 (SSTR5) receptors that are found in both the pituitary gland and pancreas, as well as in growth hormone-secreting pituitary tumours. Conversely it has a much lower affinity for somatostatin 1, 3 and 4 receptors. This confers relative specificity of action on GH secretion, making it suitable for the treatment of acromegaly.

Furthermore, the inhibitory action of lanreotide on intestinal exocrine secretion, digestive hormones and mechanisms of cell proliferation makes it a particularly suitable symptomatic treatment for digestive endocrine tumours, especially carcinoids.

Although somatostatin analogues have a much longer plasma half-life than native somatostatin, they originally still needed to be injected three times per day. Thus the development of prolonged release formulations provided a considerable advantage in terms of convenience for the patient and the prescriber, and represented a real advance in the management of the diseases.

Somatuline LA is a microparticle formulation of lanreotide administered as a single 30 mg deep intramuscular injection typically every 10 or 14 days.

The new preparation of lanreotide (Somatuline Autogel) was developed with the aim of extending the duration of the release of the active ingredient and obtaining a fixed time interval of 28 days between each injection using a pre-filled device.

Somatuline Autogel is an aqueous formulation of lanreotide and contains no organic excipients. It is presented in a pre-filled syringe requiring no reconstitution or mixing. The small injection volume (0.2–0.4 ml) given deep subcutaneously may cause less pain than an intramuscular injection.

Somatuline Autogel has a first order kinetic profile providing at least 28 days' efficacy with reduced 'burst release' just after injection and a more consistent drug release over the dose period. In addition, the absolute bioavailability of Somatuline Autogel tends to be greater than that of the microparticle formulation. The terminal half-life is approximately 4 weeks.

A linear relationship was observed between the 60, 90 and 120 mg dose of Somatuline Autogel and lanreotide serum concentrations – mean lanreotide levels after administration of these three doses are dose-proportional. As patients with acromegaly may need different dosing schedules depending on their response to treatment, three doses (60, 90 and 120 mg) of Somatuline Autogel are available for patients.

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ACROMEGALY

Acromegaly is a rare condition in adults caused by the prolonged, excess release of GH from the pituitary gland. The continuous growth of the hormone-producing cells somatotrophs results in the development of a benign pituitary adenoma or tumour.

The incidence of acromegaly is 4–6 new cases/million/year (Alexander et al, 1980). Acromegaly affects men and women equally and is diagnosed most frequently between the ages of 30 and 50 years. Because of the slow onset of symptom development many cases of acromegaly may go undiagnosed for years.

The symptoms of acromegaly include enlargement of the hands and feet, facial changes, protrusion of the jaw, sweating, oily skin, carpal tunnel syndrome and hypertension. The patient may also experience headaches, loss of libido, tiredness and lethargy, as well as joint stiffness.

If left untreated, acromegaly has been shown to cause a number of additional long-term health complications including cardiovascular complications (Giustina et al, 1996) such as hypertension or cardiomyopathy, diabetes (Weekes et al, 1996), and colon cancer and polyps (Weekes et al, 1996).

These complications lead to a 2–3-fold increase in mortality in people with acromegaly (Bates et al, 1993). Therefore, maintenance of effective long-term therapy for patients is required to reduce the risk of developing health complications associated with acromegaly (Melmed, 1990).

Treatment

The aim of treatment is to reduce the plasma GH levels below 10 mU/litre (5 ng/ml), or ideally below 5 mU/litre (2.5 ng/ml), and to achieve normalized insulin-like growth factor (IGF-1) levels for the age and sex of each individual patient.

Surgical removal of the tumour is the treatment of first choice, but success is dependent upon the size and location of the tumour. In up to 90% of cases where the tumour is small (a microadenoma), surgery is effective and restores GH secretion to normal levels. However, if GH levels remain elevated after surgery, further treatment could consist of radiotherapy, medical treatment or possibly repeat surgery, if some residual tumour can be imaged.

Radiotherapy can take up to 10 years to result in a cure of acromegaly and the patient may therefore need additional medical treatment while the radiotherapy takes effect.

Bromocriptine or cabergoline can be used orally, but are only effective in reducing GH to safe levels in about 10% of patients. Efficacy can be determined within 3 months. Treatment with a somatostatin analogue is indicated in those patients where surgery is contraindicated or unsuccessful in normalizing GH levels, and while awaiting the full effects of pituitary radiotherapy.

Clinical studies

Clinical trials (Chanson, 1995; Al-Maskari et al, 1996; Giusti et al, 1996; Caron et al, 1997) demonstrate that Somatuline LA is an effective treatment for the long-term control of plasma GH and IGF-1 concentrations with no evidence of loss of effect during prolonged administration.

A clinical efficacy and safety study by Caron et al (2002) has shown that Somatuline Autogel is at least as efficacious and well tolerated as Somatuline LA in patients with acromegaly and is likely to improve the acceptance of medical treatment for these patients who need long-term somatostatin analogue therapy. A group of 107 patients who had previously been treated with Somatuline LA for 3 months (injections administered every 14, 10 or 7 days) were switched to Somatuline Autogel (60, 90 or 120 mg respectively) for 3 months. Mean lanreotide levels obtained with Somatuline Autogel were not significantly different from the values obtained while on Somatuline LA and GH hypersecretion was effectively controlled (GH <2.5 ng/ml, age-normalized IGF-1) in 33% and 39% of patients during treatment with Somatuline LA and Somatuline Autogel respectively.

The reported clinical symptoms were similar in patients treated with either Somatuline Autogel or Somatuline LA, although the incidence of asthenia and swelling of the extremities was lower in those receiving Somatuline Autogel (21% *vs* 32% and 28% *vs* 34% respectively).

The frequency of adverse events reported by the patients tended to be lower after treatment with Somatuline Autogel than after Somatuline LA, with the exception of constipation, which was the same in both groups. Diarrhoea, mild abdominal pain and nausea lasting less than 72 hours were reported in 38%, 22% and 18% of the patients during treatment with Somatuline LA compared to only 29%, 17% and 9% of patients during treatment with Somatuline Autogel (Caron et al, 2002).

In a follow-up study, these patients continued to receive Somatuline Autogel at a dose titrated to their condition for up to 15 months (unpublished data, PH Caron, 2002). The results show that when administered at the titrated doses, Somatuline Autogel is as effective at reducing

GH and IGF-1 levels as Somatuline LA when given at a fixed dose, but variable injection intervals. Overall the results demonstrated an increase in the percentage of patients with GH below 2.5 ng/ml and a decrease in mean IGF-1 levels.

CARCINOID TUMOURS

Carcinoid tumours are rare, slowly progressive tumours which are usually located in the gastrointestinal tract, commonly in the appendix and the ileum. They are also more rarely found in the bronchi and genitourinary tract. The incidence of carcinoid tumours has been estimated to be 13 cases/million/year (Watson et al, 1989).

Most carcinoid tumours are malignant and secrete vasoactive substances (serotonin, prostaglandins, calcitonin, catecholamines, vasoactive intestinal peptide and substance P) which are responsible for causing the carcinoid syndrome.

The prognosis for patients with a carcinoid tumour is dependent on the location of the primary tumour and the stage of the disease at diagnosis.

Treatment

Surgery is the first-line treatment, with the aim of removing all of the primary tumour and its metastases. However, this is not always possible and other treatments are then required.

Conventional medical treatments of carcinoid tumours are mostly ineffective, for example methyldopa, chlorpromazine and corticosteroids. Chemotherapy has only a moderate antitumour effect and is poorly tolerated. Treatment therefore tends to be palliative.

Hepatic embolization is helpful only if the volume of liver metastases is moderate. One of the risks of embolization (as with surgery) is the occurrence of a carcinoid crisis, which can be avoided by the use of somatostatin analogues. Interferon has also been used in this situation, but appears to be less effective than somatostatin analogues and can cause a characteristic syndrome simulating an influenza-type episode.

The use of somatostatin analogues markedly improves the symptoms such as flushes and diarrhoea in most of these patients.

Clinical studies

Clinical studies have been carried out in patients with digestive neuroendocrine tumours, monitoring the effects on symptoms as the major evaluation criteria. There have been two open multicentre studies with Somatuline LA carried out in patients with symptomatic carcinoid tumour. Analysis of these studies by Ruszniewski et al (1994) and Scherübl et al (1994) demonstrated that a reduction in the number and severity of flushes and diarrhoeal stools was achieved at the beginning of treatment and maintained for at least 6 months.

A study by Wymenga et al (1999) demonstrated that Somatuline LA is able to bring about a significant improvement in quality of life for patients with neuroendocrine tumours. The effect on quality of life was assessed at baseline and at 1, 3 and 6 months using the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire. The questionnaire assessed function (physical, role, cognitive, emotional and social), symptoms (fatigue, pain, nausea and vomiting), a global health status/quality of life scale and six single item measures (dyspnoea, appetite, sleeping problems, constipation, diarrhoea and financial problems). The study showed that after 1 month of treatment with Somatuline LA, emotional and cognitive functioning improved significantly, as did global health status, fatigue, sleeping problems and diarrhoea.

An open, multicentre crossover study undertaken by O'Toole et al (2000) has directly compared the efficacy of Somatuline LA *vs* subcutaneous short-acting octreotide in terms of patient acceptability, preference and symptom control. The study demonstrated that Somatuline LA and octreotide were capable of reducing the intensity of flushing episodes in >50% of patients, as well as significantly reducing stool frequency. Although there was no difference in the quality of life scores between those patients who received octreotide and those who received Somatuline LA, patients significantly preferred Somatuline LA because of its simplified mode of administration. There are currently no studies comparing Somatuline LA or Somatuline Autogel to octreotide long-acting release in terms of patient acceptability and preference.

TOLERABILITY, SAFETY AND SIDE EFFECTS

The side effects of lanreotide reported in clinical trials are mainly local and gastrointestinal. Moderate transitory pain at the injection site is sometimes associated with local redness. Gastrointestinal side effects are the most common and include diarrhoea or soft stools, abdominal pain, flatulence, anorexia, nausea and vomiting. In general, all these side effects are mild to moderate in intensity. In most cases the frequency and the intensity of such effects appears to diminish or to resolve with continued therapy. Cases of asymptomatic and sympto-

matic gallbladder stones have been reported in patients during prolonged treatment. Gallbladder echography is recommended initially and every 6 months thereafter. Glucose sugar levels should be monitored in diabetic patients. In patients with hepatic or renal dysfunction kidney or liver function should be monitored and the dose adjusted if necessary.

CONCLUSIONS

Somatuline Autogel is a new pharmaceutical form of lanreotide. It is an aqueous formulation of lanreotide with no organic solvents and is the first long-acting somatostatin analogue that can be given by a single, monthly, deep subcutaneous injection from a pre-filled syringe.

It is indicated for the treatment of acromegaly when the circulating levels of GH and/or IGF-1 remain abnormal after surgery and/or radiotherapy or in patients who otherwise require medical treatment. Somatuline Autogel is also indicated for the treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours. HM

Conflict of interest: Professor Lightman has also written the expert report on Somatuline Autogel which was submitted to the Committee for the Safety of Medicines.

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KEY POINTS

- The cost of managing the complications associated with acromegaly may be considerable. Effective treatment can normalize the excess mortality and morbidity.
- The symptoms associated with neuroendocrine tumours are often severe and debilitating. Symptomatic control with a somatostatin analogue, such as Somatuline Autogel, can greatly improve the patient's quality of life.
- Somatuline Autogel is a preparation that released the somatostatin analogue lanreotide in a predictable manner with a remarkably smooth profile. It provides an effective control of growth hormone and insulin-like growth factor 1 in acromegaly and is easy to administer subcutaneously once a month using a pre-filled syringe with an injection volume less than 0.5 ml.