Lanreotide Autogel Therapy in Patients with Acromegaly – Current Role and Perspectives for the Future

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Abstract

Lanreotide Autogel is a long-acting (effective for four to six weeks after a single injection) somatostatin analogue that normalises growth hormone (GH) and insulin-like growth factor I levels in about 50% of patients. It causes tumour volumes to shrink by more than 20% in 72–85% of patients. These effects are similar to those with octreotide long active release (LAR). Similarly, there are no differences between octreotide LAR and lanreotide Autogel in improvement of cardiac function, glycometabolic effects or occurrence of side effects, including cholelithiasis. In comparison to octreotide LAR, lanreotide Autogel has the advantage of being available in a convenient pre-filled syringe and it can be injected subcutaneously by patients or their care-givers/partners, omitting the necessity of injections by healthcare professionals. The efficacy of lanreotide can be increased by combination with dopamine agonists. Co-administration of lanreotide Autogel with pegvisomant appears to be safe and to improve hormonal control in a majority of patients with acromegaly partially controlled by somatostatin analogues alone.

Keywords

Acromegaly, pituitary adenoma, somatostatin analogues, lanreotide

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Acromegaly is caused by excessive secretion of growth hormone (GH), almost always from a benign pituitary adenoma. When not treated, it is a disfiguring and debilitating disease causing severe co-morbidity and premature death.[1] The available treatment modalities for acromegaly are selective trans-sphenoidal adenomectomy, radiotherapy, medical treatment and a combination of these. The effects of surgery depend greatly on the experience of neurosurgeons. Even in experienced neurosurgical departments, however, the possibilities of curing acromegaly are limited. In the Department of Neurosurgery in Erlangen, success rates for removal were as follows.[2]

- Microadenomas: 75.3%.
- Intrasellar macroadenomas: 74.2%.
- Suprasellar macroadenoms without compression of the optic pathway: 41.5%.
- Suprasellar macroadenomas with compression of the optic pathway: 33.3%.
- Giant adenomas: 10%.

In radiotherapy there are intervals of many years to normalisation of GH and insulin-like growth factor 1 (IGF-I) levels, especially with fractionated irradiation, which causes a high incidence of adverse effects, such as hypopituitarism.[3] The three most important groups of drugs used for medical treatment of acromegaly are dopamine agonists, somatostatin analogues and GH receptor (GHR) modulating drugs. Among them, the long-acting somatostatin analogues remain the most often used medicaments. Two such analogues are available: octreotide LAR and lanreotide Autogel. First reports about octreotide LAR appeared in 1996.[4] The experience with lanreotide Autogel is much shorter[5] and it has been used in fewer patients. Although several detailed studies on lanreotide Autogel were published recently,[6–9] the objective of this article is to further support knowledge about the role of lanreotide Autogel in the treatment of acromegaly.

Pharmaceutical Properties

The first pharmaceutically available form of lanreotide was relatively short-acting, requiring multiple daily dosing (BIM23014). Subsequently, a long-acting form of lanreotide was developed by incorporating the drug into biodegradable polylactide-polyglycolide microspheres so that the injection interval could be extended to 14 days (lanreotide SR). It was subsequently discovered that lanreotide had the unique property of self-aggregation in water into perfectly hollow and monodisperse (24nm wide) nanotubes, with molecular packing in the walls of a nanotube.[10] This formulation of the drug is named lanreotide Autogel and is produced by Ipsen under the trade name Somatuline Autogel in most countries, Somatuline Depot Injection in the US and Ipstyl Autogel in a few European countries. Maximal serum concentrations are reached after 3.8–7.7 days in acromegalic patients, depending on the dose administered.[11] The serum half-life amounts to 25.5 days.[12]

Antisecretory Efficacy

There are great differences in the reported antisecretory efficacy of lanreotide Autogel by individual authors. In some reports only 35–37% of patients treated for three to 12 months had normalised IGF I values.[13,14] By contrast, in another study[15] eight out of 10 patients had normalised GH and IGF-I levels at week 28 of treatment. Similar differences were reported with octreotide LAR – efficacy was as low as 34% of patients with normalised IGF-I after 48 weeks of treatment[16] and

as high as 70.1% after a median follow-up of 48 months.[17] Studies in each larenotide group remain difficult to compare because of various remission criteria, various treatment times, different dosages, pre-selection bias, baseline GH and IGF-I levels, pituitary tumour size, whether lanreotide was used as primary or adjunctive therapy and, last but not least, variability of GH and IGF-I assays. In their review on therapy of acromegaly with lanreotide, Roelfsema et al.[7] collected data from 10 studies using lanreotide Autogel. In seven of these studies the number of successfully age-adjusted IGF-I levels varied in a close range between 48 and 55%.

Biochemical Efficacy of Lanreotide Autogel Versus Octreotide LAR

A number of studies have been carried out to compare the biochemical efficacy of octreotide LAR and lanreotide SR, but prospective randomised studies are lacking. In two meta-analyses[18,19] of these results it was concluded that the biochemical efficacy of octreotide LAR was moderately more efficacious than lanreotide SR. Five studies have compared the efficacy of octreotide LAR and lanreotide Autogel in a total of 74 patients.[15,20–23] The results were analysed by Murray and Melmed.[19] The studies suggested that lanreotide Autogel and octreotide LAR were equivalent in the control of symptoms and biochemical markers in patients with acromegaly. In one of these studies[23] of the 10 patients who completed the study, four had normalisation of IGF-I levels on both therapies, but three patients had different treatment responses with biochemical normalisation during one therapy and not the other. Consequently, the change from octreotide LAR to lanreotide Autogel or *vice versa* may be useful in some patients with treatment failure or side effects.

Effects of Lanreotide

Glucose Homeostasis

GH excess in acromegaly is frequently associated with insulin resistance and impaired glucose tolerance as well as the development of diabetes. These disturbances may be in part responsible for the increased cardiovascular morbidity and mortality associated with acromegaly.

Reports on the effects of somatostatin analogues on glucose homeostasis have given contradictory results.[24] Most of these studies involved only small numbers of patients and did not evaluate glucose metabolism as the main clinical end-point. A recent meta-analysis by Mazziotti et al.[25] concludes that the effects of somatostatin analogues on glucose homeostasis generally only have a marginal clinical impact, even when significant deleterious glycometabolic effects may be observed in some patients. Consequently, glycometabolic follow-up needs to be carefully carried out in patients with acromegaly. In pooled data of 332 patients, treatment-related abnormalities in glycaemic control (hyperglycaemia, hypoglycaemia and diabetes) occurred in 7%.[6]

The meta-analysis[25] demonstrates that somatostatin analogues decrease fasting serum insulin levels without consistent effects on glucose homeostasis. Some impairment of glucose metabolism was observed early after starting treatment, becoming less important as therapy progressed.[26] The decrease in insulin levels may have been caused by suppression of insulin secretion with somatostatin analogues, but the prevailing cause is usually the decrease of insulin resistance with normalisation of GH and glucagon secretion. Consequently, lack of growth hormone control may predispose to a worsening of glucose metabolism.

The meta-analysis shows that somatostatin analogues may be safe in acromegalic patients with pre-existing diabetes.[25] Worsening of glucose metabolism with somatostatin analogues is, however, possible and may be an indication to switch treatment to or add pegvisomant.[27]

Two studies[28,29] and the meta-analysis[25] demonstrated that lanreotide and octreotide do not have substantially different effects on glucose metabolism. The only notable difference was a more evident increase in glucose levels after oral glucose tolerance test during lanreotide treatment compared with octreotide.

The Heart

Acromegaly is associated with increased cardiac morbidity and mortality. Recognised cardiac manifestations include chronic cardiac failure due to systolic or diastolic dysfunction.[30] Hradec et al.[31] and others[32] have demonstrated that treatment with lanreotide, similar to octreotide, improves structural and functional cardiac parameters. This is mainly in terms of a decrease in left ventricular mass hypertrophy. It also leads to a lower degree of improvement in ejection fraction and left ventricular end-diastolic dimension. The changes were associated with improved exercise tolerance. These positive effects are correlated with the GH and IGF-I control.

Tumour Mass

Almost all of the studies with lanreotide Autogel had biochemical control of acromegaly as the clinical end-point. In their recent study, Mazziotti and Giustina[33] identified only five studies that mentioned the effects of lanreotide Autogel on tumour size. In one of these studies the percentage of patients with tumour shrinkage was not defined and in another study of only seven patients,[22] the authors did not find tumour shrinkage in any patient but their criterion for shrinkage was a 50% or greater decrease in volume compared with three other studies,[34–36] where the criterion of shrinkage was 20–25%. In these studies[34–36] with 20–27 patients each and 12–18 months duration of treatment, 72–85% of patients receiving lanreotide Autogel were found to have tumour shrinkage.

The comparison of individual studies and effects of various somatostatin analogues is difficult. Primary therapy is accompanied by a higher degree of tumour shrinkage compared with secondary therapy, presumably because of surgery- and radiotherapy-induced fibrosis altering tumour anatomy.[8] The sensitivity of somatotroph tumour cells to the antiproliferative action of somatostatin analogues depends in part on the receptor subtype distribution pattern. This varies considerably among somatotroph adenomas.[37] Other variables are tumour size (micro- versus macroadenoma), somatostatin analogue doses and duration of treatment. Moreover, reports of drug effects on tumour size are limited by heterogenous imaging techniques and measurements.

Biochemical response to somatostatin analogues may have some role. There is often a discrepancy observed, however, between biochemical and morphological response to somatostatin therapy.[8] It may point to different mechanisms by which somatostatin analogues influence GH secretion and cellular proliferation.[8]

Tumour progression in patients taking lanreotide Autogel has not yet been reported, but it is rare with other somatostatin analogues and occurs in less than 2% of patients.[18] On the other hand, complete disappearance of GH-secreting adenomas with complete biochemical remission and long recurrence-free time is unusual. Only one such

case, with a remission of 24 months, has been reported with lanreotide Autogel.[38]

The antiproliferative effects of somatostatin analogues are mediated by several mechanisms including induction of cell cycle arrest, stimulation of apoptosis and inhibition of angiogenesis.[37] In consequence, somatostatin analogues have been suggested to be radioprotective[39] and it was proposed to interrupt their treatment before the irradiation of pituitary adenomas. Recent investigation in rats, however, demonstrated that despite promoting apoptosis, lanreotide was not radioprotective and had a significant radiosensitising effect.[40]

Side Effects

Lanreotide Autogel treatment for up to four years was generally well tolerated in patients with acromegaly. The most frequent side effects of lanreotide are diarrhoea (37%), abdominal pain (19%) and nausea (11%).[6] These symptoms generally start shortly after an injection, decrease subsequently and tend to decrease in severity with continuing treatment. Lanreotide reduces motility of the biliary duct, which leads to an increased predisposition to the formation of gallstones. In pooled data, cholelithiasis and gallbladder sludge occurred in 20% of patients, with cholelithiasis thought to be associated with the dose and duration of exposure. Despite this, many of these patients had gallstones present at baseline. In two studies, new cholelithiasis was reported in only 8.7[7] and 12%[6] of patients. The most frequently reported local adverse reactions were injection site pain (4.1%) and injection site mass (1.7%).[6] These local signs did not decrease the efficacy of the drug.[6] Other adverse events reported were sinus bradycardia (3%), hypertension (5%) and anaemia (3%).[6] As lanreotide treatment may decrease heart rate, the use of concomitant bradycardia-inducing agents such as beta-adrenoceptor antagonists may result in an additive effect and careful follow-up is necessary. Limited data suggest that lanreotide Autogel is as well tolerated as octreotide LAR and there were no significant differences in the incidence of gastrointestinal signs.[41] Local adverse events occurred less frequently with lanreotide Autogel treatment than with octreotide LAR.

Dosage and Administration

Lanreotide Autogel comes in a long-acting aqueous-gel formulation that is administered via deep subcutaneous injections and provides consistent drug release.[42] The product is volume-dependent and not concentration-dependent, with volumes ranging from 0.3–0.5cc for delivery of the 60, 90 and 120mg doses. It is provided in a ready-to-use pre-filled syringe, which obviates the need for drug reconstitution prior to administration. This advantage enables self-administration or partner administration of the drug. A recent study by Salvatori et al.[43] found that 100% of patients or care-givers/partners were able to inject lanreotide Autogel correctly and no patient reported a preference to receive the injection by a healthcare professional. Consequently, the majority of these patients preferred lanreotide Autogel over octreotide LAR for future use. Similar results were previously reported by Bevan et al.[44]

Treatment Strategies

There are two main strategies on how to start the treatment. According to the first one, treatment-naïve patients receive 60mg once every 28 days. After three months, the dose is individualised according to the patient's response – it either remains stable or is gradually increased first to 90 and then to 120mg. The other possibility is to start with 90mg every 28 days for three months and adjust the dose thereafter. It is generally advised to regularly adjust the dose in relation to serum IGF-I and GH levels in order to obtain the best effect on disease activity at the lowest dose.

Usually, with continuing long-term treatment, the dose requirement progressively decreases.[45] Whenever acromegaly is well controlled, there are two options: reduce the actual dose or prolong the interval between injections. With lanreotide Autogel, the time interval between injections can often be increased to six to eight weeks without loss of efficacy, thereby improving the subject's comfort and reducing the cost of treatment.[46] In pharmacokinetic studies with lanreotide Autogel, significant levels were still found eight weeks after drug administration.[47,48]

Due to the wide therapeutic window of lanreotide, it is not necessary to alter the dose in hepatic or renal impairment or in the elderly. Similarly, there are no reports of other drugs affecting the metabolism of somatostatin analogues.

There is limited experience with lanreotide Autogel at doses higher than those presented in product monographs, i.e. more than 120mg every 28 days. Only recently, Wuster et al.[49] presented data of two patients who required 180mg every three weeks to achieve or maintain their initial response. This high dose was given for three months in one patient and six months in the other without any unexpected adverse events.

To date, it is unknown whether somatostatin analogues may also provoke long-lasting disease remission after drug discontinuation, similarly to the definitive cure of prolactinomas frequently induced by dopamine agonists. The recent study by Ronchi et al.[50] is the only one that challenges the concept that therapy with somatostatin analogues is a lifelong requirement. The authors demonstrated remission in five patients out of 27 more than 12 months (median 24 months) after the discontinuation of chronic somatostatin analogue therapy.

To avoid life-long administration of somatostatin analogues, we have adopted a strategy to irradiate all adenoma remnants after surgery by Leksell gamma knife if <2.5cm in diameter and not touching the optic pathway.[51] Similarly, with the same conditions we have irradiated adenomas intended to be treated with pharmacological primotherapy. Consequently the pharmacological therapy, mostly with somatostatin analogues, was limited to the interval between irradiation and normalisation of IGF-I levels. The mean interval to IGF-I normalisation was 4.5 years.[51] The side effects of Leksell gamma knife irradiation are rare. Hypopituitarism can be avoided by keeping the mean dose of irradiation given to pituitary tissue surrounding the adenoma below 15Gy and that to the distal infundibulum below 17Gy.[52,53]

Combination Treatment

Lanreotide Plus Cabergoline

The efficacy of lanreotide Autogel can be improved by co-treatment with cabergoline. In a study by Cozzi et al.,[54] 1.5–3.5mg cabergoline weekly normalised IGF-I in 42% of patients with acromegaly previously insufficiently controlled with lanreotide SR or octreotide LAR. The percentage suppression of GH and IGF-I was significantly greater with combined treatment in two other studies.[55,56] Presumably, lanreotide Autogel will accordingly profit from combination with cabergoline. The only concern with cabergoline is an increased risk of fibrosis development, particularly cardiac fibrosis with valvular defects. There are at least 10 studies demonstrating that the doses used in the treatment of prolactinomas do not cause serious valvular defects.[57] A

different situation may occur in acromegaly, however, where active disease leads to a specific form of cardiomyopathy that involves not only the myocardium and conduction system but also the heart valves.[30]

Lanreotide Plus Pegvisomant

Pegvisomant, a GH-receptor antagonist, is the most effective drug available for decreasing IGF-I levels. If given at appropriate doses, it can normalise IGF-I in 95–97% of patients with acromegaly. Pegvisomant monotherapy requires daily injections, however, and is costly. The drug acts on peripheral tissue and does not affect the pituitary tumour. In the European Acrostudy, progression in adenoma growth was reported in 5.1% of 469 patients.[58] Several studies have demonstrated the advantages of co-administration of pegvisomant with somatostatin analogues compared with pegvisomant monotherapy.[59–62] The median pegvisomant dose is approximately half that required during studies of pegvisomant monotherapy.[62] This significantly reduces the annual costs.

Somatostatin analogues, even when not fully effective, decrease pituitary GH secretion and consequently there are fewer endogenous GH molecules for pegvisomant to compete with. Moreover, somatostatin analogues reduce insulin secretion from the pancreas and therefore reduce the number of GHRs available in the liver, which again decreases the pegvisomant dose required.[8] Accordingly, in most cases pegvisomant could be injected once or twice weekly. This is important for the patient's comfort. In terms of pituitary tumour size, combined therapy might be safer than pegvisomant monotherapy. In combination, treatment shrinkage occurred in 19% of the treated adenomas.[61] Shrinkage was not observed with pegvisomant monotherapy. Long-term combined treatment for more than four years seems to be safe.[61] The normalisation of IGF-I was attained in all subjects with the maximal 80mg dose of pegvisomant twice weekly[60] and in 95% of patients taking with 80mg pegvisomant weekly.[8] In a recent study by van der Lely et al.,[62] however, co-administration of lanreotid Autogel 120mg monthly and pegvisomant up to 60mg twice weekly normalised IGF-I levels in only 78.9% of patients. It has been reported that withdrawal of octreotide LAR before pegvisomant can be detrimental for liver function.[63] It can be presumed that lanreotide treatment should not be discontinued during pegvisomant therapy either. With respect to quality of life, pegvisomant may have additional effects in patients on somatostatin analogue therapy. In a recent study, the weekly administration of pegvisomant 40mg improved quality of life without affecting IGF-I levels.[64]

Place of Lanreotide Autogel in the Management of Acromegaly

In recent guidelines for acromegaly management,[65] surgery on the pituitary adenoma is recommended if surgical cure is expected and when the tumour is causing compression symptoms. Primary pharmacological therapy is recommended if post-operative disease persistence is expected. This should be started before surgery to alleviate severe co-morbidities that may prevent or could complicate immediate surgery (see below). Moreover, it is generally accepted that pharmacological intervention is indicated where surgical intervention presents an unacceptable risk and when a patient refuses surgery.

Adjunctive treatment is indicated if surgery has failed to achieve biochemical control and in cases where adenoma is irradiated to provide disease control in the time between administration of radiation therapy and the onset of maximum benefit attained from radiation therapy. It is questionable, however, whether primary pharmacological therapy in patients should be recommended where post-operative persistence is expected. This is because of the well-known effect of surgical debulking on the improvement of pharmacological therapy and radiation results. In a study by Karavitaki et al.,[66] the figures for normal IGF-I after lanreotide treatment were 42.3% before surgery and 88.5% after surgery.

Another indication for primary medical treatment of acromegalic patients is presurgical treatment. This aims first to normalise GH and IGF-I levels to improve the presurgical state of the patients, such as improving cardiac function, helping to compensate for diabetes or facilitate intubation during anaesthesia. Second, it may be aimed at improvement of surgical outcome. Data on the latter factor were conflicting; however two recent progressive randomised studies – one with six months of octreotide LAR[67] and the second with four months of lanreotide SR[68] pretreatment – suggest that the surgical cure in macroadenomas may be improved.

In 2008, the Polish Society for Endocrinology presented a consensus statement in terms of presurgical somatostatin analogues in acromegaly.[69] It was suggested that depot somatostatin analogue (octreotide LAR or lanreotide Autogel) be administered at least three months before surgery in microadenomas and six months before surgery in macroadenomas, until maximal possible reduction of GH and IGF-I concentrations. Using such a uniform approach in a nationwide measure will allow further objective evaluation of the long-term efficacy of the treatment.

Currently, the following three classes of pharmacotherapeutic agents are available for the management of acromegaly: somatostatin analogues, dopamine agonists (e.g. cabergoline) and GHR antagonists (e.g. pegvisomant).

Although relatively inexpensive and available as tablets, dopamine agonists only achieve normalisation of GH and IGF-I in a minority of patients. It is recommended they are only tried in selected patients with modestly elevated IGF-I levels and markedly elevated prolactin.[65] Pegvisomant is generally well tolerated and achieves IGF-I normalisation in more than 95% of patients if the dose is appropriate. Therapy is expensive, however, with the necessity of daily injections. It is unable to prevent pituitary adenoma growth or cause adenoma shrinkage. Consequently, in many countries its use is recommended only in patients unresponsive to or intolerant of somatostatin analogue therapy.[6]

For these reasons, the primary drugs to be used in most patients with acromegaly are long-acting the somatostatin analogues octreotide LAR and lanreotide Autogel. Both drugs are comparable in the efficacy. The advantage of lanreotide Autogel is the possibility of injections by the patient or care-giver/partner without medical supervision.

Future Perspectives

The present formulations of somatostatin analogues can be classified as second-generation effective GH-suppressive drugs.[7] These agents are clearly not adequate for all patients, however, depending on tumour somatostatin receptor status. Pituitary tumours express both somatostatin and dopamine receptors, each of which has five specific subtypes: somatostatin receptor 1–5 (SST1–SST5) and dopamine

receptor 1–5 (D1–D5). There are two different isoforms of SST1 and D2. Approximately 90% of GH-secreting adenomas express SST2 and SST5.[70] Octreotide and lanreotide both act preferentially via SST2 and have a lower affinity for SST5. Moreover, a proportion of tumours fail to respond to somatostatin analogues despite expressing high levels of SST2 and SST5. This situation may be explained by the identification of two novel truncated variants of SST5 – SST5TMD5 and SST5TMD4 – which are absent in the normal pituitary but expressed in pituitary tumours.[71] The presence of SST5TMD4 is related to the reduced ability of octreotide to normalise hormone secretion.[71]

Pasireotide

One of the new somatostatin analogues in clinical trials is pasireotide (SOM230). It exhibits high-affinity binding to somatostatin receptors 1, 2, 3 and 5.[72] Compared with octreotide, pasireotide has an *in vitro* binding affinity that is 40-fold higher for SST5, 30-fold higher for SST1 and five-fold higher for SST3 but two-fold lower for SST2.[72] Although octreotide and pasireotide have only slightly different binding activities at SST2 receptor, pasireotide lacks the ability to stimulate SST2 internalisation.[73,74] Consequently, it is unable to produce a measurable antagonistic effect at SST2 receptors.[73,74] It may be inferred that the main role of pasireotide will be in the treatment of prevalently SST5 receptor-positive adenomas.

Recently the results of a short-term randomised phase II trial with pasireotide were published.[75] The study included 60 patients. After three months of pasireotide 200, 400 and 600µg injected subcutaneously twice daily, only 27% of patients achieved a biochemical response and 39% of patients had a >20% reduction in pituitary tumour volume. Seventy-five per cent of patients experienced drug-related adverse effects, mainly nausea, diarrhoea, abdominal pain and flatulence.

Larger studies of longer duration are ongoing, but it may be presumed that pasireotide will not replace lanreotide and octreotide. It will likely be a complementary treatment for adenomas with receptors other than SST2, mainly SST5.

Novel Chimeric Compounds

Dopamine receptors are present both in prolactin secreting and non-prolactin-secreting adenomas.[76] Their presence and intensity of expression is predictive of the response to treatment with dopamine agonists. Recently, a functional interaction between the D2 and SST receptors has been reported,[77,78] suggesting a potentional benefit from the combined targeting of these receptors. Clinical reports have demonstrated that the combination of somatostatin analogues and dopamine agonists is more effective in reducing GH levels in somatotropinomas than individual use of these drugs.[79]

Based on these observations, a novel class of chimeric compounds that contain structural elements of both somatostatin analogues and dopamine agonists that retain the ability to selectively interact with receptors of both families – dopastatins – has been developed.[80] The compound dopastatin (BIM 23A760) was selected as one of the most efficacious members of this group. It is a potent and selective agonist of the D2 and SST2 receptors and a modest agonist of the SST5 receptor. Non-clinical pharmacological studies have demonstrated that it is more effective in suppressing GH secretion in cultured human GH-secreting adenomas than individual somatostatin analogues and dopamine agonists.[81] The drug is injected subcutaneously at weekly intervals. BIM 23A760 is now in phase II multicentre clinical trials. The results of these trials may indicate to what extent dopastatin will replace long-acting lanreotide and octreotide. ■

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