# Lanreotide Depot in the Management of Acromegalic Patients

*a report by*
**Lewis S Blevins, Jr, MD**

*Medical Director, California Center for Pituitary Disorders, University of California, San Francisco*

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Somatostatin analogs are novel therapeutic agents that can be employed in the management of acromegalic patients who have residual disease after surgery or radiotherapy and in those who are not candidates for surgery as a primary therapeutic intervention. The use of this class of medications has, in just over a decade, dramatically altered the landscape and natural history of acromegaly.

Octreotide for subcutaneous injection—the first commercially available somatostatin analog—was first approved by the US Food and Drug Administration (FDA) in 2003. The long-acting depot form of the drug, Octreotide LAR, was granted FDA approval in 1998. Lanreotide autogel depot, the second commercially available somatostatin analog, was approved by the FDA in 2007.

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Somatostatin analogs exert their effects on growth hormone (GH)-secreting tumors by binding to somatostatin receptors expressed on cell surface membranes. Receptor subtypes 2 and 5 are involved in the control of GH secretion in normal and in more than half of tumoral GH-secreting cells.[1,2] Expression of the type 2 receptor seems to correlate with clinical responsiveness in patients with acromegaly.[2] In addition to inhibiting GH secretion, activation of somatostatin receptors appears to have beneficial antiproliferative effects on GH-secreting tumors.[3–5] Histopathological studies have demonstrated that somatostatin analogs induce cell cycle arrest and thus reduce the mitotic rate, may inhibit angiogenesis, and slightly reduce the size of GH-producing cells.

Lanreotide depot is a synthetic octapeptide in an aqueous slow-release formulation that is available in 60, 90, and 120mg dosages. The drug is supplied in a single-use syringe with an 18-gauge needle intended for deep subcutaneous administration. Several studies have documented the efficacy, tolerability, and acceptability of lay person or patient self-administration of the drug.[6,7] After a single injection of the drug, the bioavailability is approximately 70% and the half-life is 23–30 days. Thus, in contrast to the previous slow-release formulation of this drug, which required administration every seven to 14 days, the autogel depot formulation can be administered approximately every 28 days.[8] The half-life of the drug is increased in elderly subjects, patients with hepatic dysfunction, and in those with end-stage renal disease (ESRD) requiring dialysis.

Therapy with lanreotide depot should be initiated with the 90mg dose administered every four weeks for three months. The 60mg dose is recommended for patients with renal and hepatic dysfunction. GH and insulin-like growth factor (IGF)-I (immunoglobulin) levels should be evaluated toward the end of the month after the third injection. The manufacturer recommends maintenance of the starting dose if the IGF-I level is normalized, clinical symptoms and signs of acromegaly are controlled, and the GH level is between 1 and 2.5ng/ml. The dosage should be increased to 120mg every four weeks if the IGF-I level is elevated, the GH is greater than 2.5ng/ml, and clinical symptoms remain uncontrolled. The dosage may be lowered to 60mg every four weeks if the GH level is less than 1ng/ml, the IGF one level is normal, and clinical symptoms are controlled. Alternatively, one might consider extending the inter-injection period to six weeks in this setting. Abrams et al. demonstrated that prolongation of the time interval between injections from four to six weeks was possible without loss of therapeutic efficacy in seven of nine subjects who normalized IGF-I and GH levels during treatment.[6]

A dosage change requires re-evaluation of clinical and biochemical parameters of disease activity three months later. During long-term therapy and follow-up—usually at six-month intervals—dosages should be adjusted according to clinical and biochemical parameters of disease activity. Those patients who are post-radiotherapy or who have radiographic evidence of spontaneous necrosis of their pituitary tumors may ultimately successfully discontinue therapy. A decline in the IGF-I and GH levels to low or low normal values on stable therapy should therefore prompt treating physicians to attempt to taper the dosage as tolerated, and based on indicators of disease activity.

Lewis S Blevins, Jr, MD, is Medical Director of the California Center for Pituitary Disorders at the Univeristy of California, San Francisco (UCSF). He is also Clinical Professor of Medicine and Neurological Surgery at UCSF. He has been awarded numerous teaching awards throughout his career.

E: BlevinsL@neurosurg.ucsf.edu

**Table 1: Adverse Effects of Lanreotide Depot***

| Adverse Effect | % |
|---|---|
| Diarrhea | 37 |
| Abdominal pain | 19 |
| Flatulence | 7 |
| Loose stools | 6 |
| Cholelithiasis | 20 |
| Sinus bradycardia | 7 |
| Hyperglycemia | 7 |

** pooled from full prescribing information.*

The clinical efficacy of lanreotide depot has been demonstrated in several studies. Caron et al. treated 107 patients who had previously been treated with a shorter-acting form of the drug.[9] They demonstrated normalization of the IGF-I and GH levels in 39% of patients. They concluded that the autogel depot form of the drug was as efficacious as the sustained-release form of the drug administered every two weeks.

In a long-term study of 14 acromegalic patients, Caron et al. achieved age- and sex-normalized IGF-I levels and GH levels lower than 2.5mcg/l in 46% of patients.[10] Data on file with the manufacturer of lanreotide depot pertaining to a 48-week open-label multicenter study with intent to treat demonstrate normalization of age-adjusted IGF-I concentrations in 43% of acromegalic patients. The efficacy of lanreotide depot is improved by surgical debulking of invasive GH-secreting pituitary tumors even when a surgical cure is unobtainable.[11] Lanreotide depot may significantly reduce pituitary tumor size in a small number of patients. In a meta-analysis of long-acting somatostatin analog therapy of acromegaly, Freda et al. reported IGF-I normalization in 42% of random acromegalic patients treated with lanreotide slow release, 56% of those preselected for somatostatin responsiveness, and 47% of all treated subjects.[12] They concluded that octreotide LAR was more efficacious than lanreotide SR with regard to normalization of IGF-I and tumor shrinkage. It is not clear, however, whether they evaluated the new longer-acting monthly depot formulation of lanreotide separately from the slow-release preparation of the drug.

Alexopoulou et al. conducted an open-label multicenter study to evaluate the efficacy and tolerability of lanreotide depot autogel.[13] They compared the efficacy of treatment with that obtained during prior treatment with octreotide LAR. They determined that lanreotide depot was as effective as octreotide LAR in lowering IGF and GH concentrations. They also noted an improvement in the acromegalic symptoms score, as well as a small but significant reduction in pituitary tumor size. In a 12-month randomized cross-over study design comparing lanreotide autogel and octreotide LAR, Andries et al. illustrated that the efficacy of both drugs was comparable.[14] They noted, however, that efficacies and side effect profiles were somewhat different, suggesting that a change from one therapeutic agent to the other may be beneficial in patients with treatment failure or limiting side effects. It is anticipated that sleep apnea, hypertension, acromegalic cardiomyopathy, impaired glucose tolerance, and other comorbidities of acromegaly will be improved by successful long-term treatment.[15]

Side effects of lanreotide depot are similar to those seen with octreotide and are related to its ability to inhibit other endocrine and neuroendocrine systems. Reduced gallbladder motility may lead to gallbladder sludge and gallstone formation. Inhibition of insulin secretion may lead to hyperglycemia. Impaired intestinal motility and inhibition of various digestive processes may result in gastrointestinal discomfort, including diarrhea, abdominal pain, flatulence, constipation, and nausea. Bradycardia occurs in approximately 3% of patients. Injection-site reactions—including pain and development of injection site induration or granulomas—occur in approximately 5% of patients.

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In summary, lanreotide depot is the newest somatostatin analog approved by the FDA for use in acromegaly. The formulation allows for convenient monthly self-administered injections. The efficacy is probably similar to that of octreotide LAR. Long-term studies are required to assess the impact of this new preparation on the comorbidities of acromegaly. ■


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