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Somatostatin agonists for treatment of acromegaly

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Abstract

The discovery of somatotropin-release inhibitory factor (SRIF) in hypothalamic extract in 1970 led to the synthesis of the first somatostatin analog octreotide, discovery of five somatostatin receptor subtypes, and development of additional somatostatin receptor ligands (SRL) as pharmacotherapy for acromegaly and other neuroendocrine tumors. Long-acting formulations of SRL (octreotide LAR Depot, lanreotide SR and lanreotide autogel) assure improved patient compliance with weekly up to monthly injections, and are commonly used as primary or adjuvant treatment of acromegaly. We review SRL currently available, emphasizing long-acting compounds and their efficacy in controlling acromegaly. Disease control is evaluated by biochemical markers, tumor shrinkage, and disease-symptom improvement balanced against drug-related side effects.

Keywords

Acromegaly; Somatostatin analogs; Efficacy; Side effects

1. Somatostatin agonists currently available for treatment of acromegaly

Somatostatin is an endogenous peptide derived from the hypothalamus and gastrointestinal tract to regulate neuroendocrine secretion and proliferation. SRL have been widely used as safe and effective treatments for pituitary and neuroendocrine tumors (Low, 2004; Patel, 1999; Weckbecker et al., 2003).

Two SRIF agonists are available for treatment of acromegaly; octreotide (Novartis) and lanreotide (Ipsen). Both short and long-acting derivatives of these molecules have been developed. Octreotide compounds are approved for clinical use in the USA, while both lanreotide and octreotide compounds are approved for use elsewhere.

1.1. Octreotide acetate (Sandostatin®)

Octreotide is a cyclic octapeptide prepared as an acetate salt solution for administration by deep subcutaneous (intra-fat) or intravenous injections. One milliliter ampules containing 50, 100, or 500 μg or 5 mL ampules containing 200 and 1000 μg/mL of octreotide acetate are available. The typical starting dose is 100–250 μg thrice-daily but up to 1.5 mg/24 h can safely be given (Barnard et al., 1986; Freda, 2002). Octreotide binds somatostatin receptor subtype 2 (sst2) with high affinity, and to a lesser extent to sst5 and sst3 (Patel, 1999). After subcutaneous injection to patients with acromegaly, octreotide (100 μg) is absorbed rapidly and peak concentrations of 2.8 ng/mL are attained within 40 min, with a volume of distribution of ~21.6 ± 8.5 L and total body clearance of 18 L/h. In the plasma ~41% of drug is bound mainly to lipoprotein and to a lesser extent to albumin. Plasma elimination half-life is 1.7–1.9

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h (vs. ≤3 min for endogenous SRIF) but duration of tumor action can last up to 12 h. About 30% is excreted unchanged in the urine.

1.2. Octreotide LAR (Sandostatin LAR® Depot)

Octreotide long-acting release (LAR) Depot comprises octreotide acetate encapsulated within microspheres that when added to diluent (carboxymethylcellulose sodium, mannitol and water) forms a suspension administered as an intramuscular injection every 4 weeks. Microspheres are comprised of a biodegradable glucose star polymer ($_{D,L}$-lactic and glycolic acid co-polymer) that degrades mostly through hydrolysis. The compound is available as 5 mL vials containing 10, 20 or 30 mg free peptide. Once octreotide is released from the microspheres into the circulation, it distributes and is eliminated as outlined above. The starting dose of octreotide LAR Depot is 20 mg monthly and the drug dose can be titrated up to 40 mg depending on the clinical and biochemical response.

In patients with acromegaly an injection of octreotide LAR Depot (30 mg) is followed by peak drug levels of 1.3 ng/mL at day 1, followed by plateau concentrations of 2.0 ng/mL at ~28 days that are maintained for 2 more weeks. When injected every 4 weeks, steady state (2.1–2.6 ng/mL, peak to trough variation 44–68%) is achieved after the third injection without further drug accumulation. The dose should be adjusted in the elderly; however, the compound has not been studied in patients with renal or liver impairment (http://www.rxlist.com) (McKeage et al., 2003).

1.3. Lanreotide (Somatulin SR®)

Lanreotide slow release (SR) contains the SRIF analog lanreotide (BIM23014) that exhibits high affinity to sst2 and less to sst5. The drug is incorporated into a biodegradable polymer microparticle to allow prolonged release. This compound is injected intramuscularily every 7–14 days. Thirty and 60 mg injections are available for intramuscular administration. Initial rapid release is observed 1–2 h after injection followed by a prolonged release phase peaking 2 days later. The half-life is 5.2±2.5 days and bioavailability is 46±17% in both healthy volunteers and in patients with acromegaly (Biermasz et al., 2005).

1.4. Lanreotide autogel®

Lanreotide autogel is a depot preparation of lanreotide delivered as an aqueous, small-volume mixture of 60, 90, or 120 mg in pre-filled syringes for deep subcutaneous administration (Biermasz et al., 2005). Maximal serum concentrations are achieved between 10 and 16 h after the first injection after which there is a slow decline, with therapeutic levels of 1 ng/mL maintained for 28 days. Ninety percent of the steady state is achieved after 4 injections, the half-life is 23–29 days and bioavailability is 58–79% (Biermasz et al., 2005; Cendros et al., 2005).

2. Efficacy of long-acting SRIF analogs in treating acromegaly

Accepted criteria defining acromegaly control are used to determined SRIF agonist efficacy for primary or secondary pharmacotherapy. The reports cited below employ a mean fasting random GH plasma level of <2.5 μg/L as “safe” cutoff values for biochemical control. Achieving this value does not predict disease cure but correlates with reduced mortality for treated acromegaly patients (Rajasoorya et al., 1994). Moreover, relevant evidence suggests that the GH plasma nadir after a glucose load should be <1 μg/L (Holdaway et al., 2004) to reduce acromegaly-related mortality rates to those of the general population. Gender and age-matched IGF-1 plasma level normalization is an important therapeutic goal, however, its utility is somewhat challenging due to poor assay standardization (Melmed et al., 2005a). Disease control is also assessed by drug effect on pituitary tumor growth and regression of disease-

related signs and symptoms. Biochemical and clinical efficacy are measured against both drug side effects and cost.

2.1. Biochemical control

SRIF agonists are the primary pharmacotherapy available for acromegaly; however, they are only partially effective in disease control. Table 1 summarizes the percentage of patients attaining disease control, defined as fasting random mean GH plasma levels <2.5 μg/L or normalization of age and gender-matched IGF-1 plasma levels or both, in studies with a treatment duration >6 months and comprising at least 10 patients per study. We chose to concentrate on results achieved by octreotide LAR and not octreotide since the former is preferred by clinicians due to its ability to maintain constant drug plasma levels throughout treatment, and preferred patient compliance. Octreotide LAR suppressed GH and IGF-1 levels in 65 and 63% of patients, respectively, while lanreotide SR 30 mg every 7 or 10 or 14 days suppressed GH and IGF-1 levels in 55 and 54% of patients, respectively. A higher dose of lanreotide SR 60 mg (q21/28d) increased the GH response to 76% but maintained IGF-1 control in 52% of patients. lanreotide autogel at doses up to 120 mg q21/28d did not substantially improve drug efficacy. Whether or not octreotide LAR has an advantage over lanreotide SR, was implied in a recent attempt to analyze by meta-analysis but limited by its statistical power and open-label rather than randomized, placebo-controlled trials (Freda et al., 2005). Several important points have to be taken into account when interpreting these results and comparing the compounds' efficacy. There is a considerable variability between studies including sample size, treatment duration, drug dosages used for different and even the same patients, differences between assays utilized in different clinics and prior treatments to which subjects were exposed before study enrolment. In addition, most patients enrolled in lanreotide treatment trials were previously tested for octreotide responsiveness unlike those enrolled for octreotide LAR studies, who were sometimes treatment-naïve. If considering only GH levels <1 μg/L to be the cutoff for "normalizing" mortality, 33% of octreotide LAR (Chanson et al., 2000a;Cozzi et al., 2003;Lancranjan and Atkinson, 1999;Lancranjan et al., 1996) and 25% of lanreotide SR (Attanasio et al., 2003;Chanson et al., 2000a) treated patients achieved disease control, implying that ~50% of SRIF agonist treated GH-"controlled" patients may still be at higher risk for higher mortality rates. Prolonged treatment duration improves biochemical control as GH and IGF-1 plasma levels continue to decrease with time (Ayuk et al., 2004;Colao et al., 2001;Cozzi et al., 2003,2006;Davies et al., 1998;Freda et al., 2005;Jallad et al., 2005;Ronchi et al., 2006).

Primary pharmacotherapy is an optional treatment for selected patients (Ben-Shlomo and Melmed, 2003; Colao et al., 2006b). Several papers in recent years report the efficacy of primary pharmacotherapy in achieving biochemical disease control. Similar rates of patient control were achieved in the primary and adjuvant groups, with GH plasma levels ≤2.5 μg/L (64%) and/or normalization of IGF-1 (64%) (Amato et al., 2002; Ayuk et al., 2002, 2004; Bevan et al., 2002; Colao et al., 2001, 2006c; Cozzi et al., 2003, 2006). Even though *de novo* patients had higher pre-treatment GH or IGF-1 levels or both, than those already treated with surgery and/or radiotherapy, patients achieved the same ultimate level of biochemical control by the end of the study (Colao et al., 2001; Cozzi et al., 2003).

2.2. Tumor shrinkage

Evidence from studies including mostly patients with SRL as adjuvant therapy, suggest that overall 20% of tumors exhibit significant shrinkage (~50%) while 37% shrinkage was observed with primary SRL pharmacotherapy (Melmed et al., 2005b). Fewer than 2% of GH-secreting tumors were reported to grow during treatment with SRL (Freda, 2002; Freda et al., 2005) and the remainder were unchanged in size (Freda, 2002). Table 1 summarizes both primary and adjuvant pharmacotherapy results from studies lasting ≥6 months on >10 patients and shows

70% shrinkage with octreotide LAR, 26% with lanreotide SR 30 mg and 39% with lanreotide SR 60 mg. Recent studies of primary SRL pharmacotherapy suggest mean 79% tumor shrinkage with octreotide LAR (Colao et al., 2001, 2006c; Cozzi et al., 2003, 2006) and 50% with lanreotide 60 mg (Attanasio et al., 2003) or 25% with lanreotide 30 mg(Amato et al., 2002; Baldelli et al., 2000). Basal GH levels correlated positively with the degree of shrinkage which was >75% in 44% of patients in one study (Cozzi et al., 2006) and >50% in 60% of patients in another (Colao et al., 2001). Tumor shrinkage was progressive with prolonged treatment, and longer follow-up is needed for efficacy analysis. No patient had tumor expansion during treatments and tumor volume shrinkage, biochemical markers, and drug dose did not correlate (Colao et al., 2001). A recent study retrospectively summarized results of tumor shrinkage in 99 patients treated for 12 months with either octreotide LAR or lanreotide SR with different therapeutic regimens (Colao et al., 2006a). GH levels ≤2.5 μg/L were achieved in 58%, IGF-1 normalization in 46%, and tumor shrinkage ≥25% in 77% of patients. Decreased IGF-1 levels were the best predictor for tumor shrinkage, followed by age and degree of GH decrease.

2.3. Symptom control

2.3.1. Cardiovascular system—Both octreotide LAR (Colao et al., 2003, 2000, 2002) and lanreotide SR (Baldelli et al., 1999; Hradec et al., 1999; Lombardi et al., 2002) reduced left ventricular hypertrophy and improved diastolic dysfunction especially in younger patients with shorter disease duration. Increased exercise capacity, normalization of ejection fraction (Colao et al., 2002) and suppression of ventricular premature beats were also observed (Lombardi et al., 2002). A recent retrospective critical analysis of 18 studies found that SRL treatment is associated with significant reduction of heart rate, LV mass index and improved exercise capacity, that correlate with IGF-1 or GH levels decrease and younger age (Maison et al., 2007). Electrocardiographic QT complex (QTc) interval (which is significantly longer in patients with active acromegaly and can contribute to fatal arrhythmias) was significantly shortened and normalized after 3–63 months octreotide LAR or lanreotide SR treatment, along with reduction of heart rate. Six patients with acromegaly had pathologically prolonged QTc which normalized after treatment (Fatti et al., 2006).

2.3.2. Sleep apnea—Reduction in severity of sleep apnea was observed with improved sleep-disordered breathing in 14 patients treated with octreotide LAR for 6 months, and correlated with GH and IGF-1 level reduction. The apnea-hypopnea index improved in 55% and snoring episodes were reduced in 66% of patients (Ip et al., 2001).

2.3.3. Glucose metabolism—The effect of long-acting SRL on glucose metabolism in patients with acromegaly is complex. On the one hand, SRL reduce insulin resistance induced by increased GH levels, and on the other hand they also suppress insulin secretion from islet β-cells. The balance between the two effects determines whether long-acting SRL improve glucose metabolism or not. Few studies have designed glucose metabolism during long-acting SRL pharmacotherapy as a primary endpoint. Ronchi et al. compared 10 patients treated with lanreotide SR 30 mg for 6–60 months (mean 19 months) and after a 3-month washout period with octreotide LAR for 6–36 months (mean 21 months). In 8 non-diabetic patients octreotide LAR was more diabetogenic than lanreotide SR (but also more efficient in GH/IGF-1 control) increasing fasting glucose levels (83–104 mg/dL; 20% increase), Haemoglobin A_{1C} (5–5.5%; 10% increase), glucose response to OGTT (AUC value 18–22 g/dL/120 min; 28% increase), and 2 octreotide LAR treated patients developed impaired glucose tolerance 6 months after treatment initiation (Ronchi et al., 2002). Fasting insulin and serum insulin during OGTT (AUC) were higher at baseline and decreased 42% (16–8 μU/mL) and 39% (10–6 μU/L/120 min), respectively with lanreotide SR vs. 46% (16–7 μU/mL) and 56% (10–6 μU/L/120 min), respectively with octreotide LAR. Insulin resistance index (IR) measured by homeostatic

model assessment (HOMA-IR) decreased ~40% with both treatment regimens. Two diabetic patients had worsening of fasting glucose and HbA_{1C} with octreotide LAR treatment but not with lanreotide SR (Ronchi et al., 2002).

Baldelli et al. designed a prospective study of 24 patients with acromegaly treated for 6 months with octreotide LAR and showed significant improvement in insulin sensitivity measured by euglycaemic hyperinsulinemic clamp (4.5 mg/kg/min at baseline at baseline to 7.2 mg/kg/min after 6 months therapy, compared to 5.7 mg/kg/min in normal controls) (Baldelli et al., 2003). However, in non-diabetic patients, significantly higher peak glucose levels were measured 2-h after oral glucose loading (102 mg/dL at baseline vs. 133 mg/dL after 6 months therapy) along with a significant decrease in peak insulin levels (94–68 UI/L after 6 months therapy). HbA_{1C} increased significantly from 4.7% at baseline to 5.1% after 6 months therapy (Baldelli et al., 2003).

In a retrospective analysis 36 patients treated with either drug for a median period of 66 months were analyzed for glucose metabolism as compared to 33 cured acromegaly patients (Ronchi et al., 2006). In the groups treated and responding to long-acting SRL fasting glucose levels and AUC of glucose levels during an OGTT were increased and HbA_{1C} increased ~1% (from ~5 to 6%). Basal fasting insulin and stimulated insulin secretion levels (measured by HOMA-β) decreased. Insulin sensitivity measured by HOMA-IR, quantitative insulin check index (QUICKI) and composite index derived from OGTT ($OGTT_{ISI}$) decreased significantly (Ronchi et al., 2006).

Long-acting SRL generally exhibits moderate detrimental effects on glucose metabolism; however, most reported changes are within the normal range. For patients who develop diabetes mellitus, some investigators suggest using antiglycemic drugs that increase insulin secretion from islet β cells (e.g. sulphonylureas) rather than those that improve insulin sensitivity. Periodic monitoring of glucose tolerance and antidiabetic treatments during therapy with these drugs is recommended.

2.3.4. Lipid profile—Lipid profile improves with SRL treatment. In a prospective study, 14 patients with acromegaly were treated for 6 months with octreotide LAR. Plasma triglyceride levels decreased significantly (~28%), as did small dense LDL (~15%) and remnant-like particle (RLP;~32%) concentrations. An increase in HDL (~23%), HDL2 (~75%), and HDL3 (~15%), Apo A1 (~18%), and LPL activity (~42%) was also observed (Tan et al., 2003). Ronchi et al. compared patients treated with lanreotide SR and later on with octreotide LAR and found ~30% increase in HDL and ~18% decrease in LDL levels. Triglyceride levels did not change and there was no difference between the two treatment formulas (Ronchi et al., 2002). In the study by Baldelli et al. triglyceride levels decreased significantly by ~30% (Baldelli et al., 2003).

2.3.5. Other symptoms—Other symptoms of acromegaly which improve have been thoroughly reviewed (Colao et al., 2004) and their improvement varies significantly between the studies. Improvement in headache (21–48% subjective improvement reported), perspiration (21–59%), paresthesias (14–78%), fatigue (25–47%), osteoarthralgia (21–61%), carpal tunnel syndrome (15–81%) and reduction in soft tissue enlargement (up to 100% of patients) is reported in patients treated with long-acting octreotide LAR (Colao et al., 2001, 2006c; Lancranjan and Atkinson, 1999; Lancranjan et al., 1996). Both lanreotide SR and autogel reduced headache (30%), perspiration (20%), asthenia (30%), swelling of extremities (30%), and arthralgias (38%) (Caron et al., 2002). However, in a Phase III clinical trial lanreotide autogel 120 mg was 50% more efficient in reducing headache and perspiration than lanreotide SR 30 mg (Lucas and Astorga, 2006).

3. Side effects

Table 2 summarizes most of the side effects reported for long-acting SRL. Reports of side effects (SEs) for octreotide LAR are mostly derived from manufacturer data while those of lanreotide SR and autogel are extrapolated from the literature and presented with wide ranges reflecting large differences between studies. Between 50 and 100% of patients describe some adverse effects, most of which are mild to moderate and dissipate with continuation of therapy.

The most common SEs include gastrointestinal manifestations, in particular, abdominal discomfort and diarrhea, injection site pain and biliary tract abnormalities. Asymptomatic gallstones or sludge develops in up to 30% of patients within the first 2 years of treatment. Rarely patients require cholecystectomy with either octreotide LAR or lanreotide SR treatment, however, two lanreotide autogel studies describe relatively high rates of acute cholecystitis [2 of 13 (Caron et al., 2006) and 1 of 11 (Gutt et al., 2005)], an observation that needs further investigation since lanreotide autogel injections contain higher doses of lanreotide.

As mentioned above, long-acting SRL can have a detrimental effect on glucose metabolism. In patients with type 1 diabetes mellitus treated with insulin, octreotide suppression of counterregulatory hormones, increase in peripheral insulin-mediated glucose metabolism and storage, and reduction of energy expenditure can reduce insulin requirements and expose the patient to hypoglycemia (Bruttomesso et al., 2001). On the other hand, in patients with type 2 diabetes mellitus SRL reduce peripheral insulin resistance but also decrease insulin secretion therefore causing a net hyperglycemia.

In most studies dropout rates due to unbearable SEs are very low; however, two studies have reported high dropout rates. One study reported 50% dropout rates where patients chose to switch to lanreotide, undertake surgery, or bromocriptine was added, nevertheless, no information was given about SE-related dropout (Cozzi et al., 2006). Another study reported 25% withdrawal from treatment protocol because of drug ineffectiveness in 47%, adverse events in 27%, and other medical events in 26% of patients (Chanson et al., 2000b).

4. Summary

For the last 30 years SRL have been the first choice pharmacotherapy for treating patients with acromegaly, with >50% of patients exhibiting biochemical control and >30% of patients having tumor shrinkage. These percentages are significantly lower if criteria for disease-control are tightened. Many SRL responders also experience a substantial improvement in disease symptoms. Side effects are mild to moderate, mostly transient, involving mainly gastrointestinal tract, biliary tract abnormalities and injection site reactions. Using SRL as primary pharmacotherapy has proven to be clinically effective and should be considered in selected patients.

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Table 1

Efficacy of long-acting SRL

Treatment duration (range)	Patient number	GH ≤2.5 μg/L	IGF-1 normalization	Tumor shrinkage >20%	References
Octreotide LAR 10–40 mg q28d	837	65% (33–85)	63% (35–75)	70%	Ayuk et al. (2002, 2004), Bevan et al. (2002), Chanson et al. (2000a), Colao et al. (2001, 2006c), Cozzi et al. (2003, 1999, 2006), Davies et al. (1998), Flogstad et al. (1997), Jallad et al. (2005), Lancranjan and Atkinson (1999), Lancranjan et al. (1996), Turner et al. (1999)
Lanreotide SR 30 mg q7/10/14d	421	55% (41–78)	54% (41–67)	26%	al-Maskari et al. (1996), Amato et al. (2002), Baldelli et al. (2000), Caron et al. (1997), Chanson et al. (2000a), Chanson et al. (2000b), Turner et al. (1999), Verhelst et al. (2000)
Lanreotide SR 60 mg q21/28d	102	76% (63–90)	52% (40–65)	39%	Ambrosio et al. (2002), Attanasio et al. (2003)
Lanreotide autogel 60, 90, 120 mg q28d	211	44% (33–54)	45% (40–55)	N/A	Caron et al. (2002, 2006), Gutt et al. (2005), Lucas and Astorga (2006)

Percentages derived from calculation of weighted mean percent (sum of responders/sum of participants).

Table 2

Side effects of long-acting SRL

	Side effect	Frequency[a] (%)		
		Octreotide LAR	Lanreotide autogel	Lanreotide SR
Cardiovascular system	Sinus bradycardia	25[b]	6	—
	Conduction abnormalities	10[b]	—	—
	Arrhythmias	9[b]	—	—
Gastrointestinal tract	Diarrhea	36	44–51	48–76
	Abdominal pain/discomfort	29	41–50	18–62
	Flatulence	26	42	12–33
	Constipation	19	—	23
	Nausea	10	14	18–22
	Vomiting	7	17	5
	Dyspepsia, anorexia, hemorrhoids, weight loss, steatorrhea, constipation	5–15	—	41 (steatorrhea)
Gallbladder	Biliary abnormalities[c]	52	38–41	24–38
	Cholelithiasis	22	15–41	3–38
	Requiring cholecystectomy	1	9–15	0–5
Glucose metabolism	Hypoglycemia	2	—	2
	Hyperglycemia	0–15	N/A[d]	N/A
Thyroid	Hypothyroidism	2	—	0[e]
	Goiter	2	—	—
Injection site	Pain (dose dependent)	11 (at 30 mg)	7–69	2–59
Central nervous system	Fatigue, dizziness, headache,	16–20	17	6–12
	Memory loss	9[f]	—	—
Hematology	Iron deficiency anemia	N/A[g]	—	—
	B12 deficiency	7[h]	—	—
Skin	Allergy	5–15	—	—
	Hair loss	9	—	9

(–) No mention of this side effect in the literature; N/A, not ascertainable since absolute number of patients suffering from this side effect is not given.

[a] Frequencies are adopted from: *octreotide LAR*: http://www.rxlist.com according to manufacturer reports (Colao et al., 2001; Cozzi et al., 2003; Davies et al., 1998; Flogstad et al., 1997; Jallad et al., 2005; Lancranjan and Atkinson, 1999; Lancranjan et al., 1996; Stewart et al., 1995); *lanreotide autogel*: (Bronstein et al., 2005; Caron et al., 2002, 2006; Lucas and Astorga, 2006); *lanreotide SR*: (al-Maskari et al., 1996; Attanasio et al., 2003; Caron et al., 1997; Chanson et al., 2000a,b; Giusti et al., 1996; Gutt et al., 2005; Lucas et al., 2003; Marek et al., 1994; Morange et al., 1994; Verhelst et al., 2000).

[b] ECG was performed in patients with acromegaly receiving octreotide acetate sc injections, not in octreotide LAR.

[c] Including gallstones, microlithiasis, sediment, sludge and dilatation.

[d] Absolute number of patients with hyperglycemia is not clear but the study observed a deterioration in glucose metabolism as compared to lanreotide SR.

[e] Giusti et al. (1996) and Morange et al. (1994).

[f] From Jallad et al. (2005).

[g] From Lancranjan et al. (1996).

[h] From Flogstad et al. (1997).