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SOMATOSTATIN ANALOGS IN THE TREATMENT OF PITUITARY TUMORS

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ABSTRACT

Recently the medical approach to patients with secreting and nonsecreting pituitary adenomas has received great impulse thanks to the availability of new somatostatin analogs provided with slow release, such as lanreotide (LAN) and octreotide-LAR (OCT-LAR). In acromegaly, disease control (GH ≤ 2.5 µg/l as fasting value or ≤ 1 µg/l after glucose load, together with age-normalized IGF-I) is achievable in more than half patients under treatment with LAN and OCT-LAR. Improvement of cardiomyopathy, sleep apnea and arthropathy has been reported during treatment with these somatostatin analogs. LAN displayed beneficial effects also in TSH-secreting adenomas, while the results of treatment with these peptides in patients with clinically nonfunctioning adenomas are still rather limited and controversial.

INTRODUCTION

In recent years, new somatostatin (SST) analogs (SSTA) provided in slow release formulations, such as lanreotide (LAN) and octreotide (OCT)-LAR (OCT-LAR) have greatly improved the pharmacotherapy to pituitary adenomas. In particular, SSTA have been successfully employed in patients with GH- and TSH-secreting tumors. Whether these drugs should be employed as first line therapy or after unsuccessful surgery in patients with acromegaly is currently under debate. Conversely, SSTA are generally considered beneficial in patients affected with either GH- or TSH-secreting tumors with persistent disease after surgery. Results in patients with clinically nonfunctioning adenomas are, conversely, rather disappointing and no effect was proven in PRL-secreting and ACTH-secreting adenomas.

In this chapter, the most recent studies pointing out the effects of LAN and OCT-LAR in patients with pituitary adenomas are reviewed with particular
emphasis on debated issues such as the pre-surgical treatment and their potential use as first line therapy in acromegaly.

SST ANALOGS IN GH-SECRETING PITUITARY ADENOMAS

The objectives of treating acromegaly are the tumor removal with resolution of its mass effects, the restoration of physiological GH secretion (both basal and stimulated) and the relief of symptoms directly caused by GH excess. The treatment is performed also to possibly prevent the progressive disfigurement, bone expansion, osteoarthritis and cardiomyopathy, which are disabling long-term consequences, hypertension, insulin resistance, diabetes mellitus and lipid abnormalities, that are risk factors for vascular damage. The prognosis of acromegaly is poor since the mortality rate of untreated patients is double that of healthy subjects after the age of 45 yrs (1-6). Whether the suppression of GH and IGF-I is able to reverse the poor long-term outcome is still questioned. To date the disease is considered controlled when fasting GH levels are ≤2.5 µg/l, glucose-load suppressed GH levels are ≤1 µg/l and IGF-I levels are normalized for age (7). When discussing the successful outcome of LAN and OCT-LAR treatment, these criteria are considered.

The currently available treatment options for acromegaly include surgery, irradiation and pharmacological suppression of GH levels by means of dopamine-agonists (DA) or SSTA, either alone or in combination. Surgical removal of the pituitary adenoma still remains the first therapeutic option in most cases (3,5,8,9), although primary pharmacotherapy has been recently proposed (10,11). Irradiation or pharmacological suppression of GH excess can be used following unsuccessful surgery or as individualized primary therapy in elderly patients (5,8,9). Selective D₂ DA, like cabergoline, have been recently shown to induce a higher GH and IGF-I suppression than bromocriptine (12-14). However, DA were universally recognized less potent than SSTA in controlling acromegaly.

OCT, the first long-acting synthetic SST analog introduced in the clinical practice, has a half-life of 80-100 min (15). Its use to treat acromegaly was started in the middle of the 80’s (16). Many subsequent studies demonstrated that s.c. OCT reduced GH concentrations in over 90% of patients suppressing GH levels <5 µg/l in half of them (5, 8, 9, 15). A combined analysis of 557 patients treated worldwide showed that OCT administration normalized IGF-I levels in 48.5% and reduced tumor size of at least 20% of baseline size, in 40.3% of patients (5). Soon after the administration of the first doses of s.c. OCT clinical signs and symptoms, in particular headache, hyperhidrosis and joint pain, are significantly reduced (3-5, 8, 9, 15). The long-term treatment with s.c. OCT was also shown to improve obstructive and central sleep apnea, one of the most severe complications of acromegaly: both the number of apneic episodes and the degree of blood oxygen desaturation were reduced after treatment (17). Beneficial effects of both short-term and long-term s.c. OCT treatment were also demonstrated in decreasing cardiac size (18-21), and improving the diastolic function (18,21). A remarkable improvement of systolic function was obtained in patients with overt heart failure refractory to