REVIEW

Lanreotide for the Treatment of Acromegaly

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ABSTRACT

Lanreotide is an eight-amino acid peptide, which is an analog of the native somatostatin peptide, physiological inhibitor of growth hormone (GH). The drug shows high binding affinity for somatostatin receptors, SSTR2 and SSTR5, which is the primary mechanism considered to be responsible for decreasing GH secretion and GH cell proliferation in acromegaly. Two different formulations of lanreotide are currently available: lanreotide slow release, which requires intramuscular injection every 7-14 days, and lanreotide autogel, which requires deep subcutaneous injection every 4-8 weeks. Several studies have been published to date on the use of lanreotide in acromegaly. Antisecretory efficacy has been reported in 35%-70% of cases; this huge variability is probably explained by different indications (eg, primary or adjunctive postsurgical treatment), or the fact that some studies were based on patients known to be responders to somatostatin analogs. As a primary treatment, antisecretory efficacy was very similar, confirming the possibility of lanreotide as an option in cases of unsuccessful surgery, contraindication, or surgery refusal. Lanreotide also has antitumoral effects as it induces a decrease in tumor volume of >25% in 30%-70% of patients. This could be beneficial before transsphenoidal surgery, as a pretreatment, to decrease tumor volume and ease surgery; however, to date, advantages in terms of final remission or uncured status remain a matter of debate. Side effects are rare; the most frequent being gastrointestinal discomfort and increased risk of gallstone formation, and glucose metabolism modifications. Comparison with the other somatostatin analog, octreotide, tends to show identical levels of efficacy between both drugs. Lanreotide thus seems to be an effective treatment in acromegaly. To date, however, lanreotide is still considered as only suspending GH secretion, thus requiring prolonged and costly treatment.

Keywords: acromegaly; lanreotide; macroadenoma; microadenoma; pituitary adenoma; somatostatin; somatostatin analogs; transsphenoidal surgery
INTRODUCTION

Acromegaly is a rare disease, with a prevalence of 60 cases per million people and three to four new cases per million diagnosed every year; it occurs mainly due to a somatotroph pituitary adenoma.\textsuperscript{1-2} In addition to local effects due to compression by the adenoma, the over-secretion of growth hormone (GH) and consequently insulin-like growth factor-1 (IGF-1) can lead to cardiac and metabolic complications.\textsuperscript{1} A recent meta-analysis reported that the standardized mortality ratio (ratio of observed deaths to expected deaths) of patients with acromegaly was 1.72.\textsuperscript{3} Surgery still remains a first-line treatment for acromegaly even though recent studies on somatostatin analogs have raised the question of their role as a primary treatment. Since the development of octreotide in the early 1980s, two long-release formulations of somatostatin analogs have become widely available. This review will focus on lanreotide (Ipsen Pharma, Paris, France) in its slow-release (SR) and recent autogel (ATG) formulations.

METHODS

A search for original articles, published between 1990 and 2009 and focusing on lanreotide in acromegaly, was performed in MEDLINE and PubMed. The search terms used were “lanreotide,” “acromegaly,” “growth hormone,” “pituitary adenoma,” and “somatostatin.” Reports based on fewer than 10 patients were excluded from the review, as well as articles dealing with lanreotide in endocrine tumors. A total of 59 articles were used in this review.

PHARMACEUTICAL PROPERTIES

Somatostatin is the main physiological inhibitor of GH secretion in humans, which was identified by the pioneering work of Roger Guillemin\textsuperscript{4} and is produced by neuroendocrine neurons of the periventricular nucleus in the hypothalamus. These neurons project to the median eminence, where somatostatin is released into hypothalamo-hypophysial portal circulation.\textsuperscript{5} Somatostatin action is mediated through five specific G-protein-coupled somatostatin receptor subtypes (SSTRs), differentially expressed in a tissue-specific pattern. Somatotrophs preferentially express SSTR2 and SSTR5, which regulate GH release from GH-secreting cells.\textsuperscript{6} However, even though SSTR5 may play a part in some GH tumors, SSTR2 is probably the main receptor mediating GH suppression.\textsuperscript{7} Long-acting somatostatin analogs were developed because the use of natural somatostatin is limited by its very short half-life of less than 3 minutes.\textsuperscript{5} Since the development of subcutaneous octreotide in the early 1980s, pharmacological properties of this drug were improved, mainly in terms of its length of action. Octreotide long-acting release (LAR), lanreotide SR, and more recently lanreotide ATG have thus been reported as effective treatments of GH-secreting adenomas, particularly in cases of unsuccessful surgery.\textsuperscript{1} They can also be used for the treatment of endocrine tumors;\textsuperscript{8} however, this specific point will not be detailed in this review.

Lanreotide is an eight-amino acid peptide that is made cyclic through a disulfide bridge, which is an analog of the biologically active core of the native 14-amino acid somatostatin peptide.\textsuperscript{9} As reported in Table 1, the drug shows high binding affinity for human SSTR2, -3, and -5, and reduced affinity for human SSTR1 and -4.\textsuperscript{5} Activity at SSTR2 and -5 is the primary mechanism considered to be responsible for decreasing GH secretion and GH cell proliferation in acromegaly.\textsuperscript{10} In vitro and in vivo, lanreotide sensibility (as with octreotide) is mainly