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BRIEF COMMUNICATION

Serial follow-up of presurgical treatment using pasireotide long-acting release with or without octreotide long-acting release for naïve active acromegaly

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The aim of the present study was to evaluate the serial changes of GH and IGF-1 in seven patients with naïve, active acromegaly following presurgical treatment of the somatostatin analog pasireotide long-acting release (LAR) and octreotide LAR. The patients were treated with pasireotide LAR with or without octreotide LAR for two years and underwent transsphenoidal adenomectomy. After treatment with the somatostatin analogs, the surgical cure rate was similar to that in patients who underwent transsphenoidal surgery alone. Diabetes insipidus was not identified in any patients after the operation. Pasireotide LAR was effective on GH as well as IGF-1 suppression and tumor size decreasing when used as the primary therapy. Future large-population studies to investigate the surgical curative rate after presurgical treatment with somatostatin analogs in patients with acromegaly and macroadenomas close to the cavernous sinus are warranted. However, that hyperglycemia developed following pre-surgical treatment with pasireotide should take into consideration.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Introduction

Acromegaly usually results from hypersecretion of growth hormone (GH) from pituitary adenoma. Patients have significant morbidity and mortality, with serum GH levels higher than 2.5 μg/L and higher serum insulin-like growth factor (IGF)-1 levels than age- and sex-matched controls.[1]

Currently, transsphenoidal adenomectomy is the first-line treatment option for patients with acromegaly.[2] Despite the high success rate (75—95%) of surgery for intrasellar microadenomas, disease control rates decrease to 26—68% in patients with macroadenomas. Somatostatin analogs have been used as adjuvant therapy to control GH hypersecretion. Primary therapy with somatostatin analogs has been increasingly considered in recent years.[3]

Pasireotide is a novel multireceptor ligand somatostatin analog with high affinity for somatostatin receptor Types 1—3 (sst_{1-3}) and somatostatin receptor Type 5 (sst_5).[4] Owing to the heterogeneous expression of the sst_2 and sst_5 subtypes in GH-secreting adenomas, pasireotide may be more effective than octreotide, which is primarily for sst_2.[5]

Previous studies that aimed to answer the question whether presurgical somatostatin analog treatment can improve the operative outcome in acromegaly were few in number and had conflicting results.[6—9] Although this study was a small part of a multicenter randomized double-blind clinical trial that investigated pasireotide long-acting release (LAR) and octreotide LAR in patients with active acromegaly,[10] we present the serial changes and not just the head to head comparison of the effects of these two drugs. In addition, only naïve patients were included in the present study.

Methods

Study design

This study was a small part of a clinical trial that evaluated the effectiveness and side effects of pasireotide LAR with or without octreotide LAR for 24 months in patients with naïve active acromegaly. The clinical trial was a prospective, multicenter, randomized, double-blind Phase III study that included patients with active acromegaly whether naïve or not (ClinicalTrials.gov NCT00600886).

After baseline screening, the patients were divided into three groups. In the first group, patients received pasireotide LAR treatment for the first 12 months in a blinded core study and continued the treatment in an extension study. In the second group, patients received octreotide LAR treatment for the first 12 months in a blinded core study and then received pasireotide LAR treatment in an extension study. In the third group, patients received blinded treatment with either pasireotide LAR or octreotide LAR for 12 months. Then, they were either retained on their initial blinded treatment in an extension study if the treatment had been effective or changed to the other blinded arm for an additional 12 months if the previous treatment had not been effective. After presurgical treatment, all the patients underwent transsphenoidal adenomectomy.

Patients

Patients aged >18 years who were diagnosed with pituitary adenoma and had naïve active acromegaly confirmed by using a 5-point GH profile (>5 μg/L within a 2-hour period) and elevated IGF-1 (compared with age- and sex-matched controls) were recruited for the study.

The main exclusion criteria were tumor compression of the optic chiasm, resulting in visual field defects, or the presence of signs or symptoms of tumor compression; previous treatment with somatostatin analogs, dopamine agonists, GH receptor antagonists, or radiotherapy within the last 10 years, or for poorly controlled diabetes mellitus (hemoglobin A1c level >8%); and history of transsphenoidal adenomectomy.

The study was approved by the Institutional Review Board of the National Taiwan University Hospital. All the patients provided written informed consent to participate in the trial.

End points

The primary efficacy outcome was surgical cure after presurgical somatostatin analog treatment. Surgical cure was defined as GH < 2.5 μg/L and normal IGF-1 as age- and sex-matched controls after transsphenoidal adenomectomy. Secondary evaluation included analyses of GH < 2.5 μg/L and normal IGF-1 (age and sex matched) at the end of the core and extension periods prior to the operation. Pituitary magnetic resonance imaging for detecting tumor volume was performed at prestudy screening and at follow-up every 6 months. Safety assessments and monitoring of adverse events were performed throughout the study period. Fasting plasma glucose level was assessed once per month, and glycated hemoglobin level, every 3 months.

Hormone assays

GH and IGF-1 levels were assayed using validated chemiluminescent enzyme immunometric assays at the central laboratory of Quest Diagnostics Nichols Institute Laboratory, Chantilly, VA, USA.

Results

Seven patients were recruited in this study, of whom six had macroadenoma and one had microadenoma. Prior to the operation, Patient 2, Patient 3, Patient 5, and Patient 7 received octreotide LAR for 12 months and pasireotide LAR in an extension study for an additional 12 months. In this group, only two patients had GH < 2.5 μg/L and none exhibited normal IGF-1 in the first 12 months of octreotide LAR treatment. After switching to pasireotide LAR in the extension study, three patients had GH < 2.5 μg/L, two patients had normalized IGF-1, and one patient had both GH < 2.5 μg/L and normal IGF-1. The IGF-1 of Patient 7 was elevated under the octreotide LAR treatment and decreased after the treatment was switched to pasireotide LAR (Figure 1A).