Somatostatin Analogs in Ectopic Corticotropin Production

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Eutopic corticotroph pituitary adenomas and adrenal cortisol-producing adenomas do not usually express somatostatin receptors. However, ectopic corticotropin (ACTH)-producing tumors often express somatostatin receptors. Thus, the octreoscan can detect and localize tumors in 80% of patients with ectopic ACTH syndrome, and so it can be used to differentiate between eutopic and ectopic ACTH-dependent bilateral adrenal hyperplasia. Octreotide therapy can produce a rapid and sustained reduction of ACTH and cortisol levels in patients with ectopic ACTH-dependent Cushing's syndrome and, in some, may be the only long-term therapy possible. Although no large series have been reported, a review of the literature reveals a large number of case reports that have demonstrated the effectiveness of octreotide.

THE INTRODUCTION of the somatostatin analog octreotide into clinical medicine has opened up new opportunities for the medical treatment of patients with somatotroph and thyrotroph pituitary adenomas. Octreotide effectively lowers growth hormone (GH) and thyrotropin (TSH) levels in the majority of patients, leading to improvement of quality of life, particularly in patients in whom trans-sphenoidal surgery has been unsuccessful or before the effects of radiotherapy are realized. Although clinically nonfunctioning pituitary adenomas and gonadotropinomas often express somatostatin and octreotide receptors, therapeutic results with long-term therapy with somatostatin analogs are usually disappointing.[1] Somatostatin and octreotide do not inhibit corticotropin (ACTH) secretion from corticotrophinomas, since these tumors usually do not express somatostatin receptors.[2] However, removal of glucocorticoid activity from the incubation medium of these tumors in vitro makes basal- and corticotropin-releasing hormone (CRH)-stimulated ACTH release sensitive to the inhibitory effect of somatostatin and octreotide.[2] In agreement with these in vitro data, somatostatin infusion suppresses elevated ACTH levels in patients with untreated Addison's disease[3] and occasionally in patients with infiltrating ACTH-secreting Nelson tumors, which appear after bilateral adrenalectomy. These studies suggest that in Cushing's syndrome, elevated cortisol levels inhibit the expression of somatostatin receptors of tumorous corticotrophs.[4]

In contrast to these observations in eutopic ACTH hypersecretion due to corticotroph pituitary adenomas, ACTH secretion from nonpituitary tumors is often sensitive to octreotide administration.[4-9] Previous studies have demonstrated that the majority of neuroendocrine tumors, such as carcinoids, islet cell tumors, C-cell tumors of the thyroid, pheochromocytomas, and small-cell lung cancers express somatostatin and octreotide receptors.[1] Since these receptors can be detected in vivo using labeled octreotide, somatostatin receptor scintigraphy (octreoscan) can be used for the occasionally difficult differential diagnosis between eutopic and ectopic ACTH-dependent bilateral adrenal hyperplasia.[1,12] Thus, in contrast to patients with Cushing's disease with a corticotroph pituitary adenoma or patients with Cushing's syndrome due to autonomous cortisol-producing adrenal adenomas, in whom no tumor can be visualized with somatostatin receptor scintigraphy, tumors can be detected and localized in 80% of patients with ectopic ACTH syndrome or even the rare CRH syndrome.[1]

The octreoscan was found to be negative in patients with small-cell lung cancers that were devoid of octreotide receptors in vitro after successful chest surgery.[1] It is not clear whether the excess cortisol secretion induced by ectopic ACTH hypersecretion will also have an inhibitory effect on somatostatin receptor expression in these neuroendocrine tumors. Studies with adrenolytic agents or cortisol receptor antagonists (RU 486) have been performed.[1] However, it is too early to determine whether these compounds have a beneficial effect on sustaining somatostatin receptor expression. On the other hand, these compounds may be useful as an early medical treatment in those patients who have life-threatening complications due to hypercortisolism.

The results achieved with somatostatin receptor scintigraphy can also be extrapolated to the results of medical therapy of ACTH-dependent hypercortisolism. Whereas somatostatin analogs have no place in the treatment of Cushing's disease due to eutopic ACTH hypersecretion,[2] they are occasionally useful in the management of the ectopic ACTH syndrome. Although no large series have been reported, a review of the literature reveals a large number of case reports,[10-14] which have demonstrated the effectiveness of octreotide (Table 1).

This has also been demonstrated in the case of a young girl, who initially had a bronchial carcinoid-producing ACTH tumor leading to Cushing's syndrome. The tumor was removed by thoracotomy and the patient seemed to be cured. During her first pregnancy 2 years later, Cushing's syndrome recurred, although the localization of the tumor responsible for elevated ACTH levels could not be detected. She was treated with octreotide for more than 1

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0026-0495/96/4508-0040$03.00/0

Table 1. Effect of Octreotide on the Ectopic ACTH Syndrome

Author	Tumor	Dose (μg)	Treatment Duration	Cortisol		ACTH	
				Reduced by 50%	Reduced to Normal	Reduced by 50%	Reduced to Normal
Souquet et al (1987)	Gastrinoma	100 tid	3 days	No	No	No	No
Ruszniewski et al (1988)	Gastrinoma	50 tid	37 weeks	Yes	Yes	Yes	Yes
Lamberts et al. (1988)	Gastrinoma	330/d	6 months	Yes	Yes	Yes	Yes
Bertagna et al (1988)	Gastrinoma	150-600/d	4 months	Yes	Yes	Yes	Yes
Hearn et al (1988)	Bronchial carcinoid	100 tid	10 weeks	Yes	Yes	Yes	Yes
Johansen et al (1988)	Bronchial carcinoid	50 stat	Single dose	—	—	Yes	No
Burrel et al (1989)	Thymic carcinoid	50-1,000/d	34 days	No	No	No	No
Invitti et al (1990)	Hepatocellular carcinoma	100-600/d	24 days	Yes	No	Yes	No
Cheung & Boyages (1990)	1 bronchial carcinoid, 1 not identified	300/d	6 days	No	No	No	No
Müller & von Werder (1992)	Bronchial carcinoid	Up to 1,500/d	1 year	Yes	Yes	Yes	Yes
de Rosa et al (1993)	Bronchial carcinoid	300/d	54 weeks	Yes	No	Yes	No
Woodhouse et al (1993)	1 islet cell tumor, 3 biochemically proven ectopic ACTH syndrome	500 tid	Up to 20 days	Yes (3)	Yes (3)	Yes	Yes
Philipponneau et al. (1994)	Bronchial carcinoid	800-1,200/d	30 days	Yes	Yes	Yes	No

Abbreviation: tid, thrice daily.

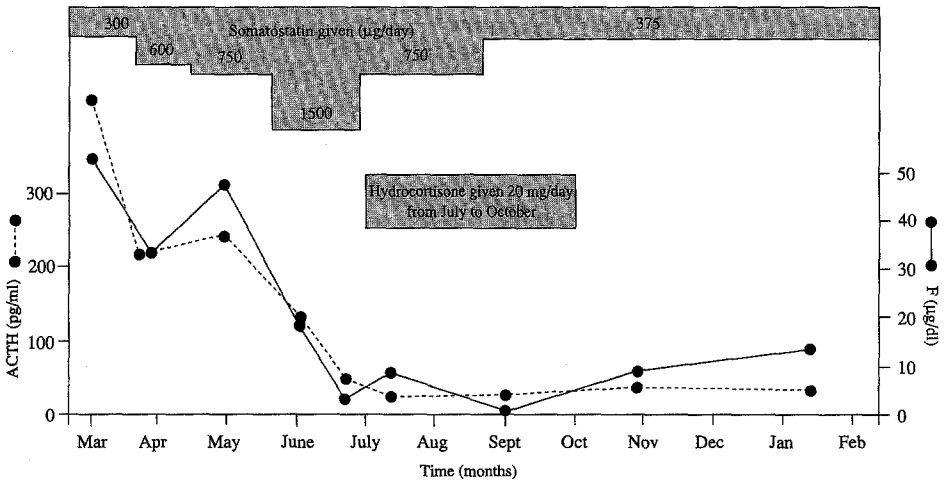

Fig 1. Ectopic ACTH syndrome in a 23-year-old woman with recurrence of hypercortisolism 2 years after removal of a bronchial carcinoid. She developed adrenal failure after increasing the octreotide dosage up to 3 × 500 μg/d.[5]

year, which controlled ACTH hypersecretion from the unknown source and hypercortisolism (Fig 1). In fact, there was a period of several months during which we had to give her substitute therapy with cortisol, because of oversuppression of ectopic ACTH secretion. Only single cases are usually reported and articles have appeared with case reports demonstrating that octreotide failed to control biochemical and clinical features of hypercortisolism.[15,16] This may be biassed opinion about the efficacy of octreotide in treating the ectopic ACTH syndrome.[16]

However, in summary, we can confidently state that octreotide can produce a rapid and sustained reduction of ACTH and cortisol levels in a large number of patients with ectopic ACTH-dependent Cushing's syndrome. In some patients with these semimalignant tumors, octreotide may be the only long-term therapy possible. This therapy may be even more attractive when depot preparations become generally available. In addition, a trial of octreotide may be useful in the differential diagnosis of ACTH hypersecretion when receptor scintigraphy with labeled octreotide is not available.[9]

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