

CENTRAL HYPOTHYROIDISM ASSOCIATED
WITH RETINOID X RECEPTOR-SELECTIVE LIGANDSSTEVEN I. SHERMAN, M.D., JAYASHREE GOPAL, M.D., BRYAN R. HAUGEN, M.D., ALICE C. CHIU, M.D.,
KEVIN WHALEY, M.D., PREM NOWLAKHA, M.D., AND MADELEINE DUVIC, M.D.**ABSTRACT**

Background The occurrence of symptomatic central hypothyroidism (characterized by low serum thyrotropin and thyroxine concentrations) in a patient with cutaneous T-cell lymphoma during therapy with the retinoid X receptor-selective ligand bexarotene led us to hypothesize that such ligands could reversibly suppress thyrotropin production by a thyroid hormone-independent mechanism and thus cause central hypothyroidism.

Methods We evaluated thyroid function in 27 patients with cutaneous T-cell lymphoma who were enrolled in trials of high-dose oral bexarotene at one institution. In addition, we evaluated the *in vitro* effect of triiodothyronine, 9-*cis*-retinoic acid, and the retinoid X receptor-selective ligand LGD346 on the activity of the thyrotropin β -subunit gene promoter.

Results The mean serum thyrotropin concentration declined from 2.2 mU per liter at base line to 0.05 mU per liter during treatment with bexarotene ($P < 0.001$), and the mean serum free thyroxine concentration declined from 1.0 ng per deciliter (12.9 pmol per liter) at base line to 0.45 ng per deciliter (5.8 pmol per liter) ($P < 0.001$) during treatment. The degree of suppression of thyrotropin secretion tended to be greater in patients treated with higher doses of bexarotene (> 300 mg per square meter of body-surface area per day) and in those with a history of treatment with interferon alfa. Nineteen patients had symptoms or signs of hypothyroidism, particularly fatigue and cold intolerance. The symptoms improved after the initiation of thyroxine therapy, and all patients became euthyroid after treatment with bexarotene was stopped. *In vitro*, LGD346 suppressed the activity of the thyrotropin β -subunit gene promoter in thyrotrophs by as much as 50 percent, an effect similar to that of triiodothyronine and 9-*cis*-retinoic acid.

Conclusions Hypothyroidism may develop in patients with cutaneous T-cell lymphoma who are treated with high-dose bexarotene, most likely because the retinoid X receptor-selective ligand suppresses thyrotropin secretion. (N Engl J Med 1999;340:1075-9.)

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THE secretion of thyrotropin and therefore of thyroid hormone is regulated by triiodothyronine bound to a thyroid hormone receptor, acting at a response element near the transcription start site of the thyrotropin β -subunit gene and perhaps involving interaction with nuclear cofactors, including the retinoid X receptor. Other hormones known to affect the production and release of thyrotropin include thyrotropin-releasing hormone, glucocorticoids, dopamine, and somatostatin. Studies in animals have suggested that pharmacologic amounts of retinoids may decrease serum thyrotropin concentrations, but clinical hypothyroidism has not been described as a consequence of this decrease.¹⁻³ *In vitro*, 9-*cis*-retinoic acid partially inhibits the activity of the thyrotropin β -subunit gene promoter, possibly through its ability to activate retinoid X receptors and bind to specific DNA response elements upstream from both the thyroid hormone response element and the transcription start site.²

The efficacy and safety of treatment with bexarotene, a ligand whose specificity for retinoid X receptors is 100 times that for retinoic acid receptors, for a variety of tumors is being investigated.⁴⁻¹⁰ We assessed a cohort of patients with cutaneous T-cell lymphoma who were receiving bexarotene and who had evidence of reversible central hypothyroidism (suppression of both thyrotropin and thyroxine secretion) and, in most cases, symptoms and signs of thyroid hormone deficiency.

METHODS**The Index Patient**

The index patient was a 76-year-old man who had been given a diagnosis of mycosis fungoides in 1982. He had previously received topical therapy with a glucocorticoid, mechlorethamine hydrochloride, and bexarotene (Targretin, Ligand Pharmaceuticals, San Diego, Calif.); systemic therapy with pentostatin, interferon alfa, isotretinoin, cyclophosphamide, methotrexate, etoposide, and dexamethasone; and electron-beam radiotherapy. Because of progressive disease, he was enrolled in an open-label study of oral bexarotene at a dosage of 650 mg per square meter of body-surface area per day. Before enrollment, his only symptoms that were suggestive of thyroid dysfunction were chronic constipation and impaired hearing, and no goiter was palpable.

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At enrollment, his serum thyrotropin concentration was 7.6 mU per liter (normal, 0.3 to 5.0), and his serum thyroxine concentration was 5.3 μ g per deciliter (68 nmol per liter; normal, 4.5 to 12 μ g per deciliter [58 to 154 nmol per liter]). During the first two weeks of bexarotene therapy, cold intolerance, depression, and fatigue developed. On day 15, the serum thyrotropin concentration was 0.48 mU per liter, and serum thyroxine could not be measured because of lipemia. Bexarotene was discontinued, and within two weeks, the patient's symptoms had resolved, his serum thyrotropin concentration was 10.5 mU per liter, and his serum free thyroxine concentration was 0.8 ng per deciliter (10.3 pmol per liter; normal, 0.9 to 1.8 ng per deciliter [11.6 to 23.2 pmol per liter]). Treatment with bexarotene was resumed at a dose of 500 mg per square meter per day, but the symptoms of hypothyroidism returned 19 days later, and the serum thyrotropin and free thyroxine concentrations were both low. The patient's symptoms improved after treatment with thyroxine. After further disease progression, bexarotene was discontinued, after which he became clinically and biochemically euthyroid.

Because of this patient's clinical course, we hypothesized that high doses of a retinoid X receptor-selective ligand such as bexarotene could cause central hypothyroidism.

Other Patients

We subsequently studied 23 additional patients with advanced cutaneous T-cell lymphoma who were also participating in the open-label study of high-dose oral bexarotene. The inclusion criteria were stage IIB to IVB disease according to the tumor-node-metastasis (TNM) system without central nervous system involvement, lack of response to or progressive disease despite systemic treatment, and a Karnofsky performance score of at least 60 (on this scale, 0 represents death and 100 represents normal health). The starting dose of bexarotene was initially 650 mg per square meter, but because of the high frequency of leukopenia and hypertriglyceridemia it was decreased stepwise to 300 mg per square meter. The patients were evaluated two and four weeks after the initiation of therapy and every four weeks thereafter as long as treatment with bexarotene was continued. Treatment was withheld in the event of grade 3 (moderate) or grade 4 (severe) adverse effects, according to the Common Toxicity Criteria of the National Cancer Institute, or hypertriglyceridemia (serum triglyceride concentration above 1200 mg per deciliter [13.5 mmol per liter]); once the effects subsided, subsequent doses of bexarotene were reduced. Bexarotene was discontinued when it was no longer deemed to be effective.

We also studied 10 patients with early cutaneous T-cell lymphoma (TNM stage IA to IIA) who were participating in an open-label multicenter trial of oral bexarotene. Three patients were receiving a low dose of 6.5 mg of bexarotene per square meter, and seven were receiving a high dose of 650 mg per square meter. The inclusion criteria for this study were acceptable performance status and general health together with lack of response to or progressive disease despite treatment with at least two of the following: oral methoxsalen (psoralen) and ultraviolet A radiation, electron-beam radiotherapy, interferon alfa, and topical mechlorethamine hydrochloride. All three patients who received low-dose bexarotene had disease progression and were switched to high-dose therapy, with follow-up studies and adjustments in the dose according to the protocol for the advanced stage of the disease.

Both studies were approved by the surveillance committee of the M.D. Anderson Cancer Center, and informed consent was obtained from each patient. The results of the clinical trials of bexarotene therapy for cutaneous T-cell lymphoma will be reported later.

Hormone Analyses

Serum samples were assayed at the time of collection. Serum free thyroxine was measured by a direct chemiluminescence immunoassay (Chiron Diagnostics, Norwood, Mass.) in which the normal range was 0.9 to 1.8 ng per deciliter (11.6 to 23.2 pmol per liter). Serum triiodothyronine was measured by chemiluminescence immunoassay (Chiron), with a normal range of 80 to 181 ng per deciliter (1.2 to 2.8 nmol per liter). Serum thyrotropin was measured by a chemiluminescence immunoassay (Chiron) in which the normal range was 0.5 to 5.0 mU per liter. Antithyroid peroxidase antibodies were assayed by a radioimmunoassay (Kronus, San Clemente, Calif.) with a limit of sensitivity of 0.3 U per milliliter. The interassay coefficients of variation were 7 percent for serum free thyroxine, 5 percent for triiodothyronine, 3 percent for thyrotropin, and 3 percent for antithyroid peroxidase antibodies.

TABLE 1. THYROID FUNCTION AT BASE LINE AND DURING THERAPY WITH BEXAROTENE IN 27 PATIENTS WITH CUTANEOUS T-CELL LYMPHOMA.

VARIABLE*	BASE LINE	BEXAROTENE THERAPY	P VALUE†
Serum thyrotropin (mU/liter)			
Geometric mean	2.2	0.05‡	<0.001
95% Confidence interval	1.7–2.8	0.03–0.08	
Serum free thyroxine (ng/dl)	1.0±0.1	0.45±0.18‡	<0.001
Serum triiodothyronine (ng/dl)	131±24	82±20‡	<0.001
Serum antithyroid peroxidase antibodies (% of patients)	25	25	

*Plus-minus values are means \pm SD. To convert values for serum free thyroxine to picomoles per liter, multiply by 12.87, and to convert values for serum triiodothyronine to nanomoles per liter, multiply by 0.015.

†Statistical analysis was performed with Student's t-test.

‡This value represents the nadir.

cence immunoassay (Chiron), with a normal range of 80 to 181 ng per deciliter (1.2 to 2.8 nmol per liter). Serum thyrotropin was measured by a chemiluminescence immunoassay (Chiron) in which the normal range was 0.5 to 5.0 mU per liter. Antithyroid peroxidase antibodies were assayed by a radioimmunoassay (Kronus, San Clemente, Calif.) with a limit of sensitivity of 0.3 U per milliliter. The interassay coefficients of variation were 7 percent for serum free thyroxine, 5 percent for triiodothyronine, 3 percent for thyrotropin, and 3 percent for antithyroid peroxidase antibodies.

Transient Transfection Studies

TtT-97 thyrotropic tumors were propagated in hypothyroid LAF-1 mice, primary cell cultures were prepared, and transient transfection assays were performed as previously described.¹¹ The LAF-1 mice used in these studies were treated in accordance with National Institutes of Health guidelines on animal use and care. A total of 20 μ g of the murine thyrotropin β (–390 to +40) promoter-luciferase reporter plasmid and 1 μ g of pCMV β -galactosidase plasmid (added to adjust for the efficiency of transfection) were transfected by electroporation into 7 million to 10 million TtT-97 cells. The cells were then incubated at 37°C for 16 hours in Dulbecco's modified Eagle's medium with charcoal-filtered 10 percent fetal-calf serum in the absence or presence of triiodothyronine (Sigma, St. Louis), 9-*cis*-retinoic acid (Sigma), and LGD346 (Ligand Pharmaceuticals), a second-generation retinoid X receptor-selective ligand with even greater specificity than bexarotene (Heyman R: unpublished data). The cells were harvested, extracted by cycles of freezing and thawing, and assayed for both luciferase and β -galactosidase as previously described.¹² Each transfection assay was performed in four to eight replicates.

Statistical Analysis

Statistical analyses were performed with paired Student's t-tests, analysis of variance, or Wilcoxon rank tests, as appropriate. Serum thyrotropin values were logarithmically transformed to stabilize variance and reduce skewness. Analyses were performed with JMP software (version 3.0.1, SAS Institute, Cary, N.C.). Unless otherwise noted, the results are presented as means \pm SD. All statistical tests were two-sided. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Of the 34 patients who received high-dose bexarotene for cutaneous T-cell lymphoma, 27 (14 men

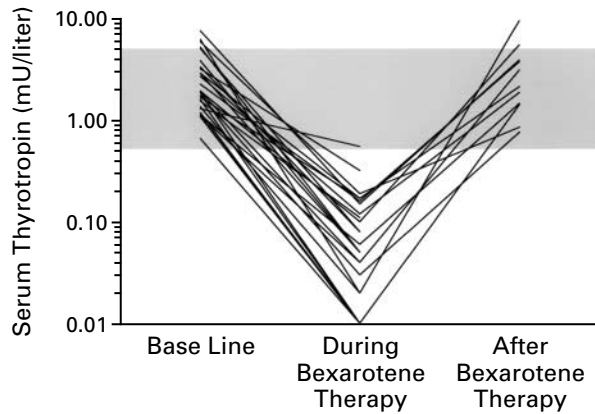


Figure 1. Serum Thyrotropin Concentrations in 27 Patients with Cutaneous T-Cell Lymphoma Treated with Bexarotene.

In each patient, serum thyrotropin was measured before treatment with bexarotene, periodically during treatment, and at least four weeks after the discontinuation of bexarotene. Values obtained during therapy represent the nadir. The shaded region represents the normal range for serum thyrotropin values.

and 13 women) had a base-line assessment of thyroid function and at least one subsequent assessment. The mean age of these 27 patients was 65 ± 14 years. No patient was receiving thyroid hormone therapy at the time of the initiation of bexarotene treatment. The results of thyroid-function studies at base line in these 27 patients are shown in Table 1. Five patients had slightly elevated serum concentrations of thyrotropin (5.1 to 7.6 mU per liter), all of whom also had elevated serum concentrations of antithyroid peroxidase antibody.

Thyroid Function during Bexarotene Therapy

The results of thyroid-function studies during bexarotene therapy are shown in Table 1. All patients were ambulatory outpatients at the time of blood sampling. In 26 patients, serum thyrotropin concentrations declined below normal during therapy (Fig. 1). The decrease in serum thyrotropin concentrations, expressed as the ratio of the nadir value to the base-line value, was greater in patients who received higher doses of bexarotene (>300 mg per square meter per day) (Fig. 2). Two patients were given thyrotropin-releasing hormone, which increased serum thyrotropin concentrations by a factor of approximately 10. The serum concentrations of free thyroxine and, to a lesser degree, triiodothyronine also declined during therapy with bexarotene.

Nineteen patients reported symptoms or had signs of hypothyroidism that were not present at base line (Table 2). In some patients, cold intolerance was occasionally severe enough to necessitate turning off the air conditioning during the summer months. One patient noted that palpitations associated with

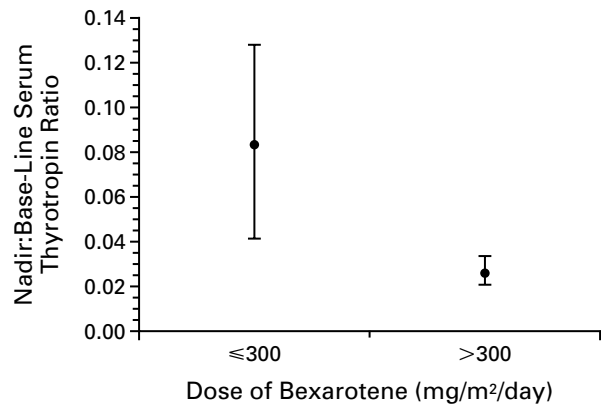


Figure 2. Mean (\pm SE) Decrease in Serum Thyrotropin Secretion as a Function of the Dose of Bexarotene.

The decrease in serum thyrotropin concentrations is expressed as the mean ratio of the nadir value to the base-line value, as a function of the dose of bexarotene at the time of the nadir value. $P=0.08$ by Student's t-test.

chronic atrial fibrillation disappeared during treatment with bexarotene and recurred once treatment was discontinued. Seventeen of the patients with symptoms were treated with thyroxine (mean daily dose, $93 \mu\text{g}$; range, 25 to 200), of whom 15 reported improvement in their symptoms. No patient reported symptoms of other types of pituitary dysfunction, but no additional hormonal studies were done.

Thyroid Function after Bexarotene Therapy

Eleven patients were studied after bexarotene was discontinued. Among the 10 patients who had nor-

TABLE 2. SYMPTOMS AND SIGNS CONSISTENT WITH THE PRESENCE OF HYPOTHYROIDISM DURING BEXAROTENE THERAPY IN 27 PATIENTS WITH CUTANEOUS T-CELL LYMPHOMA.

SYMPTOM OR SIGN	NO. OF PATIENTS
Easy fatigability	18
Cold intolerance	13
Impaired cognition	7
Constipation	5
Delayed relaxation of deep-tendon reflexes	4
Depression	3
Edema of legs	3
Myalgia	2
Hoarseness	2
Hearing impairment	2
None	8

mal thyroid function at base line, serum thyrotropin concentrations returned to normal in 9 (Fig. 1); this recovery occurred as early as eight days after bexarotene was discontinued. In patients with high serum thyrotropin concentrations at base line, thyroxine therapy was continued.

Effect on Thyroid Function of Prior Interferon Alfa Therapy

Twenty-one patients had previously received interferon alfa therapy, five of whom (24 percent) had high serum concentrations of antithyroid peroxidase antibodies at base line. Four of these patients were in the subgroup with slightly elevated serum thyrotropin concentrations at base line, but only one patient had a low serum free thyroxine concentration. In these 21 patients, the nadir serum concentrations of free thyroxine were 55 percent lower during bexarotene therapy than at base line, as compared with a decrease of 44 percent in the patients who had not previously received interferon alfa ($P=0.14$).

Effect of Retinoids on the Activity of the Thyrotropin β -Subunit Gene Promoter in Thyrotrophs

To correlate these observations with a potential molecular mechanism, TtT-97 thyrotroph tumor cells were transiently transfected with a thyrotropin β promoter–luciferase reporter plasmid. The transfected cells were incubated with triiodothyronine, 9-*cis*-retinoic acid (which binds to both retinoic acid and retinoid X receptors), or LGD346, a retinoid X receptor–selective ligand. The activity of the thyrotropin β -subunit gene promoter was suppressed by 53 percent by triiodothyronine and by 52 percent by 9-*cis*-retinoic acid (Fig. 3), as reported in a previous study.² LGD346 decreased the activity of the thyrotropin β -subunit gene promoter by as much as 50 percent.

DISCUSSION

We found that the retinoid X receptor–selective ligand bexarotene caused reversible central hypothyroidism in patients with cutaneous T-cell lymphoma. The decrease in serum thyrotropin concentrations was greater in patients who received higher doses of bexarotene, although this difference did not reach statistical significance, and the *in vitro* studies demonstrated the role of the retinoid X receptor and its ligands in suppressing the activity of the thyrotropin β -subunit gene promoter.² Although low serum thyrotropin and thyroxine concentrations in patients with cancer who are receiving therapy could be due to nonthyroidal illness, our patients were not seriously ill, and their serum triiodothyronine concentrations were relatively normal. The high base-line frequency of mild autoimmune thyroid dysfunction in our patients is typical of patients treated with interferon alfa.¹³ Sixty-seven percent of recent patients with hypothyroidism at our cutaneous T-cell lymphoma clinic had previously received interferon alfa

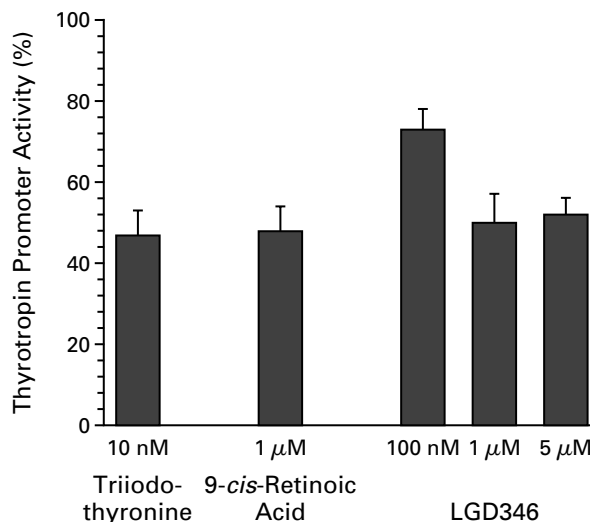


Figure 3. Thyrotropin β -Subunit Gene Promoter Activity in the Presence of Triiodothyronine, 9-*cis*-Retinoic Acid, and LGD346. TtT-97 cells were transfected with a murine thyrotropin β promoter–luciferase reporter plasmid and incubated with triiodothyronine (six replicates), 9-*cis*-retinoic acid (eight replicates), or various concentrations of LGD346, a retinoid X receptor–selective ligand (four replicates at each concentration). The results are presented as means (+SE) of the percentage of promoter activity in the absence of any ligand.

(unpublished data). Although some patients had no symptoms of hypothyroidism, most reported characteristic symptoms, such as cold intolerance and fatigue, that responded to thyroxine therapy.

These observations contrast with findings of a phase 1–2 trial that suggested that bexarotene therapy does not affect the pituitary–thyroid axis⁹; however, the doses of bexarotene given to most patients in that trial were lower than those used in our study. Moreover, the patients in that study had a heterogeneous group of malignant diseases, although nine of them had cutaneous T-cell lymphoma. In contrast, all our patients had cutaneous T-cell lymphoma, a rare disease that ranges from an indolent proliferation of epidermotropic T cells (mycosis fungoides) to erythrodermic leukemia (Sézary syndrome).^{14–16} Further study will be required to determine whether hypothyroidism develops during treatment with retinoid X receptor–selective ligand in patients with other cancers,^{9,10,17} hyperlipidemia,¹⁸ or diabetes mellitus.¹⁹

The suppressive effect of both all-*trans*-retinoic acid and 9-*cis*-retinoic acid on the activity of the thyrotroph-specific thyrotropin β -subunit gene promoter has been traced to a promoter region distinct from the area near the transcription start site that is thought to mediate the suppressive effect of triiodothyronine.^{1,2,20} Our data indicate that a retinoid X receptor–selective ligand may also mediate the suppression of the activity of the thyrotropin β -sub-

unit gene promoter, suggesting that ligand binding to the retinoid X receptor is sufficient to mediate this effect. Given that coincubation with 9-*cis*-retinoic acid and triiodothyronine resulted in greater suppression of the activity of the thyrotropin β -subunit gene promoter,² retinoid X receptor-mediated suppression of thyrotropin may be additive to that due to the triiodothyronine receptor.²⁰ However, a retinoid X receptor-mediated effect on the regulation of thyrotropin secretion by thyrotropin-releasing hormone cannot be ruled out.²¹ What is unlikely, given the symptoms of hypothyroidism reported by so many of our patients, is that bexarotene bound to retinoid X receptor activates triiodothyronine receptor-retinoid X receptor heterodimers and mediates the activation of thyroid hormone response elements on DNA.²²

In summary, retinoid X receptor-selective ligands can suppress thyrotropin secretion, resulting in central hypothyroidism. In a cohort of patients with cutaneous T-cell lymphoma who were treated with high-dose bexarotene, the effect was clinically important, requiring concurrent therapy with thyroxine.

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