EUTHYROID PATIENTS WITH CHRONIC HEPATITIS C TREATED WITH PEGYLATED INTERFERON ALFA AND RIBAVIRIN SHOW SIMILAR CHANGES IN CELLS THAT COORDINATE IMMUNE RESPONSES AND MAINTAIN IMMUNOLOGIC TOLERANCE, BUT DISPLAY A SPECTRUM OF DIFFERENT THYROID DISEASES

Soldevila B, Alonso N, Martínez-Arconada M J, Morillas RM, Granada, M L, Planas R, Pujol-Borrell R, Martínez-Cáceres E, Sanmartí A. A prospective study of T- and B-lymphocyte subpopulations, ThI/Th2 balance and regulatory CD4+CD25+CD127low/-FoxP3+ T cells in patients with chronic hepatitis C virus infection developing interferon-induced thyroiditis. Clin Endocrinol (Oxf). May 19, 2011 [Epub ahead of print]. doi: 10.1111/j.1365-2265.2011.04112.x.

SUMMARY • • • • • • • •

BACKGROUND

Interferon-alfa treatment can precipitate a wide spectrum of thyroid diseases in susceptible individuals, probably through actions on the immune system as well as through toxic effects on the thyroid, but the precise mechanisms and/or genetic propensities involved remain unknown.

METHODS

A total of 120 Spanish patients with chronic hepatitis C who had never undergone treatment were given weekly peginterferon alfa-2a plus ribavirin 1 to 1.2 g daily for 48 weeks (for patients with hepatitis C virus [HCV] genotype 1 or 4) or plus ribavirin 0.8 g daily for 24 weeks (for HCV genotype 2 or 3). They were then were followed for 24 weeks to determine whether their HCV RNA levels remained suppressed. All patients had normal thyroid-function tests and negative antithyroid tests at baseline. Any patient who was positive for hepatitis B surface antigen, had alcoholism, was an intravenous-drug abuser, or had the human immunodeficiency or other virus was excluded from the study. Peripheral-blood mononuclear cells (PBMCs) were prepared and frozen at the beginning of the study, at the midpoint of treatment, at the end of treatment, and 24 weeks after the end of treatment.

Some form of thyroid disease developed in 11 patients: 5 had destructive thyroiditis, 3 had Hashimoto's

thyroiditis, 1 was euthyroid but had positive antithyroid antibodies, 1 had Graves' disease, and 1 had non-autoimmune hypothyroidism. Additional PBMCs were drawn when thyroid disease was detected. Eleven patients who had undergone the same treatments were retrospectively selected to be controls, based on the sex and age of the patients in whom thyroid disease had developed. The controls apparently were not matched based on body-mass index or smoking status.

RESULTS

Flow cytometry was performed on PBMCs obtained from patients when their thyroid diseases appeared, and the lymphocyte populations were compared with the PBMCs obtained from the matched controls at the midpoint of their treatment. The PBMC's obtained from the patients upon the development of thyroid disease displayed a higher response in type 1 helper T (Th1) cells, which coordinate immune responses, and a greater percentage of natural T regulatory cells, which maintain immunologic tolerance. No differences in lymphocyte populations were detected among the different thyroid diseases that developed. Development of thyroid disease was not associated with the patients' antiviral responses.

CONCLUSIONS

Peginterferon alfa-2a plus daily ribavirin affected Th1 cell responses and the percentage of T regulatory cells in patients in whom a variety of thyroid diseases developed.

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COMMENTARY • • • • •

Prior to therapy, some patients with hepatitis Calready have positive antithyroid antibody levels, although the percentage varies according to the assays used, the geographic location, and the genetic makeup of the population under study. Products from a variety of viruses, including hepatitis C, have been detected in thyroid tissue from patients with Hashimoto's thyroiditis, so it is possible that antiviral responses could be involved in the induction of thyroid diseases in some of these individuals. However, the patients in the study under discussion did not have antithyroid antibodies or altered thyroid function before they started treatment, so it would seem reasonable to attribute the thyroid diseases that appeared to the therapy they received. Boceprevir, a new anti-HCV drug, was recently studied in a larger group of patients

with chronic HCV infection who had a TSH of 0.8 to 1.2 times normal or who were clinically euthyroid with a normal serum T_3 and T_4 levels at the start of the study (1). In the group of 363 patients who were given the standard peginterferon/ribavirin regimen, only 1 had hypothyroidism, while none of the 368 patients given boceprevir along with peginterferon/ribavirin for 24 weeks became hypothyroid. Assuming the assays used and the follow-up periods were reasonably similar to those in the study under discussion, the patients in the two studies seemed to differ greatly in their susceptibility to peginterferon/ribavirin-induced thyroid disease. Nonetheless, boceprevir may hold promise for an anti-HCV regimen that will cause less thyroid disease in euthyroid patients with hepatitis C.

- Stephen W. Spaulding, MD

REFERENCE

 Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-206.