Optimal TSH Suppression in Thyroid Ca Varies

ARTICLES BY BRUCE JANCIN
Denver Bureau

CHICAGO — An individually tailored approach to providing thyroid hormone replacement in thyroid cancer patients should be guided by the findings of several key studies, according to endocrinologist Giuseppe Barbesino.

The evidence at hand doesn't permit sweeping generalizations about what the target TSH level should be, said Dr. Barbesino of Harvard University, Boston.

He said that one important study that has influenced his thinking was led by Dr. Jacqueline Jonklaas of Georgetown University, Washington. She and her coinvestigators analyzed a prospective multicenter registry and showed for the first time that it isn't necessary to drive TSH levels below 0.1 mIU/L to improve overall survival in patients with stage II thyroid cancer. Survival can be improved in such patients with moderate TSH suppression in the range of 0.1 but less than 0.5 mIU/L (Thyroid 2006;16:1229-42).

That's an important observation because aggressive TSH suppression to less than 0.1 mIU/L in patients with differentiated thyroid cancer carries several downsides. It is associated with an increased risk of new-onset atrial fibrillation, an increase in left ventricular mass index and other echocardiographic abnormalities, and some as-yet-inconclusive evidence suggesting increased risks of cardiovascular mortality, fracture, and decreased bone mineral density, Dr. Barbesino noted at a satellite symposium held in conjunction with the annual meeting of the American Thyroid Association.

The abnormalities of cardiac structure and function associated with TSH suppression in thyroid cancer patients are subtle. Their clinical significance remains unclear, he said. But it's noteworthy that investigators at the University of Cagliari (Italy) have demonstrated that these abnormalities—including left ventricular posterior wall thickening, increased intraventricular septum thickness, increased left ventricular end-diastolic dimension, and an associated diminished exercise tolerance—are reversible by titrating the levothyroxine dose down to the minimum still capable of inducing TSH suppression (J. Clin. Endocrinol. Metab. 2000;85:159-64). This is a practice well worth following, the endocrinologist continued at the symposium supported by Abbott Laboratories, maker of a test for TSH.

Whether TSH suppression with levothyroxine does indeed reduce bone mineral density and increase fracture risk remains an open question.

"I've looked at meta-analyses that included studies from the same period and came to almost diametrically opposite conclusions as to whether TSH suppression is a serious risk factor for fractures," Dr. Barbesino said.

He suggested the following individually tailored approach to TSH suppression in thyroid cancer patients: Reserve aggressive TSH suppression to less than 0.1 mIU/L for patients with high-risk stage III-IV or incurable tumors, since that approach has been shown to improve overall survival.

Consider a target level of 0.1 to less than 0.5 mIU/L in patients with low-risk tumors prior to restaging, and in patients with high-risk tumors who have had several years with no disease activity, particularly if the patients are over age 60, when the increased risk of atrial fibrillation and other side effects associated with aggressive TSH suppression are likely to be most damaging.

Reserve mild TSH suppression to a target of 0.5 to less than 2.5 mIU/L for patients with microcarcinomas or tumors who are deemed low risk following negative restaging.

Dr. Barbesino added that he tries to avoid TSH levels of 2.5 mIU/L or more in thyroid cancer patients. He said he is especially careful to keep levels under 5.0 mIU/L because values above that are associated with rapid growth of metastases.

Naturally occurring hyperthyroidism has been far more extensively studied than TSH suppression with levothyroxine in thyroid cancer patients. Key unresolved questions for future research include whether the clinical impact of these two forms of TSH suppression is similar, whether TSH suppression in cancer patients can be stopped at some point without increasing the risk of relapse, and whether the adverse effects of TSH suppression in cancer patients can be mitigated with β-blockers, bisphosphonates, or other therapies, Dr. Barbesino said.

He disclosed having received honoraria from Genzyme Corp., maker of Thyrogen (thyrotropin alfa for injection). ■

High TSH Level May Enhance Brachial Artery Endothelial Flow

CHICAGO — Injection of recombinant human thyroid-stimulating hormone causes a marked and persistent improvement in brachial artery endothelial flow-mediated dilation, without affecting heart rate, blood pressure, or echocardiographic parameters, a small study has shown.

The clinical implication of this finding is that the well-established increased cardiovascular risk associated with hypothyroidism can't be explained by the elevated thyroid-stimulating hormone (TSH) levels accompanying this form of thyroid dysfunction. Indeed, TSH is, if anything, antiatherogenic, Dr. Raffaele Napoli reported at the annual meeting of the American Thyroid Association.

Increased CV risk associated with hypothyroidism can't be explained by elevated TSH levels.

DR. NAPOLI

He studied 34 patients with a history of total thyroidectomy for well-differentiated thyroid cancer who received injections of recombinant human thyroid-stimulating hormone on 2 consecutive days, followed by ultrasound assessment of brachial artery flow-mediated dilation (FMD) at 6, 24, 30, and 48 hours and again 5 days after the first injection. In addition, subjects underwent echocardiographic exams at baseline and at 24 hours, had Holter monitoring, and gave blood samples at baseline and at days 2 and 5.

FMD rose by nearly 60% from a baseline of 10.2% to 16.1% at 24 hours and remained elevated at 14.9% all the way out to day 5. The increase in FMD, seen in 33 of the 34 subjects, correlated closely with serum TSH level, which climbed from 0.07 mIU\L at baseline to 147 mIU/L on day 2 and was still high at 15 mIU/L on day 5. Free T_3 and free T_4 levels were normal at baseline and remained unchanged during follow-up, said Dr. Napoli of the University of Naples (Italy).

Echocardiography and Holter monitoring demonstrated that the rise in circulating TSH did not affect heart rate, blood pressure, left ventricular ejection fraction or diastolic diameter, or diastolic function, he reported.

In terms of atherogenic biomarkers, homocysteine levels dropped significantly from 14 micromol/L at baseline to 12.5 at 48 hours and 10.9 micromol/L at day 5. The C-reactive protein level also declined, but this trend did not reach statistical significance. Levels of the inflammatory biomarkers tumor necrosis factor–α, interleukin-6, and vascular cell adhesion molecule–1 remained unchanged from baseline.

Audience members asked why hypothyroidism increases cardiovascular risk, given the salutary effects a high TSH level apparently has on flow-mediated dilation. The endocrinologist replied that the multiple negative effects of the low free T_4 level that also defines the hypothyroid state trump the high TSH.

"Thyroid hormone is a very powerful hormone, so when you get a decrease in thyroid hormone level, that predominates," Dr. Napoli explained.

One audience member, noting that homocysteine levels are related to folic acid metabolism, said it is not plausible that homocysteine would drop so quickly—within 2 days—in response to administration of recombinant human TSH. Dr. Napoli said he, too, was dubious about that particular finding. ■

Once-Weekly Levothyroxine Deemed Safe and Effective

CHICAGO — Once-weekly levothyroxine administration in hypothyroid women proved to be a safe and well-tolerated alternative to standard daily therapy in a Brazilian randomized trial.

Echocardiographic evaluation showed no differences between the two dosing regimens in terms of cardiovascular function.

And most of the study participants preferred the convenience of once-weekly dosing, Dr. Gisah Carvalho reported at the annual meeting of the American Thyroid Association.

She presented a 12-week, randomized crossover trial in which 19 hypothyroid women spent 6 weeks taking their normal daily levothyroxine dose and another 6 weeks in which they took seven times their regular daily dose once weekly.

Mean serum TSH was significantly higher after 6 weeks of weekly therapy, at 4.41 mIU/L, as compared with 3.38 mIU/L with daily therapy. Free thyroxine was lower: 1.0 ng/dL, as compared with 1.2 ng/dL with daily therapy.

Four hours after once-weekly levothyroxine administration the mean free thyroxine was 1.8 ng/dL, compared with 1.15 ng/dL 4 hours after daily dosing. Total triiodothyronine was unaffected, according to Dr. Carvalho of the Federal University of Paraná, Curitiba, Brazil.

The weekly dosing regimen is particularly appreciated by patients who find adherence to daily therapy challenging.

Dr. Carvalho disclosed no conflicts of interest. ■

Four New Fact Sheets Focus On Thyroid Disorders

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the National Institutes of Health (NIH), has produced four new fact sheets for consumers and health care providers. The subjects of the four publications are hyperthyroidism, hypothyroidism, Graves' disease, and pregnancy and thyroid disease. More information is available at www.niddk.nih.gov. ■