

Despite this, we believe that the frequency of pages sent to the wrong physician is too high and are taking steps to reduce the potential for these errors.

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Rituximab and Thyroid Function

Report of a Case. In August 2006, a 39-year-old woman with rheumatoid arthritis (RA) was seen at the outpatient clinic for exacerbation of RA. In the previous few months, she had progressively swollen and painful joints, notably her wrists, knees, and feet. A review of her medi-

cal history revealed that in addition to an erosive, rheumatoid factor anticitrullinated protein antibody-positive RA since 1995 she had autoimmune hypothyroidism and diabetes mellitus type 1 since 1986. For these conditions she used long-acting (24 U/d) and short-acting (50 U/d) insulin and L-thyroxine (262.5 µg/d). Findings from physical examination were unremarkable except for polyarthritides (shoulders, elbows, wrists, knees, ankles, hands, and feet). Her RA disease activity score of 28 joints (DAS28) was 8.3 (low disease status, DAS28 < 3.2). Type 1 diabetes mellitus and hypothyroidism were in a well-controlled condition (hemoglobin A_{1c} level of 6.8% [reference range, 4.0%-6.0%] [to convert to proportion, multiply by 0.01], thyrotropin (TSH) level of 1.18 mU/L [reference range, 0.35-4.70 mU/L], and free thyroxine [FT₄] level of 20 pmol/L [to convert to nanograms per deciliter, divide by 12.871] [reference range, 10-23 pmol/L]). Because this patient was refractory to tumor necrosis factor-blocking agents (etanercept and infliximab) and disease-modifying antirheumatic drugs (sulfasalazine and methotrexate), B-lymphocyte depletion therapy (rituximab) was started in a 2-week cycle of 1000 mg intravenously, with the addition of 100 mg of methylprednisolone to prevent infusion-related adverse events.

Results. After 3 months of rituximab treatment, this patient was seen at the outpatient clinic of internal medicine for hypothyroidism and diabetes. At that time there were no complaints of palpitations or weight loss. Remarkably, blood test results showed decreased TSH levels (0.24 mU/L), with a FT₄ level in the high-normal range. After 5 and 6 months of treatment there was only a slight improvement of her active RA status, but blood test results revealed clinical hyperthyroidism (TSH, 0.10 mU/L; FT₄, 25 pmol/L, and total triiodothyronine [T₃], 3.1 nmol/L [to convert to nanograms per liter, divide by 0.0154] [reference range, 1.2-2.8 nmol/L]) (**Figure, A**). Both T₃ and FT₄ levels were elevated, indicating that the conversion of thyroxine in T₃ was proceeding accurately. Differential diagnostic considerations explaining the development of hyperthyroidism can be divided into

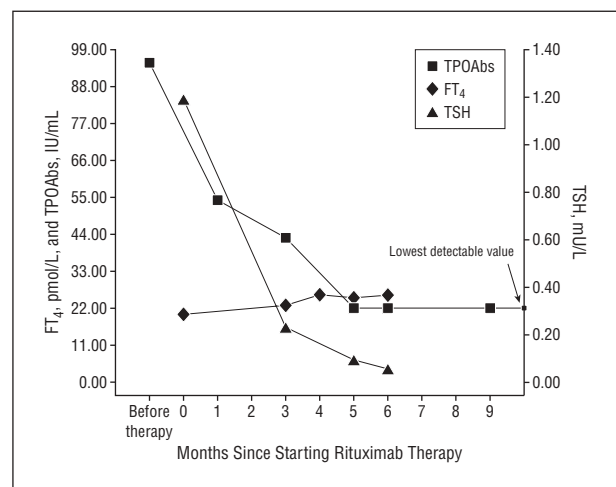


Figure. Thyroid function during 9 months of rituximab therapy. FT₄ indicates free thyroxine; TPOAbs, antibodies against thyroid peroxidase; and TSH, thyrotropin. To convert FT₄ to nanograms per liter, divide by 12.871.

exogenous (eg, pituitary TSH production) and endogenous (eg, Graves disease) causes. Both exogenous (as TSH levels were decreased, with inflated thyroxine levels), and endogenous (such as Graves disease) causes of hyperthyroidism seemed unlikely in this long-standing overt hypothyroid patient. Neither the L-thyroxine dosage nor smoking habits were changed, and the patient's type 1 diabetes mellitus remained in a well-controlled condition (hemoglobin A_{1c} level of 6.5%). Another mechanism that may explain the incidence of hyperthyroidism is an increased activation of thyroid peroxidase (TPO), an enzyme catalyzing reactions for synthesis of T₃ and FT₄. A plausible explanation for elevated TPO activity is a drop in the level of antibodies against TPO (TPOAbs) by rituximab-induced depletion of plasma cell precursors. Indeed, TPOAbs declined to undetectable levels (as measured with the Phadia ImmunoCAP System; Phadia AB, Phadia AB, Uppsala, Sweden) after 5 months of treatment (Figure, A).

Comment. Autoimmune hypothyroidism is characterized by lymphocytic infiltration of the thyroid and the presence of thyroid autoantibodies (eg, TPOAbs).¹ Another autoimmune disease characterized by (synovial) lymphocytic infiltration is RA. Rituximab, a chimeric monoclonal antibody against CD20-positive B lymphocytes, is known to decrease synovial lymphocyte aggregates in patients with RA.² Our hypothyroid diabetic patient with RA developed hyperthyroidism 4 months after initiating rituximab therapy. This is remarkable because rituximab is a novel therapy for patients with Graves disease.³ Interestingly, in NOD.H-2h4 mice exposed to sodium iodide-polluted water to induce spontaneous autoimmune thyroiditis, thyroid autoantibody responses could be reduced by B-cell depletion. Moreover, B-lymphocyte depletion in this murine study resulted in diminished B- and T-lymphocyte infiltration of the thyroid, thereby inhibiting the development of spontaneous autoimmune thyroiditis.⁴ In line with this study, our observation suggests that rituximab therapy may be beneficial for autoimmune hypothyroidism. Although this hypothesis needs confirmation in other studies, in daily clinical practice, clinicians should be aware of (transient) stimulation of thyroid function during rituximab therapy in overt hypothyroid patients.

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COMMENTS AND OPINIONS

Preadmission Use of Statins in Patients With Pneumonia

We commend Thomsen and colleagues¹ for their article about the preadmission use of statins in patients with pneumonia. As discussed by the authors, this article addresses the increasingly recognized role of statins in infectious process.

In a review of Medicare patients older than 65 years, Houck et al² found that administering antibiotics within 4 hours of the patients' arrival resulted in a decrease of mortality and length of stay. In the United States, we follow these guidelines when treating patients with pneumonia. Since the authors did not mention the timing of antibiotic use once a patient is evaluated by a physician, we would like to know if this was included in the analysis.

In a study by Frost et al,³ a statin dose dependence was observed in the reduction of mortality in influenza and chronic obstructive pulmonary disease cases. In the study by Thomsen et al,¹ the dose of statin administered was not clear, and we question whether there was a difference in outcome between intensive vs moderate lipid level lowering with statin use.

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