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.

Brian M. Wong, MD
Sherman Quan, BSc
C. Mark Cheung, MD
Dante Morra, MD, MBA
Peter G. Rossos, MD, MBA
Khalil Sivjee, MD
Robert Wu, MD, MSc
Edward E. Etchells, MD, MSc

Correspondence: Dr Wong, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Room D474, Toronto, ON M4N 3M5, Canada (Brian.M.Wong@sunnybrook.ca).

Author Contributions: All authors have made a substantial, direct, intellectual contribution to this study. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wong, Quan, Morra, Rossos, Wu, and Etchells. Acquisition of data: Wong and Quan. Analysis and interpretation of data: Wong, Quan, Cheung, Sivjee, Wu, and Etchells. Drafting of the manuscript: Wong and Etchells. Critical revision of the manuscript for important intellectual content: Quan, Cheung, Morra, Rossos, Sivjee, Wu, and Etchells. Administrative, technical, and material support: Wong, Quan, Cheung, Morra, Rossos, and Etchells. Study supervision: Morra and Etchells.

Financial Disclosure: None reported.

Funding/Support: This study was funded by the Chair of Medicine/Academic Hospitals Quality and Safety Partners Intramural Grant (Department of Medicine, University of Toronto, Toronto, Ontario, Canada).

Role of the Sponsors: The funding program had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the research letter.

Additional Contributions: Donald Redelmeier, MD, MSc, provided helpful comments on earlier drafts of this research letter and Alex Kiss, PhD, provided assistance with statistical analysis.


**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 medical 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 (26.25 µg/d). Findings from physical examination were unremarkable except for polyarthritis (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 A1c 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 [FT_4] 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 FT_4 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; FT_4, 25 pmol/L, and total triiodothyronine [T_3], 3.1 nmol/L [to convert to nanograms per liter, divide by 0.0154] [reference range, 1.2-2.8 nmol/L]). Both T_3 and FT_4 levels were elevated, indicating that the conversion of thyroxine to T_3 was proceeding accurately. Differential diagnostic considerations explaining the development of hyperthyroidism can be divided into...
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 A1c 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). 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. Our hypertrophic 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. 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. 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.

Hennie G. Raterman, MD
Suat Simsek, PhD, MD
Willem F. Lems, PhD, MD
Eelco W. Meesters, MD
Ben A. C. Dijkmans, MD, PhD
Michael T. Nurmohamed, PhD, MD

Correspondence: Dr Nurmohamed, Departments of Internal Medicine and Rheumatology, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, the Netherlands (mt.nurmohamed@vumc.nl).

Author Contributions: Study concept and design: Raterman, Simsek, and Nurmohamed. Acquisition of data: Raterman, Simsek, and Meesters. Analysis and interpretation of data: Raterman, Simsek, Lems, Meesters, Dijkmans, and Nurmohamed. Drafting of the manuscript: Raterman, Lems, and Nurmohamed. Critical revision of the manuscript for important intellectual content: Simsek, Lems, Meesters, Dijkmans, and Nurmohamed. Obtained funding: Dijkmans. Study supervision: Simsek, Lems, Dijkmans, and Nurmohamed.

Financial Disclosure: Dr Dijkmans has received an educational grant from Roche Nederland.

COMMENTS AND OPINIONS

Preadmission Use of Statins in Patients With Pneumonia

W e commend Thomsen and colleagues 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 al 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, 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, 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.

Madhavi Bollu, MD
Andres Marte-Grau, MD
Ravi K. Bobba, MD

Correspondence: Dr Bobba, Department of Internal Medicine, Salem Veterans Affairs Medical Center, 1970 Roanoke Blvd, Salem, VA 24153 (rkbobba@gmail.com).