



THYROID DISEASE IN CHRONIC
HEPATITIS C INFECTION AND
INTERFERON- α BASED
THERAPY

HUY A. TRAN

THESIS SUBMISSION

**THYROID DISEASE IN CHRONIC
HEPATITIS C INFECTION AND
INTERFERON- α BASED THERAPY**

by

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SIGNED:**13-November-2012****HUY A. TRAN**

PREFACE

This study was performed over a 7 year period addressing the fascinating topic of thyroid diseases in association with chronic hepatitis C infection and its treatment. All the manuscripts were prepared in my own time whilst working in a full-time capacity as the Director of Chemical Pathology, Hunter Area Pathology Service, New South Wales.

I am very grateful and indebted to my family, my parents and brothers whose, whilst afar, moral advice, support and belief give me the absolute strength and motivation in the desperate hours of need. My father's wise and guiding words I will take to the grave: "You have two hands and feet. Others can, why can't you?" To Justin Tran whose sharp vision did the 'spotto' on the 'typos' within the first few glances and effectively enforced a redo of the manuscript. To Audrey Tran whose beautiful and natural personality made the experience all the richer. To Xuan Nguyen, my darling wife whose life-long support of my academic adventure is much more vast and valuable than anyone realizes.

I am also very grateful for the guidance and support of Professor Geoffrey M Kellerman and the late Professor Anthony S-Y Leong whose boundless and unparalleled academic achievements have inspired me to take on this mountainous project. I would not be able to achieve this project without the wonderful support of the Hepatitis C unit and

Gastroenterology Department at the John Hunter Hospital. I am very humbled and honored to have the support of Professor Aidan Foy, Drs. Robert Pickles and Brian Hughes, nursing sisters Elizabeth A Ianna, Tracey L Jones, Melissa Young and research scientist Nadine Leembruggen whose many joyful anecdotes have seeded the full bloom of many subsequent incisive scientific reports.

DEDICATION

**THIS THESIS WAS DEDICATED TO THE
MEMORY OF**

PROFESSOR ANTHONY S-Y LEONG, MD, FRCPA, FRCPath, FCAP,
1945 - 2011.

DISTINGUISHED PROFESSOR OF PATHOLOGY AND MEDICAL
DIRECTOR OF HUNTER AREA PATHOLOGY SERVICE, NEWCASTLE,
NEW SOUTH WALES, 1999 - 2010.

A REVERED COLLEAGUE, FRIEND, MENTOR, NEIGHBOR AND
FATHERLY FIGURE. MY SI PHU.

Obituaries

Anthony Siew-Yin Leong

MB BS, MD, FRCPA, FRCPath, FCAP, FHKCPath, FHKAM(Path)



ANTHONY LEONG was born in Singapore in 1945 and graduated from the University of Malaya in 1969. He pursued postgraduate training in America, where he completed his pathology residency at the University of Washington, Seattle, between 1971 and 1973. In 1976, he migrated to Adelaide to continue his work in lymphoma and tissue processing, especially tissue staining and immunohistochemistry. He excelled in research and, in 1980, received a doctorate in medicine from the University of Adelaide, where he was Clinical Professor of Pathology from 1981 until 1996.

From 1996, he dedicated most of his effort and time to the Asia–Pacific region, where he held a number of leading posts including Professor of Anatomical and Cellular Pathology at the Chinese University of Hong Kong and Honorary Professor of Pathology at the Post Graduate Medical Institute, Beijing. From 1999, Anthony was Professor of Anatomical Pathology at the University of Newcastle and Medical Director of the Hunter Area Pathology Service. He was a Fellow of the colleges of pathologists of Australasia, the United Kingdom and America, as well as an honorary Fellow of the Hong Kong and Thai colleges. He served as President of the

International Academy of Pathology, Australasian Division in 1995–1996 and was the foundation President of the Asia–Pacific Society for Molecular Immunohistology in 2005–2006. He was also a founding member of the Society of Applied Immunohistochemistry and the International Society for Analytical and Molecular Morphology.

Anthony's most influential footprint was in the field of immunohistochemistry, where he left a great legacy of excellence in research and an unsurpassed love of pathology. He was a prolific author of over 370 original papers, reviews and book chapters, and more than 23 textbooks and monographs. He was a great teacher, a wise mentor and a wonderful leader, who was full of humour and interesting anecdotes. His favourite pastime was golf, and he was a proud member of the "four amigos" golf team at his local club. However, it is fair to say that his golfing never matched the dizzying heights of his academic record!

Anthony passed away in late June 2011 after a short battle with cancer. He is survived by his wife Wendy and two children Trishe and Joel, both pathologists.

Huy A Tran, Glenn E M Reeves, Frederick W Hetherington

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CHAPTER ABSTRACTS AND ASSOCIATED

PUBLICATIONS

CHAPTER I. INTRODUCTION

- (A) GENERAL BACKGROUND ON INTERFERON THERAPY
- (B) INTERFERON- α MONOTHERAPY IN THE TREATMENT OF HEPATITIS C
- (C) COMBINATION INTERFERON- α AND RIBAVIRIN THERAPY IN HEPATITIS C
 - (i) REGULAR INTERFERON- α
 - (ii) PEGYLATED INTERFERON- α

Summary: This chapter examines the evolution of interferon use and its subsequent graduation into the pharmacological management of many medical conditions. The initial treatment for hepatitis C involved monotherapy with interferon- α but as it soon became evident that combination therapy with ribavirin delivered a much superior outcome. As a result, it is now the current standard of practice in the treatment of chronic hepatitis C infection.

CHAPTER II. EPIDEMIOLOGY OF THYROID DISEASE, HEPATITIS C AND INTERFERON THERAPY

- (A) INTERFERON- α AND THYROID DISEASE
- (B) PREVALENCE IN AUSTRALIA
 - (i) CLINICAL EVIDENCE
 - (ii) HISTOLOGIC/POST-MORTEM EVIDENCE

Summary: As treatment for hepatitis C became readily available and further refined, an increased number of patients was anticipated to undergo treatment. As a result, adverse outcomes would also become more apparent, the commonest of which is thyroid disorders. It was essential that the prevalence of the condition be recognized, especially in Australia where few reports were available. The original research publication in this chapter addressed this concern and quantified the prevalence of thyroid disorders in an Australian cohort managed and treated in a specialized tertiary hospital unit.

Publications:

Tran HA. HEPATITIS C INFECTION, TREATMENT REGIMENS, AND THYROID ABNORMALITIES. *The Endocrinologist*, 2007; 17: 231-235.

Tran HA, Jones TL, Batey RG. THE SPECTRUM OF THYROID DYSFUNCTION IN AN AUSTRALIAN HEPATITIS C POPULATION TREATED WITH COMBINATION INTERFERON- α 2 β AND RIBAVIRIN. *BMC Endocr Disord*, 2005; 5: 8.

Tran HA, Reeves GEM, Lyons TJ, Attia JR. HISTOPATHOLOGICAL FINDINGS OF AUTOIMMUNITY IN THYROID, PITUITARY AND ADRENAL DISEASES IN CHRONIC HEPATITIS C POST-MORTEM CASES. *Endocr Pract*, 2010; 16: 566-569.

CHAPTER III. THE DEVELOPMENT OF THYROID DISEASES WITH THE CHANGE TO PEGYLATED INTERFERON

(A) COMPARISON OF REGULAR VERSUS PEGYLATED INTERFERON IN THE DEVELOPMENT OF THYROID DISEASE

Summary: As treatment continued to evolve in order to simplify and improve compliance, interferon- α was pegylated to increase its half-life. This assisted in easing the complexity of treatment and reduced the frequency of injections. Not unexpectedly, this original research meta-analysis confirmed that there was no difference between regular and pegylated interferon in the development of thyroid disorders.

Publication:

Tran HA, Attia JR, Jones TL, Batey RG. PEGYLATED INTERFERON- $\alpha 2\beta$ IN COMBINATION WITH RIBAVIRIN DOES NOT AGGRAVATE THYROID DYSFUNCTION IN COMPARISON TO REGULAR INTERFERON- $\alpha 2\beta$ IN A HEPATITIS C POPULATION: META-ANALYSIS. *J Hepatol Gastroenterol*, 2007; 22: 472-6.

CHAPTER IV. CHARACTERISATION OF THYROID DISEASE DURING TREATMENT WITH INTERFERON- α

- (A) HYPOTHYROIDISM
 - (i) PRIMARY HYPOTHYROIDISM
 - (ii) HYPOTHYROIDISM DUE TO THYROTROPIN
RECEPTOR BLOCKING ANTIBODIES
- (B) GRAVES' LIKE THYROTOXICOSIS
 - (i) CHARACTERISTICS AND NATURAL HISTORY
- (C) BI-PHASIC THYROIDITIS
 - (i) SHORT AND LONG TERM NATURAL HISTORY
- (D) TRI-PHASIC THYROIDITIS

Summary: Although the development of thyroid disorders in association with interferon therapy became evident and widely reported, there still remained uncertainty and controversy regarding the patterns of thyroid disorders in this setting. This chapter critically examines the broad and fascinating spectrum of thyroid disorders during therapy. Where available, the natural history and outcome of a number of specific thyroid disorders was addressed in these original publications. Because of the unusual and rare occurrence of the disorder, many publications are case reports published for the purpose of stimulating and encouraging more reporting in the medical literature.

Publications:

Tran HA, Reeves GEM. CHARACTERISTICS OF GRAVES' DISEASE IN A COHORT OF CHRONIC HEPATITIS C PATIENTS TREATED WITH INTERFERON- α AND RIBAVIRIN. *J Endocrinol Metab*, 2011; 1: 14-20.

Tran HA, Reeves GE, Jones TL. THE NATURAL HISTORY OF INTERFERON- α 2 β -INDUCED THYROIDITIS AND ITS EXCLUSIVITY IN A COHORT OF PATIENTS WITH CHRONIC HEPATITIS C INFECTION. *Q J Med*, 2009; 102: 117-122.

Tran HA, Jones TL, Ianna EA, Reeves GE. THE NATURAL HISTORY OF INTERFERON- α INDUCED THYROIDITIS IN CHRONIC HEPATITIS C PATIENTS: A LONG TERM STUDY. *Thyroid Res*, 2011; 8: 4 (1): 2.

Tran HA. THE SWINGING THYROID IN HEPATITIS C INFECTION AND INTERFERON THERAPY. *Q J Med*, 2010; 103: 187-191.

**CHAPTER V. THE METABOLIC EFFECTS OF THYROID DISEASE
DURING INTERFERON TREATMENT**

- (A) THYROTOXIC PERIODIC PARALYSIS
- (B) GRAVES' OPTHALMOPATHY
- (C) ADRENAL DISEASE
- (D) PITUITARY DISEASE

Summary: In parallel with the recognition of thyroid disorders, a number of other metabolic and thyroid-associated conditions became evident. These cases were carefully studied and subsequently published. Because of the rarity of such conditions, a review of other similar published cases was performed to compare and contrast the worldwide clinical experience.

Publications:

Tran HA. HEPATITIS C INFECTION AND THYROTOXIC PERIODIC PARALYSIS - A NOVEL USE OF AN OLD DRUG. *Am J Med Sci*, 2008; 336: 515-518.

Tran HA, Reeves GEM. THE INFLUENCE OF HEPATITIS C INFECTION AND INTERFERON- α THERAPY ON THYROTROPIN BLOCKING AND STIMULATING ANTIBODIES IN GRAVES' OPTHALMOPATHY: A CASE REPORT. *Thyroid Res*, 2009; Dec 2: 2(1): 12.

Tran HA, Song S, Lojewski R, Reeves GE. EXACERBATION OF HEPATITIS C INDUCED SUBCLINICAL HYPOADRENALISM BY INTERFERON $\alpha 2\beta$: A CASE REPORT. *Cases J*, 2008; 1: 157.

Tran HA, Crock PA, Reeves GEM. PITUITARY DISEASE IN CHRONIC HEPATITIS C INFECTION AND INTERFERON-A RELATED THERAPY: TWO CASE REPORTS. *J Endocrinol Metab*, 2012; (In Press).

CHAPTER VI. THYROID DISEASE FOLLOWING THE COMPLETION OF INTERFERON THERAPY

Summary: Once thyroid disorders occurring during combination treatment have been fully characterized, it remained to be determined whether they occur following treatment completion. These publications examined the need for short to medium term follow-up of thyroid status up to the time of the sustained virologic response review, 6 months after the completion of therapy. The question of whether a longer follow-up time is needed is unanswered, but is probably not warranted given the findings of these publications.

Publications:

Tran HA, Reeves GEM. THE SPECTRUM OF AUTOIMMUNE THYROID DISEASE IN THE SHORT TO MEDIUM TERM FOLLOWING INTERFERON- α THERAPY FOR CHRONIC HEPATITIS C. *Int J Endocrinol*, 2009; 2009: 241786.

Tran HA, Reeves GEM, Ianna EA, Leembruggen N. THYROID FUNCTION OUTCOMES AFTER PEGYLATED INTERFERON-A AND RIBAVIRIN THERAPY FOR CHRONIC HEPATITIS C. *Endocr Pract*, 2010; 16: 934-939.

CHAPTER VII. THE EFFECT OF THYROID DISEASE ON SUSTAINED VIROLOGIC RESPONSE

Summary: Whilst there are many factors to prognosticate outcome of hepatitis C treatment with interferon- α , it was observed in this meta-analysis that the development of thyroid disease is associated with a significant rate of sustained virologic response. Such speculation was heightened by two cases occurring in a natural experiment setting, followed by a nested case-control study. This observation is critical because, if confirmed, the finding offers a significant adjunct to the current standard of therapy.

Publications:

Tran HA, Reeves GEM, Gibson R, Attia JR. THE DEVELOPMENT OF THYROID DISEASES IN THE TREATMENT OF CHRONIC HEPATITIS C WITH INTERFERON- α MAY BE A GOOD PROGNOSTICATOR IN ACHIEVING A SUSTAINED VIROLOGICAL RESPONSE: A META-ANALYSIS. *J Hepatol Gastroenterol*, 2009; 24: 1163-1168.

Tran HA, Ianna EA, Jones TL, Reeves GEM. THE ADJUVANT ROLE OF THYROXINE IN THE TREATMENT OF CHRONIC HEPATITIS C INFECTION. *Q J Med*, 2012; 105: 683-687.

Tran HA, Jones TL, Gibson R, Reeves GEM. THYROID DISEASE IS A FAVORABLE PROGNOSTIC FACTOR IN ACHIEVING SUSTAINED VIROLOGIC RESPONSE IN CHRONIC HEPATITIS C UNDERGOING COMBINATION THERAPY: A NESTED CASE CONTROL STUDY. BMC Endocr Disord, 2011; 11: 10.

CHAPTER VIII. SUMMARY AND CLINICAL MANAGEMENT STRATEGIES

Final outcome: On the bases of the original data generated from this thesis and current literature, an evidence-based strategy for the surveillance and management of thyroid disease is formulated and proffered.

Publication:

Tran HA, Jones TL, Ianna EA, Foy A, Reeves GEM. THYROID DISEASE IN CHRONIC HEPATITIS C INFECTION TREATED WITH INTERFERON- α : MANAGEMENT STRATEGIES AND FUTURE PERSPECTIVE. *Endocr Pract*, September-2012; *In Press* (Appendix II).

SYNOPSIS

This thesis was conceived from a number of published letters in the mid 2000's, which subsequently developed and flourished into its completion (1, 2). The proposed questions and hypotheses led to the exploration of the topic of thyroid disease in the presence of chronic hepatitis C infection and combination interferon- α and ribavirin therapy.

Early in its evolution, hepatitis C infection was chronic and considered incurable. However, with the discovery and therapeutic development of interferon, the condition became readily treatable. The initial efficacy with interferon- α monotherapy was poor but, in combination with ribavirin, it soon became the gold standard for chronic hepatitis C infection.

As clinical experience with the combination therapy for hepatitis C grew, and together with the fact that this RNA virus is a highly immunogenic particle, extra-hepatic adverse events became increasingly evident. The most common of these is thyroid disease (3). This presented a golden opportunity to study this subject in great details.

Chapter 1 reviews the history of interferon and its therapeutic development, especially in the management of hepatitis C.

Chapter 2 assesses the prevalence of thyroid disease in an Australian population of 272 treated cases from a tertiary referred hospital hepatitis C unit (4). In a separate cohort (but with a similar geographic distribution to the aforementioned cohort), the histologic evidence of thyroid disease in 108 post-mortem hepatitis C cases is also presented. These subjects' major endocrine organs of pituitary, thyroid and adrenal tissues were reviewed to determine the possible underlying pathological process including autoimmunity. The histologic report is the first original study in the published English literature assessing and highlighting the magnitude of the problem in Australia (5).

Chapter 3 assesses the risk of developing thyroid diseases whilst receiving pegylated interferon therapy in comparison to regular interferon. Interferon was pegylated to improve compliance with a change from thrice to once weekly injection. It remained unknown if pegylation interferon, despite similar antiviral efficacy, differed from regular interferon in its effect on the thyroid. This analysis reassuringly found that the pegylated form conferred no additional risk (6).

Chapter 4 characterises the pattern of thyroid disease occurring during treatment. It became evident that the majority, if not all Australian cases, developed (bi-phasic) thyroiditis with complete recovery by the time of sustained virological response (SVR) assessment 6 months after the completion of therapy. This was a unique

finding in our cohort (7). A small percentage of patients developed Graves' like thyrotoxicosis *after* the end of therapy, some adjoining and following the thyroiditis, and thus the term 'tri-phasic' thyroiditis was employed. The natural history of Graves' like thyrotoxicosis was compared with the natural history of Graves' disease arising *de novo* (8,9). In addition, a 3-year long term follow-up study was carried out in these patients with thyroiditis and the outcome was reassuringly benign (10).

Chapter 5 reviews the extra-thyroid effects of interferon- α therapy. It is well documented that beside thyroid disease, other endocrine/metabolic effects may be observed. Some of these conditions such as subclinical hypoadrenalism, thyrotoxic periodic paralysis, associated Graves' ophthalmopathy and pituitary disease (11, 12, 13, 14) are reported in this chapter. A review of possible pituitary disease involvement was also performed.

Chapter 6 makes the critical observation that patients who developed thyroid disease during therapy for chronic hepatitis C also managed to achieve sustained virologic response (SVR) much more readily than their non-thyroiditis counterparts. This hypothesis was examined using pooled data for a meta-analysis (15). The result was negative although the published studies were quite heterogeneous. This observation was strengthened further in two natural experiments (16) and led to a nested case-control study that was performed to quantify the likelihood of SVR in this setting (17). The results are favorable,

particularly genotype 1 patients whose prognosis and response rate is much worse than other genotypes. Whether this will help to further refine the treatment of this condition remains to be elucidated.

Chapter 7 examines the spectrum of thyroid disorders (18) and outcomes in hepatitis C patients in the 6 months *after* the completion of treatment, at the time of SVR assessment. This is applicable to patients who did not develop thyroid disease during treatment and reassuringly, there were no excessive thyroid disease cases detected (19).

Chapter 8 summarises the current published literature on the topic and proposes an evidence-based strategy for the development of thyroid disease in this clinical setting.

In conclusion, the thesis reports the prevalence, development and natural history of thyroid disease during treatment with interferon- α based therapy for hepatitis C, the spectrum of thyroid disease seen during *and* after the period of treatment, and the possible underlying pathogenic mechanisms. These studies assist in the formulation of management strategies in this unique clinical setting. The influence of thyroid disease development on the final viral status remains encouraging but contentious and yet to be determined.

Publication:

Tran HA. THE UNCERTAIN NATURAL HISTORY OF THYROTOXIC PATIENTS TREATED WITH COMBINATION INTERFERON- α 2 β AND RIBAVIRIN. *Arch Intern Med*, 2005; 165: 1072.

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The Uncertain Natural History of Thyrotoxic Patients Treated With Combination Interferon Alfa-2 β and Ribavirin

While reading with interest the recent publication regarding thyroid dysfunction and hepatitis C in men,¹ I noted a number of conundrums. First, there was no biochemical confirmation of thyroid function tests (TFTs) in the exclusion criteria other than simply excluding "patients with known thyroid disease." Second and similarly, there were no baseline TFTs in the recruited subjects. Third, the TFT testing protocol was an additional problem. Such frequency testing in this setting depends very much on the natural history, which can vary from weeks to months and is far from being completely understood.^{2,3} Therefore, currently there is no definitive recommendation regarding TFTs during the treatment course.⁴ Without such information, the concern is the probable misclassification of destructive autoimmune (bi-phasic) type "hyperthyroidism" into the "hypothyroidism" category. This point is best highlighted by the following clinical vignette.

A 40-year-old man with chronic hepatitis C (genotype 1) was treated with combination interferon alfa-2 β identical to that in the study by Bini and Mehandru.¹ Six weeks into therapy, he complained of general lethargy and occasional myalgia. There was no history or family history of thyroid disease, and findings from examination showed peripheral stigmata of thyrotoxicosis. His serum thyrotropin level was suppressed to less than 0.03 mIU/L with free tetra-iodothyronine and free tri-iodothyronine levels of 2525 pg/dL (32.5 pmol/L) (reference range, 777-2020 pg/dL [10.0-26.0 pmol/L]) and 501 pg/dL (7.7 pmol/L) (reference range, 228-378 pg/dL [3.5-5.8 pmol/L]), respectively. His antithyroperoxidase antibody ratio was 1:6400 with undetectable thyroid-stimulating immunoglobulin and antithyroglobulin antibodies. His thyroid nuclear uptake scan was reduced at 7% (reference range, 12%-38%). A diagnosis of destructive autoimmune thyroiditis was made, and the patient was treated conservatively. His progress was reasonable but not ideal with persistent malaise and myalgia. Results from repeated TFTs at 6 weeks showed marked hypothyroidism with a thyrotropin level of 53.1 mIU/L and a free tetra-iodothyronine of 272 pg/dL (3.5 pmol/L).

Thyroxine therapy was started, and the patient's symptoms improved. At 6 months after the completion of antiviral therapy, he still required thyroxine therapy at 100 μ g/d.

According to the researchers' protocol, at 12 weeks into therapy, this patient would have been clearly misclassified. This and the absence of TFTs in the exclusion criteria and recruitment process, which would undoubtedly detect de novo hypothyroidism (either subclinical or overt), would falsely elevate the incidence of hypothyroidism in the final analysis. While the case presented may be an isolated one, further clinical studies into the natural history of this type of thyrotoxicosis are warranted so that appropriate testing frequency can be recommended.

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Correspondence: Dr Tran, Department of Clinical Chemistry, Hunter Area Pathology Service, John Hunter Hospital, Newcastle, New South Wales, Australia 2310 (huy.tran@hnehealth.nsw.gov.au).

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In reply

We appreciate Dr Tran's interest in our article¹ and welcome this opportunity to clarify the issues raised by him. Exclusion criteria for our study included a personal history of thyroid disease as well as current or prior treatment of thyroid disease. In addition, baseline thyrotropin (TSH) levels were obtained on all study subjects at week 0. Patients with abnormal TSH levels were excluded from the study.

We agree that there is a lack of consensus regarding how to screen or how often to screen for thyroid disease during interferon and ribavirin therapy. Some authors have suggested that screening for thyroid disease with a complete history and physical examination, TSH levels, and antithyroid peroxidase antibodies should be performed in all patients with hepatitis C virus (HCV) infection prior to therapy.² In addition, these authors recommended treatment of thyroid disease followed by TSH levels every 2 to 6 months during interferon and ribavirin therapy in patients with thyroid dysfunction or a clinical evaluation and TSH levels every 6 months in those without thyroid dysfunction at baseline.²

The case report by Dr Tran describes a patient with labile thyroid dysfunction during interferon and ribavirin combination therapy, cycling rapidly between hyperthyroidism and hypothyroidism. It is certainly possible that screenings for TSH levels performed every 12 weeks according to our protocol¹ or less frequently as recommended

by other investigators² would have missed transient hyperthyroidism. The case report by Dr Tran and our study highlights the need for additional studies to evaluate the optimal screening frequency for thyroid disease in HCV-infected patients treated with interferon and ribavirin therapy.

The development of recommendations to screen for thyroid disease in this population should consider risk stratification of patients. Several studies have described certain risk factors that predispose patients to develop thyroid dysfunction during HCV therapy, including female sex, personal or family history of thyroid disease, and preexisting antithyroid peroxidase antibodies.^{1,3-6} In these "high-risk" individuals, screening for thyroid dysfunction should be more rigorous during therapy for HCV.

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1. Bini EJ, Mehandru S. Incidence of thyroid dysfunction during interferon alfa-2b and ribavirin therapy in men with chronic hepatitis C: a prospective cohort study. *Arch Intern Med.* 2004;164:2371-2376.
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5. Custro N, Montalto G, Scafidi V, et al. Prospective study on thyroid autoimmunity and dysfunction related to chronic hepatitis C and interferon therapy. *J Endocrinol Invest.* 1997;20:374-380.
6. Roti E, Minelli R, Giuberti T, et al. Multiple changes in thyroid function in patients with chronic active HCV hepatitis treated with recombinant interferon-alpha. *Am J Med.* 1996;101:482-487.

Publication:

Tran HA. THYROTOXICOSIS DURING PEGYLATED INTERFERON THERAPY IN A
PATIENT WITH CHRONIC HEPATITIS C VIRUS. *Endocr Pract*, 2006; 12: 231-2.

Letters to the Editor

THYROTOXICOSIS DURING PEGYLATED INTERFERON THERAPY IN A PATIENT WITH CHRONIC HEPATITIS C VIRUS

To the Editor:

The recent report by Lin et al (1) in *Endocrine Practice* highlights the potential adverse problem with interferon-alfa-2b (IFN- α) therapy in patients with hepatitis C infection. The thyrotoxicosis in this case is specific to pegylated IFN- α (pIFN- α) only. Thyrotoxicosis associated with IFN- α is generally rare, and each case should be managed on its own merits, depending on the clinical status. To date, no published report has addressed thyroid diseases in relationship to this specific form of IFN as opposed to the standard IFN- α therapy, for which data are available but sparse. Therefore, it is difficult to make a generalized recommendation for thyroid surveillance during pIFN- α -based therapy.

Screening is clearly different from case finding, and the latter should apply only to high-risk groups, including patients with a genetic predisposition and other factors mentioned by the authors. In fact, of the two opposing thyroid conditions, primary hypothyroidism caused by IFN- α -based therapy is much more common by a factor of 2 to 3 times (2). Of note, the prevalence of primary hypothyroidism in patients with hepatitis C virus receiving IFN- α -based treatment is not higher than the prevalence in the general population. This fact also makes the case for regular testing in every patient (that is, screening) scientifically unsound and not an evidence-based strategy. Monetarily, however, the cost of surveying for thyroid disease in these patients would be relatively small in comparison with use of a full course of combination pIFN- α and ribavirin.

In the initial assessment of the patient's thyroid disease, 22 months before the start of IFN therapy, the indications for the triiodothyronine uptake and thyroid autoantibody studies are not clear and appear superfluous. In the presence of normal levels of thyrotropin and total thyroxine (or free thyroxine), no further investigation appears warranted, even in the presence of pathologically proven multinodular disease. Perhaps those investigations should be reserved in preparation for IFN- α -based therapy just before October 2002 for risk stratification because the patient clearly is in a high-risk group. In addition, the thyrotoxicosis on this occasion is more consistent with iodine-induced thyrotoxicosis on a background of multinodular goiter rather than thyroiditis, in light of the clinical details and the absence of thyroid autoantibodies from 22 months previously. Thyroiditis can certainly coexist with multinodular thyroid disease. In either situation, symptomatic treatment is all that is required, including a

β -blocking agent, a corticosteroid, or both, if thyroiditis is the correct diagnosis. With the clear-cut history of multinodularity in mind, perhaps use of a contrast agent may have been averted or minimized or prophylactic therapy may have been instituted.

In the second admission, the presence of fever, persistent tenderness of the thyroid gland, and low blood pressure in a patient with known hypertension suggests the probability of a pyogenic thyroid abscess with disseminated sepsis. Although uncommon, suppurative thyroiditis, occurring more frequently in a multinodular goiter than in the setting of a single thyroid nodule (3), can easily mimic a thyrotoxic picture and must be rigorously excluded. This is a common scenario in patients who contract hepatitis C virus by intravenous drug use and are more likely than other patients to harbor unusual infections. This is important because corticosteroid treatment should then be used with extreme caution.

In the third admission, hypothyroidism due to overtreatment with propylthiouracil is best managed by cessation of treatment or dose reduction. There is very little scientific basis for "block-replace" therapy in this particular clinical scenario. Dual therapy with levothyroxine and propylthiouracil would only exacerbate the noncompliance in this patient, who had a proven track record for such a problem. The relapse in late April 2003 is also consistent with the natural history of iodine-induced thyrotoxicosis, which can be intractable and may require prolonged antithyroid medications (4). It is rather surprising that her radioiodine scan showed high uptake and homogeneous rather than heterogeneous activity, expected in a multinodular hemithyroid. Both forms of IFN- α -related *hyperthyroidism* are usually expected to remit soon after the withdrawal of IFN- α therapy (5,6). By this time, the patient has not received any IFN- α and ribavirin for ~6 months; thus, it is probable that her thyrotoxicosis bears no relationship to the antiviral medications whatsoever.

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In Response:

Thyroid diseases are frequent side effects of interferon (IFN)- α therapy for hepatitis C virus. Among the thyroid disorders associated with interferon therapy, thyrotoxicosis is infrequently observed; a recent report indicated that thyrotoxicosis occurs in about 3.7% of patients treated with IFN- α (1). The combination of ribavirin and interferon therapy does not modify the thyroid autoantibody pattern but is associated with a higher risk of hypothyroidism (2) and thyrotoxicosis (3). Because of the potentially severe adverse outcome of this combination therapy, as detailed in the reported case by Lin et al (4), screening and monitoring of such patients by measurement of thyrotropin (thyroid-stimulating hormone or TSH) and thyroid peroxidase antibody levels are a reasonable recommendation. If that patient had been monitored by an endocrinologist, the prophylactic therapy could have been instituted earlier, when the patient was found to have a suppressed TSH level, and perhaps the use of a contrast agent might have been avoided and the outcome may have been different.

IFN-induced thyrotoxicosis can be divided into two groups—Graves'-type thyrotoxicosis and thyroiditis-type thyrotoxicosis (1)—and Graves' hyperthyroidism may develop even after a transient phase of destructive thyrotoxicosis (3). At the first admission of the aforementioned patient (4), the thyrotoxicosis was consistent with destructive thyroiditis; iodine-induced thyrotoxicosis is very unlikely, inasmuch as no iodine was given before the admission. At the second admission, a pyogenic thyroid abscess with disseminated sepsis was completely ruled out by the clinical course because the patient was responding to corticosteroid, propylthiouracil, and β -adrenergic blocker therapy without intravenously administered antibiotics and surgical interventions. The fever is one of the signs of thyroid storm!

At the third admission, the diagnosis of Graves' disease was supported by a suppressed TSH level, elevated

thyroxine level, and increased radioiodine uptake with homogeneous activity in the left lobe. The ideal management of IFN-induced Graves' disease is radioiodine treatment (5), but the patient refused this therapeutic option. I personally treat my patients with Graves' disease who refuse radioiodine therapy with propylthiouracil or methimazole for at least 12 months first, but I will add thyroid hormone if the TSH level increases, the so-called block-replace therapy, for the following reasons: (1) if the block treatment is discontinued too early, Graves' disease will relapse, especially in IFN-induced Graves' disease (4); (2) with use of dose reduction alone (without replacement therapy), maintenance of euthyroidism is extremely difficult; and (3) the possible immunosuppressive action of a thionamide could benefit Graves' disease directly, and some reports have shown that block-replace therapy could increase the remission rate (6).

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