Original Article

Thyroid Dysfunction and Long-term Outcome during and after Interferon-alpha Therapy in Patients with Chronic Hepatitis C

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Abstract

Introduction: Thyroid dysfunction (TD) is a well-established adverse effect in chronic hepatitis C virus (HCV)-infected patients, treated with interferon-alpha (IFN-α), with or without ribavirin. However, the long-term outcome is not well-studied. The purpose of this study was to estimate the prevalence and long-term outcome of TD after HCV-therapy. Materials and Methods: Retrospective analysis of 109 HCV-treated patients (for 6 to 12 months, according to HCV genotype), for the period 1996 to 2008. Thyroid function tests were performed every 3 months during therapy and after discontinuation (3 months to 12 years). Routine laboratory tests and virological assessment were performed according to generally accepted practice. Results: TD was observed in 26 patients (23.85%). The positive and negative predictive value for thyroid autoantibodies (ATA) was 80% and 72.7%, respectively. Relative risk for those with positive ATA was 2.9 (95% CI: 1.6 to 5.3, *P* = 0.014). The median duration of TD was 12.0 months (min: 3; max: 132). The median follow-up period for the patients with TD was 25.5 months (min: 12; max: 144). Finally, 15 patients developed permanent TD (57.69%), compared to 11 with temporary TD (42.31%). Sex is a risk factor for TD, as there were more females than males affected (*P* = 0.011). Genotype, viral load, time of HCV-exposure prior to therapy, and virological response did not differ between patients with and without TD. Conclusion: TD among HCV-treated patients was more frequent than usually reported, with >50% developing permanent TD. ATA status may play a role in estimating the risk of subsequent TD. Women appear to be more vulnerable to TD than men.

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Key words: Cirrhosis, Hepatitis C, Interferon, Thyroid autoimmunity, Thyroid disease

Introduction

Hepatitis C virus (HCV) infection is a major health problem, affecting more than 170 million people worldwide.[1] Its prevalence rates range from 0.5% to 2% in the developed world with 6.5% in Africa. About 90% of the HCV infected patients proceed to the development of chronic liver disease with a high risk of cirrhosis and hepatocellular carcinoma.[2]

Interferon-alpha (IFN-α) in combination with Ribavirin (R) is the cornerstone of HCV treatment, leading to the clearance of HCV-RNA and normalisation of the levels of aminotransferases in about 35% to 45% of patients. Furthermore, the newer long-acting pegylated IFN-α (PegIFN-α), deriving from the attachment of polyethylene glycol to IFN molecule, has raised the percentage of resolution of HCV infection to 50% to 60%.[2,3]

Despite its favourable effect on HCV patients, IFN-α has been associated with the induction of thyroid disorders during or after treatment, at a rate of 1% to 35% in many studies.[4] This variability can be attributed either to an underestimation of the true prevalence of thyroid dysfunction (TD) or to the diverse genetic predisposition

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of the subjects.[4] Except for IFN, there is evidence of an immunomodulatory effect of R on the thyroid gland,[5] as well as a synergistic role of HCV itself in triggering thyroid autoimmunity.[6,7]

The spectrum of TD involves hypothyroidism, which is more frequent, especially in patients with pre-existing thyroid autoimmunity, and hyperthyroidism, manifested either as destructive thyrotoxicosis or Graves' disease. This TD can be subclinical or overt. However, its reversibility remains controversial. Few studies have reported a long enough follow-up to confidently establish the natural history of thyroid disease.[4]

The aim of this study was to report the prevalence and long-term outcome of TD in a total of 109 HCV patients undergoing therapy with IFN (alone or plus R) and to estimate the impact of sex, genotype and different therapies on Thyroid Stimulating Hormone (TSH) concentration during and after treatment.

Materials and Methods

Patients

For this purpose we conducted a case-series study in a single centre. We also conducted a nested case-control study in order to estimate the role of antithyroid antibodies (ATA) in predicting the risk of TD development. We studied the medical records of 109 consecutive Caucasian adults with HCV infection from 1996 to 2008. All information was retrieved from patients' data. All patients were diagnosed and treated in a tertiary university hepatogastroenterology unit in Thessaloniki, northern Greece, and underwent therapy with IFN-α, regular or Peg IFN-α, combined or not with R. There were 56 (51.38%) males and 53 (48.62%) females; the mean age was 46.9 years (range, 22 to 73). For each patient, a detailed history, physical examination, liver function tests and thyroid function tests were performed every 3 months during and after therapy. Virological assessment was performed at baseline, at 3 months, at the end of treatment and 6 months after completion of treatment. For those with sustained virological response (SVR), HCV RNA-polymerase chain reaction (PCR) was tested every year. There was no co-infection with hepatitis B (HBV) or human immunodeficiency viruses (HIV). Informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee.

Diagnosis of HCV Infection and Assessment of Response to Therapy

The diagnosis of HCV was based on the presence of anti-HCV antibodies (assessed by a second or third generation enzyme-linked immunosorbent assay) and serum HCV-RNA [measured by PCR method, (COBAS Amplicor HCV Monitor from 1996 to 2001 and VERSANT HCV 4.40, Siemens, Germany, from 2001 to 2008)], whereas viral genotype was determined by a hybridisation technique [HCV Genotype 2.0 Assay (LIPA), Siemens, Germany]. A liver biopsy confirmed the diagnosis of chronic hepatitis.

IFN and Ribavirin Therapy

All patients underwent treatment with IFN-α for a period of 6 to 12 months, according to HCV genotype. The dosage of regular IFN-α-2b or IFN-α-2a ranged from 1 to 6 MU trice weekly. The dose of PegIFN-α-2a was 180 μg or 135 μg once weekly, while that of PegIFN-α-2b was 50 μg or 100 μg once weekly. Nine of 109 patients received IFN-α monotherapy, while R was co-administered in 100 patients at a daily dose of 600 to 1200 mg, according to bodyweight. SVR was defined as undetectability of HCV-RNA (<50 IU/ml) 6 months after end of treatment, while non-responders were classified as those who remained PCR HCV-RNA positive at 24 weeks of treatment and at this time treatment was stopped. Biochemical response was defined as normal serum transaminases levels.

Thyroid Function Assessments

TD was assessed by the serum levels of free-thyroxine (FT4) and TSH. Unfortunately, data regarding the levels of free triiodothyronine (FT3) were missing, although they comprise a more reliable marker for thyrotoxicosis than FT4. FT4 and TSH concentrations were determined by an immunochemiluminescent non-competitive assay (ICMA) (Immnulite 2500 DPC, USA) and their normal age-specific ranges were 0.8 to 1.9 ng/ml and 0.4 to 4 μIU/ml, respectively. Thyroid autoimmunity was defined by elevated antithyrogobulin (TgAb) and antithyroperoxidase antibodies (TPOAb) (normal levels <60 IU/l). TgAb and TPOAb were measured by Micro-Enzyme Immunoassay (ELISA) method (Varelisa, EliA, Sweden Diagnostics, GmbH, Freiburg, Germany). Hypothyroidism was diagnosed when TSH levels were >4 μIU/ml together with normal (subclinical hypothyroidism) or decreased (overt hypothyroidism) FT4 levels. Conversely, thyrotoxicosis was defined by suppressed TSH, combined with normal or increased FT4 (subclinical or overt, respectively). All patients with TD were followed-up by means of TSH (and FT4 when available) along with clinical assessment for a period of 3 months to 12 years after discontinuation of therapy. Patients received drug replacement therapy for TD when TSH >10 μIU/ml (thyroxine was administered to 4 of them).

We did not make adjustments to the IFN or R dosage

when hypothyroidism was discovered and the patients were managed only with thyroxine supplementation. In cases of permanent thyrotoxicosis (in particular Graves' disease), IFN was discontinued.

Statistical Analysis

Normally distributed interval data were expressed as mean and standard deviation (M ± SD). If the assumption of normally distributed population had not been met, data were expressed as median and 5th and 95th percentiles. Difference in the means of continuous normally distributed variables between 2 groups was tested by the Student's t-test (in the absence of normal distribution, Mann-Whitney U test was used). A *P* value of <0.05 was considered statistically significant for type I error.[8] Patients were divided into 2 groups according to their sex, into 4 groups according to their genotype (1, 2, 3 and 4), and into 4 groups according to the type of therapy they had received (group 1: patients on INF-α, group 2: patients on PegINF-α, group 3: patients on INF-α plus R, group 4: patients on PegINF-α plus R). TSH concentration changes in the same individuals during different phases of therapy and follow-up period were tested with Wilcoxon signed-rank test (in case of before and after comparison in not normally distributed TSH levels) or Friedman statistic (in case of multiple comparisons in not normally distributed TSH levels). Patients who developed TD during therapy or follow-up period and patients who discontinued therapy were studied as separate groups.

All statistical analyses were performed on a personal computer with the statistical packages WinSTAT® (Vers.2007.1, R. Fitch Software), VassarStats (http://faculty.vassar.edu/lowry/VassarStats.html) and Primer of Biostatistics (Statistical Software Program version 6.0, Stanton A. Glantz).

Results

Characteristics of all patients in our study are shown in Table 1. We identified 26 patients with TD or 23.85% in a period of 12 years of follow-up. Characteristics of the patients who developed TD are presented in Table 2. Fourteen patients developed hypothyroidism (53.85%), 4 developed thyrotoxicosis (15.38%) and 8 (30.77%) developed first hypothyroidism and then thyrotoxicosis or vice versa in different phases of therapy and follow-up. Thirteen patients with TD (50%) showed SVR to HCV therapy [this proportion in patients without TD was 53.75% and the difference was not statistically significant (*P* = 0.920)]. Figure 1 presents the prevalence of TD during 21 months after initiation of HCV treatment. All diagnoses of TD were made in the same period.

Table 1. Characteristics of the Study Patients at The Initiation of Therapy

Variable	Men	Women	Total	Number of Patients with Available Data
Age (years), mean ± SD	43.9 ± 13.8	50.1 ± 13.9	46.9 ± 14.1	109
Gentotype (%)				109
1	24 (22.0)	31 (28.4)	55 (50.4)	
2	9 (8.3)	10 (9.2)	19 (17.5)	
3	17 (15.6)	9 (8.3)	26 (23.9)	
4	7 (6.4)	2 (1.8)	9 (8.2)	
Therapy type (%)				109
INF	3 (2.8)	5 (4.6)	8 (7.4)	
INF + Ribavirin	5 (4.6)	8 (7.3)	13 (11.9)	
pegINF	0 (0.0)	1 (0.9)	1 (0.9)	
pegINF + Ribavirine	49 (44.9)	38 (34.9)	87 (79.8)	
[HCV RNA]x10^3 IU/ml, median, 5th–95th percentile	1000 (84–3188)	620 (175–7429)	700 (112–3860)	85
[TSH] μIU/ml, mean ± SD	1.5 ± 0.8	1.7 ± 0.9	1.6 ± 0.8	78
Exposure to HCV infection (years), mean ± SD	22.6 ± 11.2	20.4 ± 4.8	21.0 ± 10.3	23
ATA (%)				
Positive	0 (0.0)	5 (7.0)	5 (7.0)	71
Negative	34 (47.9)	32 (45.1)	66 (93.0)	

SD: standard deviation; INF: interferon; TSH: thyroid stimulating hormone; ATA: antithyroid antibodies

Table 2. Baseline Characteristics of Patients with (TD) and without (WTD) Thyroid Disorder(s)

Variable	Value	95% CI	*P*
Age (years), mean ± SD	TD (n = 26): 50.1 ± 12.3 WTD (N = 83): 46.0 ± 14.6	TD:31-71 WTD:25-68	0.195
	Sex (%)		0.011
Men	TD: 8 (30.8) WTD: 49 (59.0)	TD: 15.1-51.9 WTD: 47.7-69.5	
Women	TD: 18 (69.2) WTD: 34 (41.0)	TD: 48.1-84.9 WTD:30.5-52.3	
	Genotype (%)		0.286*
1	TD: 16 (61.5) WTD:39 (47.0)	TD: 42.5-77.6 WTD: 36.1-58.2	
2	TD: 4 (15.4) WTD: 15 (18.1)	TD: 5.0-35.7 WTD: 10.8-28.4	
3	TD: 5 (19.2) WTD: 21 (25.3)	TD: 8.5-37.9 WTD: 16.7-36.2	
4	TD: 1 (3.9) WTD: 8 (9.6)	TD: 0.7-1.9 WTD: 4.6-18.6	
	Therapy type (%)		0.246
INF	TD: 4 (15.4) WTD: 4 (4.8)	TD: 5.0-35.7 WTD: 1.6-12.6	
INF + Ribavirin	TD: 4 (15.4) WTD: 9 (10.8)	TD: 5.0-35.7 WTD: 5.4-20.1	
pegINF	TD: 0 (0.0) WTD: 1 (1.2)	TD: 0.0-12.9 WTD: 0.1-7.4	
pegINF + Ribavirine	TD: 18 (69.2) WTD: 69 (83.1)	TD: 48.1-84.9 WTD: 72.3-90.1	
[HCV RNA]x10^3 IU/ml, median, 5th–95th percentile	TD (n = 19): 660 (280-7600) WTD (N = 66): 700 (81-3300)		0.294
[TSH] μIU/ml, mean ± SD	TD (n = 21): 1.73 ± 0.91 WTD (N = 57): 1.58 ± 0.81	TD: 0.40-3.20 WTD: 0.48-3.24	0.464
	ATA (%)		0.030
Positive	TD: 4 (18.2) WTD: 1 (2.0)	TD: 5.9-41.0 WTD: 0.1-12.2	
Negative	TD: 18 (81.8) WTD: 48 (98.0)	TD: 58.9-94.0 WTD: 87.8-99.9	

SD: standard deviation; INF: interferon; TSH: thyroid stimulating hormone; ATA: antithyroid antibodies; CI: confidence interval; n or N: number of patient with available data

*Genotype 1 vs 2, 3 and 4

We identified 22 patients with TD and available data for the presence of ATA. We compared these patients with 49 patients without TD and also known status of ATA. Results and diagnostic value of ATA are presented in Table 3. There was a statistically significant difference in the 2 proportions ($P = 0.030$). Relative risk for those with positive ATA was 2.9 (95% CI: 1.6 to 5.3, $P = 0.014$). Patients with positive ATA had an extra 52.73% (95% CI: 14.80 to 71.90; $P = 0.011$) absolute risk for TD development during or after therapy for HCV infection. We could not find any difference in outcome regarding the presence of either TgAb or TPOAb.

We also found that sex distribution was different in the 2 groups ($P = 0.011$) with more females in the group which developed TD (69.23% vs 40.96%). The mean time of exposure to HCV (as this is indicated in 40 patients by the mode of infection, transfusion or intravenous drug usage) was 20.4 years in the first group and 22.4 in the second group. The difference was not statistically significant ($P = 0.763$). Moreover, we did not find any difference in genotype (1 vs 2, 3 and 4; $P = 0.286$), age distribution ($P = 0.195$)

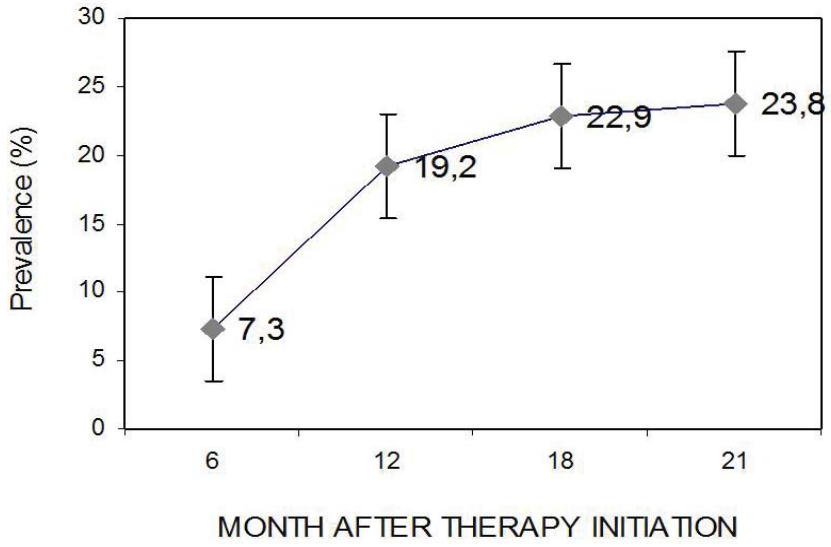

Fig. 1. Prevalence (%) of thyroid disorders after therapy initiation.

Table 3. Diagnostic Value of ATA on Thyroid Disease in Patients on Therapy for Chronic HCV Infection

Variable	Absolute value	% Value	95% CI
Prevalence	22/71	30.99%	20.84% – 43.13%
PPV	4/5	80.0%	29.9% – 98.9%
NPV	48/66	72.7 %	60.1% – 82.6 %
Sensitivity	4/22	18.18%	5.99% – 41.01%
Specificity	48/49	97.96%	87.76% – 99.89%
Accuracy	52/71	73.24%	61.20% – 82.74%
RR	2.9		1.6% – 5.3%

ATA: antithyroid autoantibodies; PPV: positive predictive value of positive ATA; NPV: negative predictive value; RR: Risk ratio

and HCV viral load before the initiation of treatment (P = 0.294) between euthyroidics and dysthyroidics with chronic HCV infection in our study population.

The median duration of TD was 12.0 (5th percentile: 3.1 – 95th percentile: 105.8) months (min: 3; max: 132). The median follow-up period for the patients with TD was 25.5 (5th percentile: 13.1 – 95th percentile: 129.3) months (min: 12; max: 144). Finally, 5 men and 10 women developed permanent TD (57.69%, 95% CI: 37.19 to 76.02%), compared to 11 patients (3 men and 8 women) who developed temporary TD (42.31%, 95% CI: 23.98 to 62.81). Permanent TD was defined when the last available TSH value was out of the normal range (0.4 to 4 μIU/ml), whereas temporary TD was diagnosed by 2 subsequent TSH values within the normal range. The duration of TD was designated by the period from the first abnormal until the first normal or until the last abnormal available TSH value.

Discussion

The primary aim of our study was to estimate the prevalence of TD during and after therapy with INF-α alone or in combination with R in chronic HCV patients and to report our experience in long-term follow-up and potential risk factors. We retrospectively found higher prevalence than this usually reported.[4,9-17] In most studies, the prevalence of TD is <12% (mainly 6% to 9%).[4, 9-12,14,15,17] Few of them are prospective.[11,14] The discrepancy regarding the frequency of TD may be partly attributed to the different reference levels of TSH, completion rates of IFN-α therapy or genetic predisposition to thyroid autoimmune disease.[4,6,9] Indeed, HCV patients with concurrent immunological disease display the major histocompatibility HLA-DR4 phenotype more frequently than HCV ones without concurrent immunological disease.[18] Although hypothyroidism is the prevalent disorder in most studies,[4,9-12,14,15,17] as well as in our study (53.85%), the different manifestation of TD can be further explained by variations in dietary iodine intake in the populations studied.[9] In general, high iodine intake is associated with hypothyroidism, whereas low iodine intake is related to hyperthyroidism.[19]

The pathogenetic mechanism for IFN-induced TD is based on a dysregulation of the immune system by IFN, as well as on its direct effects on thyroid cells. IFN seems to induce cell-cytotoxicity through an up-regulation of perforin expression in peripheral natural killer and T cells, in particular T-helper (Th) cells. It suppresses Th2 and enhances Th1 immune response.[4] The direct impact

of IFN on thyroid gland includes inhibitory effects on hormonogenesis, secretion and metabolism, as well as abnormal expression of major histocompatibility antigens on thyroid cells.[20,21] Except for IFN-α, there are also data suggestive of an immunomodulatory effect of ribavirin on thyroid gland.[5]

The role of HCV infection itself in the development of TD has been widely reported.[7,10,22-25] A large study of 630 HCV-positive subjects compared to uninfected healthy or HBV-infected controls, showed higher prevalence of hypothyroidism and presence of ATA in HCV patients, which suggests a potential synergistic role of HCV in stimulating TD during antiviral treatment.[23] Moreover, a recent retrospective cohort study of users of US Veterans Affairs health care facilities, which included 146,394 patients infected with HCV showed higher risk for thyroiditis [hazard ratio (HR): 1.06; 95% CI, 1.01 to 1.11] which increased to 1.13 (95% CI, 1.08 to 1.18) after further adjustment for race and other possible confounders.[24] Others suggested an even higher prevalence of thyroid autoimmunity [odds ratio (OR) = 1.6; 95% CI, 1.4 to 1.9] as well as of hypothyroidism (OR = 2.9; 95% CI = 2.0 to 4.1) in HCV patients.[25]

It is speculated that HCV shares partial sequences in a few amino acid segments with thyroid tissue antigens.[4] Another possible explanation is an increased expression of IFN-γ and IFN-γ-inducible chemokines, such as chemokine ligand 10 (CXCL10) (also known as IFN-γ-inducible protein 10), in the hepatocytes and lymphocytes of HCV patients. CXCL10 production is speculated to play a key role in the regulation of T-cell trafficking into the liver tissue during HCV infection, and, in particular, it seems to act by recruiting Th1 cells that secrete IFN-γ and tumour necrosis factor (TNF), which in turn induce CXCL10 expression by the hepatocytes. Increased expression of IFN-γ and CXCL10 has also been reported in patients with autoimmune thyroiditis and hypothyroidism.[26]

Nonetheless, some studies failed to show that HCV is an independent factor for TD,[6,17] although the rate of ATA positivity in HCV patients was higher than healthy controls.[6] It must be mentioned that in our study, the time of exposure to HCV, the genotype of HCV and the levels of viremia were not significantly associated with the prevalence of TD. These results are consistent with previous reports.[7,23] However, in one study, mixed HCV genotype infection and lower HCV RNA levels were significantly related to TD, although in multivariate analysis only female gender remained significantly associated with TD.[16]

The strongest risk factors associated with TD in our study were the presence of ATA and female gender. These findings are in line with most studies,[4,6,9-12,14,16,17,27] which demonstrate a higher susceptibility of developing TD in women than men and a strong predictive value of ATA-positivity prior to IFN-α therapy. Interestingly, one study showed that only female gender and the Asian origin and not thyroid autoimmunity were independent predictors of TD in a multiple regression analysis of the possible risk factors for TD.[9] We demonstrated that HCV patients with positive ATA at the initiation of therapy have an 80% probability of developing TD during or after therapy. Furthermore, 3 patients with negative ATA before treatment developed thyroid autoimmunity during therapy, which was followed by hypothyroidism in 2 and by biphasic TD in 1 patient. The prevalence of ATA among HCV patients is higher than healthy subjects and ranges between 1.6% to 42%[4,23,27,28] (in our study the estimated prevalence of ATA was 30.99%). This huge variability can be further attributed to host or viral factors, such as mixed HCV genotypes infection and lower HCV-RNA levels.[4] The predictive value of ATA regarding TD is strong, either in IFN-α monotherapy or in combination therapy with R11, 27. Thus, checking ATA before IFN-α therapy appears to be mandatory, as it can identify high-risk patients who may develop TD subsequently.

We evaluated the impact virological response on thyroid function and we concluded that it was not related to the development of TD. The lack of association of virological response to treatment with TD is also in accordance with previous reports.[9,13] We did not perform statistical analysis regarding the relationship between the type of INF treatment and incidence of TD as the number of TD cases was low and the treatment groups were very skewed towards pegINF + R treatment group.

Few studies have used a long enough follow-up period to evaluate thyroid function after discontinuation of antiviral treatment.[9-12,15,17,22,27] The mean follow-up is up to 24 months in most studies and data are controversial. Some investigators reported complete normalisation of TD after IFN withdrawal,[15,17] whereas others indicated that thyroid abnormalities are partially reversible.[9-12,22,27] Using a median follow-up period of 25.5 months for the patients with TD (min: 12; max: 144) we concluded that more than half (57.69%) displayed permanent TD. A relapse of subclinical hypothyrodism was noticed in 3 patients after more than 5 years washout period (one of which occurred on 12 year follow-up time) despite normalisation of TSH levels after discontinuation of treatment. To the best of our knowledge, this is the longest follow-up period ever been reported in the literature.

Our study had certain limitations. Its retrospective character limited its generalisability. Furthermore, our study population was limited in a certain region of northern Greece. Further studies from different centres and observations on different populations are needed in order to estimate the exact frequency of TD after HCV therapy initiation at different settings and different therapies. We also acknowledge that

ATA status was available in a subset (~65%) of the study population. It is unclear whether the unobserved 35% differs systematically (i.e. bias) from the study base. In addition, we must also underline the relatively small sample size and low "events rate" i.e. only 4 subjects with positive ATA developed TD. However, despite these limitations, there was a statistically significant difference in the 2 groups, ($P = 0.030$) supporting the notion that ATA positivity is a strong risk factor associated with the development of TD.

Conclusion

In conclusion, TD among patients who receive therapy for HCV chronic infection is more frequent than usually reported, with hypothyroidism presenting as the predominant disorder. Female gender and ATA status prior to therapy appear to be the strongest factors in estimating the risk of subsequent TD. More than half of the patients with IFN-induced TD develop permanent thyroid disease. Time of exposure or response to HCV, HCV genotype and viral load, type and dose of therapy are not associated with the development of TD. However, large prospective studies to evaluate the exact incidence and outcome and to address the optimal follow-up period are needed.

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