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INTERFERON ALPHA TREATMENT AND THYROID DYSFUNCTION

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Abstract

Interferon-alpha (IFNα) is the cornerstone therapeutic agent for chronic hepatitis C virus (HCV) infection. Prospective studies have shown that up to 15% of HCV patients receiving interferon alpha develop clinical thyroid disease, and up to 40% become thyroid antibody positive. In some cases interferon induced thyroiditis (IIT) may result in discontinuation of interferon therapy; thus, IIT represents a major clinical problem for hepatitis C patients receiving IFNα therapy. Recently, the mechanisms leading to the development of IIT are beginning to be unraveled. It is now clear that the hepatitis C Virus (HCV) itself plays a role in the disease. Moreover, recent data suggest the IFNα precipitates thyroiditis by both immune modulatory mechanisms and direct thyroid toxic effects. Genetic factors also play a major role in the etiology of IIT. IIT can manifest both as clinical autoimmune thyroiditis (i.e. Hashimoto's thyroiditis and Graves' disease) and as non-autoimmune thyroiditis (i.e. destructive thyroiditis). Early detection and therapy of these conditions is important in order to avoid complications of thyroid disease such as cardiac arrhythmias. In this review, we will review the epidemiology and clinical manifestations of IIT as well as the mechanisms causing IIT, focusing on the role of hepatitis C virus.

Keywords

Interferon; thyroiditis; autoimmunity; Hepatitis C; Hashimoto's thyroiditis

INTRODUCTION

Interferon alpha (IFNα) is a type I interferon that has been widely used as a therapeutic agent (1). IFNα binds to interferon receptors, which are transmembrane glycoproteins containing cytoplasmic domains that activate various signaling pathways, including the JAK-STAT pathway, the Crk-pathway, the IRS signaling pathway, and the MAP kinase pathway (2;3). More than two dozen interferon-induced proteins have been identified (4). In the past several decades IFNα has emerged as a major therapeutic modality for several malignant and non-malignant diseases (4). By far the most common indication for IFNα treatment is hepatitis C virus (HCV) infection. In two pivotal randomized trials, approximately 50% of patients with chronic hepatitis C, who were treated with peginterferon alpha–2a plus ribavirin, achieved a sustained virologic response (5;6).

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Despite its success, IFNα has a well known side effect profile, ranging from influenza-like symptoms to hematologic effects, neuropsychiatric symptoms, and thyroid disease, which cumulatively can lead to dose reductions in up to 40% of patients and drug discontinuation in up to 14% of patients (7). One of the most common side-effects of IFNα therapy is thyroiditis. The association between IFNα and thyroid disease was recognized as early as 1985 in patients being treated with IFNα for carcinoid tumors and breast cancer (8;9). Since then numerous studies have reported a high incidence of thyroid disease in patients treated with IFNα (10; 11). Some of these complications of IFNα therapy, especially thyrotoxicosis, can be severe and may interfere with adequate interferon therapy in hepatitis C patients (12–15). Moreover, since the symptoms of hypothyroidism such as fatigue, and weight gain might be attributable to hepatitis C or IFNα therapy (7), the diagnosis of hypothyroidism in these patients might be delayed leading to development of further complications. Thus, interferon induced thyroiditis (IIT) is a major clinical problem for patients receiving interferon therapy. This review will focus on the mechanisms leading to IIT and the role of hepatitis C virus (HCV) in the pathogenesis of IIT.

THE EPIDEMIOLOGY OF IIT

We have recently proposed a new classification of IIT into autoimmune IIT and non-autoimmune IIT (16). Autoimmune IIT includes Graves' disease (GD), Hashimoto's thyroiditis (HT) and the production of thyroid autoantibodies (TAb's) without clinical disease, while non-autoimmune IIT includes destructive thyroiditis and non-autoimmune hypothyroidism.

Autoimmune IIT

The most common clinical manifestation of IIT is HT (17–20). Most studies have shown that the presence of TAb's prior to the initiation of IFNα therapy is a significant risk factor for the development of IIT manifesting as Hashimoto's thyroiditis (11;17;21;22). The development of HT in a TAb positive patient who receives IFNα is often accompanied by a significant increase in the levels of the antibodies (21). Roti et al. calculated that having positive thyroid peroxidase (TPO) antibodies before IFNα therapy had a positive predictive value of 67% for the development of thyroid dysfunction (12). Therefore, screening for TAb's should be performed prior to the initiation of interferon therapy in order to assess the risk of developing HT (16).

Less commonly, treatment with IFNα can result in the development of Graves' disease (12; 23). A retrospective review of 321 patients with hepatitis B or C treated with IFNα found 10 patients who developed thyrotoxicosis characterized by a completely suppressed TSH (23). Six of these patients developed GD based on diffusely increased uptake on thyroid scintigraphy as well as positive thyroid-stimulating antibodies. All GD patients had symptomatic thyrotoxicosis, and in all cases, the thyrotoxicosis failed to resolve after cessation of IFNα (23). In another large multicenter study, 3 of 237 patients receiving IFNα developed GD requiring definitive treatment (24). In most reported cases of GD developing secondary to interferon alpha therapy the disease did not go into remission when IFNα therapy was completed or stopped (17;23;24). There is one case report of Graves' ophthalmopathy that developed following IFNα treatment for hepatitis C (14) underscoring the fact that interferon induced thyroiditis can result in more severe complications (15).

The most common form of thyroid autoimmunity is the presence of thyroid antibodies [including thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (Tg-Ab)], without clinical disease (25). The presence of TAb's, is usually a pre-clinical phase of AITD (26). TAb's without clinical disease have also been shown to develop during or following IFNα therapy. The TAb's can develop *de novo* during IFNα, or IFNα can cause a significant

increase in TAb levels in individuals who were positive for TAb prior to interferon therapy. Thus, it seems that IFNα can induce thyroid autoimmunity *de novo*, as well as exacerbate pre-existing thyroid autoimmunity (17;22;27). The incidence of *de novo* development of TAb's secondary to IFNα therapy varied widely in different studies from 1.9 – 40.0 %, most likely due to the different assays used to test for thyroid antibodies (16). The newer immunoassays have up to a ten-fold higher sensitivity to detect TAb's than the older assays (28;29). Indeed, recent studies are more consistent and report an incidence of TAb's in interferon treated HCV patients of around 10% (12;17;21;22;30). Marazuela et al. found that development of anti-thyroid antibodies was significantly higher in women compared to men, 14.8 % vs. 1% ($p < 0.01$), and was also directly related to increasing age (27). The majority of individuals who develop "de novo" TAb's on IFNα therapy remain TAb positive after the end of treatment. In one long-term study in which patients were followed for a median of 6.2 years (5.5–8.4 years) after completion of IFNα therapy, 72.2% of patients who became TAb positive during IFNα therapy continued to have TAb's at the end of the study (20).

Non-Autoimmune IIT

Non-autoimmune thyroiditis is seen in up to 50% of patients who develop IIT, suggesting that thyroid dysfunction may be mediated by a direct effect of IFNα on thyroid cell function and not only by immune mediated effects (12;23;31). Non-autoimmune IIT usually manifests as destructive thyroiditis. Destructive thyroiditis is a self-limited inflammatory disorder of the thyroid gland. The disease is characterized by three phases, a sudden onset of hyperthyroidism, followed by a hypothyroid phase, and eventually resolution and normalization of thyroid functions, usually within several weeks to months (32). In less than 5% of the cases permanent hypothyroidism develops (33). More than 50% of IIT patients with thyrotoxicosis have destructive thyroiditis, while the remainder have Graves' disease (11;12;21;23;24;31). The diagnosis of destructive thyroiditis in patients receiving interferon therapy is based on negative TSH-receptor antibodies (TRAb) and low thyroid radioactive iodine uptake (12;23). Since many cases of destructive thyroiditis secondary to IFNα are mild or subclinical, it is possible that subacute thyroiditis occurs more frequently than reported. On re-treatment with interferon patients may develop recurrent thyroiditis, and therefore, thyroid functions should be carefully monitored upon re-challenge with IFNα (34). Destructive thyroiditis due to IFNα therapy of hepatitis C infection is usually benign. However, in our experience, some of these patients may develop complications, such as rapid atrial fibrillation, requiring thyroid ablation prior to re-treatment with IFNα. In addition, a subset of these patients may progress to permanent hypothyroidism, usually accompanied by the development of thyroid antibodies (13).

Clinical and subclinical hypothyroidism without thyroid antibodies have also been described secondary to IFNα therapy (22;24;35). In many of these cases the hypothyroidism is transient and permanent hypothyroidism is usually seen when patients develop thyroid antibodies (12; 17;19;20).

THE ROLE OF HEPATITIS C VIRUS IN THE DEVELOPMENT OF IIT

While IIT has been reported in patients receiving IFNα for a variety of medical conditions (36), most cases of IIT have been reported in patients with chronic HCV infection. Thus, it is plausible that HCV infection plays an important role in the etiology of thyroiditis in interferon treated patients. Infectious agents have long been suspected to trigger thyroid autoimmunity (37), and among the possible infectious triggers of thyroid autoimmunity, HCV has shown the strongest association with AITD (38).

Epidemiological observations

Earlier studies of patients with hepatitis C that never received IFNα showed no significant correlation between hepatitis C infection and the presence of thyroid antibodies (39–41). For example, in one large community-based study in Sardinia, where infection with hepatitis viruses is endemic, 1310 where surveyed, and no association was found between the presence of hepatitis C antibodies and thyroid antibodies (39). On the other hand, other studies have shown a significant correlation between hepatitis C infection and thyroid disorders (21;42–45). In two studies from France of patients with hepatitis C infection who had not received IFNα therapy, the incidence of thyroid antibodies and/or dysfunction was significantly higher in the patients than in the controls (42;43). Another study from France in hepatitis C patients who have not received interferon revealed that 13.6% had positive TAb's (46). While this study lacked a control group, this incidence is greater than expected by age and gender (46;47). Moreover, in most studies examining the frequency of thyroid disorders in IFNα treated hepatitis C patients approximately 10% of the patients had positive TAb's prior to initiation of interferon therapy (12;17;27;30;48).

Some of the problems of earlier studies included the use of less sensitive TAb assays and the lack of control for factors, which may affect the development of thyroid autoimmunity, mainly iodine intake. Moreover, the definition of HCV infection was not standard across different studies. Some studies defined HCV infection as the presence of positive HCV antibodies (indicative of past and/or present infection), while other studies measured HCV RNA (indicative of current HCV infection only) (49). Thus, one could speculate that past versus current HCV infection could influence the development of thyroiditis. One recent very large study demonstrated that both hypothyroidism and thyroid autoimmunity were significantly more common in patients with hepatitis C compared to controls (45). Patients were considered having chronic HCV based on positive HCV antibodies and elevated transaminase levels for more than 6 months. The authors studied four groups: 630 interferon-naïve patients who had hepatitis C; 389 gender- and age-matched subjects from an iodine-sufficient region; 268 people from an iodine-deficient region; and 86 patients who had hepatitis B virus infection. They found that the presence of thyroid antibodies (both Tg-Ab and TPO-Ab) was significantly higher in patients with hepatitis C infection than in the other three groups. Clinical hypothyroidism was also significantly more frequent in patients with hepatitis C compared with the three control groups (45). This study controlled for both intake of iodine and treatment with IFNα. In summary, while earlier studies did not consistently show an association between HCV infection and AITD, more recent data do indeed support such an association. Moreover, pooling of data from all studies on HCV infection (as measured by either HCV antibodies or RNA) and thyroid autoimmunity demonstrated a significant increase in the risk of thyroiditis in HCV patients (49).

Pathogenesis of hepatitis C virus

Globally, hepatitis C virus infects more than 170 million people, while over 4.1 million persons have been exposed to HCV in the United States alone (50). Although some individuals may spontaneously resolve acute HCV infection, the majority of infected individuals will develop chronic HCV infection characterized by HCV antibody seropositivity and persistent viremia. Importantly, chronic HCV infection may result in significant hepatic fibrosis, cirrhosis, and hepatocellular carcinoma and is the major reason for liver transplantation in the US.

The genome of this enveloped, single-stranded, positive-sense RNA virus, is organized as a single polyprotein that encodes for multiple structural and non-structural proteins and is flanked by untranslated regulatory (UTRs). A comprehensive review of the HCV life cycle has been presented elsewhere (51). Viral replication is extremely robust. This coupled with the error-prone nature of the viral RNA polymerase (NS5B) results in production of a heterogenous viral

population, termed the viral quasispecies, within an infected individual. These viral variants may display divergent phenotypic properties, such as altered replication capacity or fitness, cell tropism, immunologic escape, and antiviral drug resistance (52). At the population level, HCV also consists of multiple genotypes, an important determinant of the virologic response to HCV therapy (53).

Interestingly, there is also some suggestion that a portion of the HCV genome could share partial sequence homology with thyroid tissue antigens (101). Thus, persons with chronic HCV infection might be more susceptible to autoimmune thyroid diseases.

Innate Immunity to HCV

Viral infection triggers activation of several antiviral effectors, including interferons (IFN), that represent an early host defense mechanism that occurs prior to the development of adaptive immune responses. Nonetheless, it is rare that these innate antiviral responses completely eliminate virus production. Several HCV proteins, including core, E2, NS3/4A, and NS5A have been implicated in inhibition of IFN-inducible genes and/or key components of IFN signaling pathways (54). Furthermore, host immune selection pressures may drive the outgrowth and selection of viral variants capable of persisting despite the presence of an antiviral response directed against HCV or antiviral treatment. Thus, HCV can both trigger *and* control the response to infection, and HCV's ability to antagonize these antiviral responses is crucial to its persistence in a host.

Among the structural proteins, the two envelope glycoproteins (E1 and E2) interact with components of the adaptive immune response and are essential for host cell entry. Several cell surface molecules have been proposed to play a role in mediating HCV attachment and entry, including CD81, scavenger receptor class B type I (SR-BI), heparan sulfate, DC-SIGN/L-SIGN, and the low-density lipoprotein (LDL) receptor (55). Importantly, a recent study has demonstrated that hepatic binding of envelope glycoproteins – without productive HCV infection – results in a cascade of intracellular signals that modulate cellular gene expression, in particular genes critical to innate immune responses and lipid metabolism (56). Furthermore, cross-linking of CD81 by HCV E2 protein blocks NK cell activation, cytokine production, cytotoxic granule release, and proliferation and results in costimulatory signals for T cells (57;58). Similarly, engagement of CD81 on B cells by E2 protein and anti-CD81 antibody triggers the JNK pathway and leads to proliferation of naïve B lymphocytes. Thus, any cell type that expresses potential HCV receptors and/or entry co-factors, including thyrocytes, could potentially engage HCV glycoproteins, even in the absence of productive HCV infection. This engagement can then activate intracellular signaling pathways triggering a tissue inflammatory response. Indeed, we have recently shown (unpublished data) expression of CD81 in thyroid cells. Thus, it is possible that CD81 engagement by HCV E2 proteins in thyrocytes can trigger intracellular signaling cascades that ultimately induce thyroiditis and may contribute to the etiology of ITT.

Extrahepatic replication of HCV

While hepatocytes are the major site of HCV replication, a number of extrahepatic complications of HCV infection also exist, including autoimmune diseases, rheumatic diseases, and lymphoproliferative disorders (59). HCV is also lymphotropic; thus, extrahepatic reservoirs of viral replication are relevant to the maintenance of viral persistence. However, accurately demonstrating extrahepatic HCV replication has been challenging due to the lack of robust models of HCV replication *in vitro*. Thus, to date, such studies have been performed almost exclusively using cells and tissues collected from HCV-infected persons. Because hepatitis C virions themselves contain positive-sense RNA genomes, the detection of positive-strand HCV RNA is not sufficient to demonstrate HCV replication; rather, detection of actively

replicating viral genomes – as indicated by negative-strand HCV RNA (so called 'replicative intermediates) is necessary.

Using highly sensitive, strand-specific polymerase chain reaction, negative-strand HCV RNA has been amplified in the peripheral blood, granulocytes, monocytes/macrophages, dendritic cells, and lymphocytes (59). Negative-strand HCV RNA has also been demonstrated in the thyroid. For instance, Laskus *et al.* investigated extrahepatic replication of HCV in various tissues from HCV-infected patients who died of AIDS-related complications and detected negative-strand HCV RNA in the thyroid of 2 individuals (60). However, the immunologic, virologic, and genetic factors that regulate HCV replication in extrahepatic sites, such as the thyroid, have not been explored, nor have the precise cell type(s) supporting replication been identified.

Is the thyroid exposed to HCV virus?

While intact, infectious hepatitis C virions are responsible for productive infection, viral proteins that are shed for virions or that are part of non-infectious virions may also have important physiological consequences. For instance, it has been demonstrated that HCV E2 proteins induce apoptosis through STAT1 induction and upregulation of Fas ligand and the pro-apoptotic molecule Bid (61–63). The pro-inflammatory cytokine interleukin 8 (IL-8) is also upregulated by HCV E2 protein (64). These data suggest that HCV proteins themselves could significantly impact the thyroid environment and contribute to thyroid dysfunction. Hence, it is possible that HCV infection of thyrcoytes and/or exposure of thryocytes to HCV proteins could trigger a thyroidal innate immune response to HCV which, together with exogenous IFN therapy, may activate interferon-stimulated genes, resulting in thyroidal inflammation. Similarly, it is currently unknown if thyroid-tropic variants of HCV exist and what role if any these may have on thyroid dysfunction.

GENETIC PREDISPOSITION TO IIT

Autoimmune thyroid diseases (AITD) are strongly influenced by genetic factors (reviewed in (65)). Therefore genetic factors are likely to influence the etiology of IIT. In fact, the combination of HCV infection and IFNα therapy might trigger thyroiditis in genetically predisposed individuals (16). Epidemiological data support a genetic predisposition for IIT. IIT is more common in females than in males (11;17;27;30;66). In a compilation of data from different studies, females were shown to have a 4.4 times higher risk of developing thyroid dysfunction secondary to interferon therapy compared to males (10). While the female preponderance of IIT may potentially be explained by the effects of estrogenic sex steroids in promoting autoimmunity (67), it could also be secondary to X-chromosome susceptibility genes, as has been suggested for AITD (65). How can a susceptibility gene on the X-chromosome explain the increased frequency of IIT in females? Since females have two X chromosomes and males have only one, females are more likely to inherit an X-chromosome susceptibility gene (68).

Variations in the prevalence of a disease among ethnic groups could be another indication that genetic factors influence its etiology. Indeed, one study found that Asian origin was an independent predictor of thyroid dysfunction in patients receiving IFNα (66). The influence of ethnicity on the incidence of IIT could be due to genetic factors. However, no other studies have shown that ethnicity influenced the incidence of IIT.

Additional evidence for a genetic predisposition to IIT comes from data showing that the presence of baseline TAb's is a strong risk factor for the development of IIT (11;12;17). The presence of TAb's is a pre-clinical stage of AITD, and may represent a marker for genetic predisposition to AITD (26). Data from pooled studies showed that the risk of developing

thyroid dysfunction in patients with baseline positive thyroid autoantibodies was 46.1% compared to only 5.4% in patients with baseline negative thyroid auto-antibodies (11). Specifically, the presence of TPO-Ab before treatment was a statistically significant risk factor for developing thyroid disease in patients treated with interferon (12;17). Thus IFNα may trigger AITD in genetically predisposed individuals, as manifested by the presence of baseline TAb's.

Additional evidence for genetic predisposition to IIT comes from our studies which have suggested that α accelerates thyroiditis in a thyroiditis-prone mouse model, the NOD-H2h4 mouse (69). We treated NOD-H2h4 mice with interferon alpha for eight weeks and examined for the development of thyroiditis. In the interferon-injected group 6/13 (46.2%) developed thyroiditis and/or thyroid antibodies, while in the saline –injected group, only 4/13 (30.8%) developed thyroiditis and/or thyroid antibodies; however, this difference was not statistically significant and more studies are needed to examine the effects of interferon-alpha on thyroiditis in NOD-H2h4 mice (69;69).

In recent years several genes have been found to be associated with thyroid autoimmunity (70). The AITD genes include genes involved in immune regulation such as HLA-DR (71; 72), CTLA-4 (73–75), and PTPN22 (76;77), and thyroid specific genes, including thyroglobulin (78) and TSHR (79). It is likely that some of these genes also contribute to the genetic susceptibility to IIT. Two studies examined the HLA gene locus for association with IIT (18;80). In one study from Japan an association was found between HLA-A2 and IFNα induced autoimmune thyroid disorders (80), and another small study in a Caucasian population reported an association with DRB1*11, an allele that is not known to be associated with AITD (15). We recently tested several candidate genes for association with IIT. Our preliminary data showed evidence for association of IIT with polymorphisms in the CTLA-4 and CD40 genes (81). Taken together, this preliminary evidence supports a genetic role in the etiology of IIT.

THE ETIOLOGY OF IIT

The mechanisms by which IFNα induces thyroid autoimmunity are still unknown. However, recent data from several groups, including our group, have suggested that both immune mediated and direct thyroid-toxic effects of IFNα play a role in the etiology of IIT.

Immune mediated effects of interferon-alpha

IFNα exerts various effects on the immune system, many of which might be implicated in the development of autoimmunity. IFNα receptor activation results in activation of the JAK-STAT pathway (82), leading to activation of a large number of interferon-stimulated genes (ISGs) including cytokine and adhesion molecule genes (83;84). These combined effects can induce thyroid autoimmunity. One of the cardinal effects of IFNα is to increase MHC class I antigen expression on cells. Indeed, IFNα was shown to increase the expression of MHC class I antigens on thyroid epithelial cells (12). Over-expression of class I antigens is associated with activation of cytotoxic T cells, and thus can lead to tissue damage and inflammatory response (83).

Another potential mechanism of IIT is that IFNα shifts the immune response to a Th1 mediated pattern (85), resulting in the production of IFN-γ and IL-2, two potent proinflammatory cytokines (86). Indeed, it was recently reported that hepatitis C patients that developed IIT showed Th1 polarization of their innate immune response (87). However, in some patients with IIT the clinical picture is that of Graves' disease (GD), which is generally believed to be a Th2 mediated disease (88;89). Since INFα has been shown to drive Th1 lymphocyte switching it is unclear how IFNα can induce GD in some patients. One clue to this puzzle comes from recent studies by Rapoport and colleagues suggesting that the initiation of GD is likely to be Th1 mediated (90).

Other potential mechanisms of IIT exist, as IFNα exerts many effects on the immune system. IFNα enhances the activity of lymphocytes, macrophages, and NK cells (1;83;91;92). In addition IFNα stimulates neutrophil and monocyte activation (83). IFNα can induce the release of other cytokines, such as IL-6 (83), a cytokine that has been associated with autoimmune thyroiditis (93). Thyroid cells have been shown to have specific binding sites for IL-6 (83), which decreases TSH-mediated iodine uptake, TSH-mediated expression of thyroid peroxidase mRNA, and TSH-mediated thyroid hormone release *in vitro* (83;94). In addition, IFNα can alter immunoglobulin production and decrease T regulatory cell function, thereby promoting an autoimmune inflammatory response (95;96).

Direct effects of interferon alpha on the Thyroid

Since up to 50% of patient with IIT have non-autoimmune thyroiditis, it is likely that IFNα exerts direct effects on the thyroid. When type I interferons were cultured with human thyroid follicular cells, they were found to inhibit TSH-induced gene expression of thyroglobulin (Tg), TPO, and sodium iodide symporter (NIS) (97). We have recently tested the expression levels of the TSHR, Tg, and TPO genes in rat thyroid cell line. Our results were consistent with the results of Caraccio et al showing an early increase but a late decrease in the levels of Tg and TPO. In addition, we have shown upregulation of the TSHR gene upon exposure of thyroid cells to IFNα, as well as increased thyroid cell death induced by IFNα (98). Combined, these results demonstrate that IFNα has direct toxic effects on the thyroid. Such effects may be responsible for the non-autoimmune thyroiditis induced by IFNα

DIAGNOSIS AND MANAGEMENT OF IIT

Recently, we have suggested an algorithm for the diagnosis and treatment of IIT (16). It is important that hepatologists and endocrinologists work together in the care of these patients.

Diagnosis of IIT

Previous studies have shown that IIT can result in serious complications from hyper-or hypo-thyroidism (12–15;27;99); therefore, careful screening of all HCV patients before, during, and after IFNα treatment is recommended. Since many symptoms of thyroid dysfunction could be attributed to HCV infection or IFNα therapy, clinicians should routinely look for signs of thyroid dysfunction such as tachycardia or bradycardia, sweating, heat or cold intolerance, unexpected weight loss or weight gain, and extreme fatigue and weakness.

Regardless of symptoms we recommend that all hepatitis C patients should be screened for thyroid disease prior to starting IFNα therapy. We recommend testing TSH levels to screen for abnormal thyroid functions, as well as thyroid antibody (TPO-Ab, Tg-Ab) levels since positive TAb's are associated with significantly higher frequency of IIT (11). If the TSH is normal and TAb's negative, TSH levels should be followed every three months until interferon therapy is completed. If TSH levels are normal, but TAb's are positive (either TPO-Ab and/or Tg-Ab) the patient is at a higher risk of developing clinical thyroid dysfunction (12;12;17). Therefore, in these cases we recommend that TSH levels be followed every two months to monitor for the development thyroid dysfunction, either hypothyroidism or hyperthyroidism.

If the patient develops hypo- or hyperthyroidism a full workup needs to be completed. If serum TSH is low, fT4 and fT3 levels should be measured. Workup should also include checking TSH receptor antibody (TRAb), and TPO-Ab, and Tg-Ab levels. If the etiology of hyperthyroidism cannot be revealed by these tests a thyroid I-123 uptake and scan may be performed, as well. If serum TSH is high, fT4 and fT3 levels should be measured to confirm the diagnosis of primary hypothyroidism.

Treatment of IIT

Hyperthyroidism—If the workup is consistent with destructive thyroiditis (i.e. negative TAb's, and low radio-iodine uptake on I-123 scan), the patient should be treated with a beta-blocker, if symptomatic. Patients with destructive thyroiditis should be monitored for the development of hypothyroidism, which usually follows the hyperthyroid phase within a few weeks. Corticosteroids, while helpful in subacute thyroiditis, are generally contraindicated in patients with chronic hepatitis C infection. In cases of symptomatic thyrotoxicosis, withholding IFNα therapy should be considered in consultation with an endocrinologist (23). It is should be remembered that re-challenge with IFNα may result in a recurrence of destructive thyroiditis and hyperthyroidism (sometimes severe) (34), and, therefore, the patients need close monitoring of thyroid if they are re-treated with IFNα. If the workup is consistent with Graves' disease, treatment with radioactive iodine and/or surgery should be considered (100). We do not recommend treating patients with interferon-induced Graves' disease with antithyroid medications since they worsen the liver dysfunction.

Hypothyroidism—Treatment usually consists of thyroid hormone replacement, with no need to stop IFNα therapy. Patients need to be monitored with thyroid functions every two months since the disease may progress leading to increased T4 requirements. In addition, T4 replacement requirements may increase if patients are treated with a second course of interferon, or may decrease or end altogether after cessation of IFNα treatment (19;27).

CONCLUSIONS

Interferon induced thyroiditis (IIT) is common among HCV patients treated with interferon-alpha (10;11). Preliminary studies suggest at least two different models by which IFNα may induce thyroid dysfunction, immune-mediated effects and direct thyroid-toxic effects of IFNα. Chronic HCV infection most likely plays a significant role in the triggering of thyroiditis among IFNα treated patients. Given the high prevalence of this disease, it is essential that physicians treating patients with IFNα are aware of the clinical spectrum of IIT, and screen their patients for IIT.

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