Review Article

Autoimmune thyroid disorders in hepatitis C virus infection: Effect of interferon therapy

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ABSTRACT

The hepatitis C virus infection represents an important public health problem and is associated with various hepatic and extrahepatic manifestations. Symptoms outside of the liver can occur in multiple organ systems, including hematologic, renal, dermatologic, endocrine, and rheumatologic systems. Among these different organ systems, special attention has focused on the endocrine system because it affects almost every organ in the body. Among the endocrine disorders, thyroid problems are the most common and the thyroid is one of the principal target organs for extrahepatic manifestations in HCV infected patients. In addition, research data suggest that interferon treatment may be associated with immune-mediated thyroid lesions. However, case reports suggest that the response of thyroid extrahepatic manifestations to interferon in patients with chronic HCV is greatly different. The objective of this study was to summarize currently available data on thyroid conditions associated with chronic HCV infection. Moreover, we investigate the incidence of the development of immune mediated thyroid disorders during interferon therapy in these patients.

Key words: Hepatitis C virus, interferon, thyroid manifestations

Introduction

Hepatitis C is an infectious liver disease that may also be associated with extra hepatic manifestations (EHM). A variety of conditions ranging from endocrinopathies to different skin diseases have been described in HCV infection.[1,2] More than 50% of HCV-positive patients manifest symptoms of at least one EHM during the course of the disease. These symptoms are frequently the first and only clinical signs of a chronic hepatitis C[3] and are observed in various organ-specific and organ-nonspecific immunological diseases and malignancies.[2,4]

Different factors like genetic or environnemental, may be reponsible for thyroid disorders associated with HCV infection.[5,6] In most cases, the mechanisms through which HCV may trigger or exacerbate thyroid manifestations remain unknown and need further studies. The various thyroid manifestations of HCV can be categorized with respect to a proven or suspected etiology. 1) Primary causation due to direct HCV infection of the thyroid. This hypothesis was confirmed by the detection of antigenomic HCV-RNA in the thyroid of chronically infected patients.[7] 2) Thyroid manifestations may be secondary to a generalized autoimmune phenomenon induced by HCV infection.[8]

Interferon (IFN), is the drug of choice for the treatment of hepatitis C that stimulates the immune system. In addition to its antiviral activity, IFN can produce side effects affecting many different organs such as thyroid. The response of thyroid to IFN therapy is unpredictable and the role of IFN in post-treatment persistence of thyroid manifestations requires to be assessed.

IFN-induced thyroiditis can be autoimmune in nature, such as Graves' disease (GD), as well as non-autoimmune, like destructive thyroiditis.[9] The issue is further complicated by the multiple IFN regimens [i.e.,± pegylated

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interferon (a long-acting form of IFN ± ribavirin (RBV)] used in practice.[10]

The aim of the present study is to review of the literature concerning the association between HCV infection and various thyroid manifestations. Another objective was to monitor the role of IFN-based treatment of HCV infection in thyroid manifestations.

Autoimmune Thyroid Diseases in Patients with Chronic Hepatitis C Virus Infection

Thyroid gland is one of the important organs of the human body and is highly susceptible to AITDs. AITDs are conditions where the immune system attacks its own thyroid gland, interfering with their normal function. Although there are a number of types of AITDs, the two main forms are so called Grave's disease (GD) and Hashimoto's thyroiditis (HT). Each of these diseases can behave differently and have their own causes, symptoms, and methods of treatment. Nonetheless, some of the immunologic features of Grave's and Hashimoto's mirror each other and the disease may progress from one state to another as the autoimmune process changes.[11]

The etiology of AITDs is not definitely known and several hypotheses have been proposed. It seems that both genetic predisposition and environmental factors have been implicated in the mechanism underlying the pathogenesis of thyroid autoimmunity. Thus far, no single environmental exposure has been consistently identified as a causal factor in AITDs and several observations suggest that a number of environmental factors like viral infection, drug exposure, smoking, stress and iodine intake are associated with the disease progression.[11,12]

Among the different environmental factors, more attention has been given to infectious agents and several observations suggest that certain viral infection may lead to AITDs in genetically susceptible individuals.[13] HCV is one of the viruses that has been gaining an increasing interest as a possible inducer of thyroid autoimmunity in subjects having genetic predisposing factors.[14,15]

The concept of association between AITDs and HCV formed on the basis of several important observations. A number of studies have reported a high prevalence of HCV antibodies (anti-HCV antibodies) in patients with AITDs. For example, a survey amongst subjects with AITDs indicated that 11.6% of the patients versus 2.3% of controls had antibodies to HCV.[16] Another investigations of anti-HCV antibodies in connection with AITDs have been conducted. Results from these experiments appear to be somewhat inconsistent.[17-19]

Many of the factors contributing to this controversy such as geographical heterogeneity in the prevalence of AITDs and HCV infection.[20,21] Moreover, certain HCV genotypes may predispose the infected patients to AITDs. For instance, Giannitti, *et al.* indicated AITDs is prevalent in Italian patients infected with HCV genotype 2c.[22] The presence of antigenomic HCV RNA in the thyroid of chronically infected patients[7] can also provide confirmatory proof of the association between AITDs and HCV infection.

Another important point is an increased prevalence of anti-thyroid antibodies in patients with chronic hepatitis C before IFN therapy.[23] This subject has been first described by Pateron, *et al.*[24] and has generated a great deal of discussion amongst clinical and basic science investigators. The prevalence of anti-thyroid antibodies in patients with chronic HCV varies largely, between 2-48%.[25] Moreover, there is a greater prevalence of thyroid abnormalities in HCV infected patients than in controls (17 vs 4%).[26] There are multiple contributory factors to this variation, such as poor internal controls, differences in the sensitivity of the assay methods, and other factors like iodine intake and medications.[15,27]

Pathogenesis of Thyroid Autoimmunity in Chronic HCV Infection: Emerging Insights into Molecular Mechanisms

The exact pathogenesis of hepatitis C virus-related thyroid disorders has not been elucidated completely and previous studies have failed to definitively explain the precise mechanism linking HCV infection with thyroid autoimmunity. However, major advances in our understanding of the underlying mechanisms have recently been made and several mechanisms have been suggested to explain the association of HCV infection with autoimmune thyroiditis including: Changes in self-antigen expression due to viral infection, or recognition of cryptic epitopes;[13] bystander activation of auto reactive T-cells by cytokine release during the local inflammatory response caused by virus;[5] molecular mimicry or cross-reactivity may occur between viral antigens and thyroidal antigens;[28] heat shock proteins expression in thyroid gland;[29] and abnormal expression of MHC class II molecules by thyrocytes.[30,13]

Cytokines, chemokines and their receptors may contribute either directly or indirectly in above-mentioned mechanisms. These factors are low molecular weight, function as

chemical messengers and are interact with one another in complex ways. They are synthesized by multiple cell types and can have various functions depending upon the cell that produces it and the cell upon which the cytokine acts. Therefore, it is difficult to draw conclusions with regard to the specific role of each cytokine in mediating the observed pathophysiological effects. However, there is, a growing recognition that aberrant cytokine expression appears to play an important role in the pathogenesis of many human autoimmune diseases, including virus-induced thyroid autoimmunity. Consequently, the involvement of these mediators in disease cannot be ignored.

Different studies have revealed upregulation of interferon-gamma (IFN-γ) expression[31] and IFN-γ-inducible chemokines,[32] such as chemokine (C X C motif) ligand 10 (CXCL10) (a powerful chemoattractant for T helper 1 (Th1) lymphocytes secreting IFN-γ), in the hepatocytes and lymphocytes of HCV-positive patients.[33,34] A direct association was observed between the expression pattern of these factors and the degree of inflammation.[35,36] In addition, several studies have suggested that CXCL10 assessment is a suitable indicator of aggressive Th1-mediated autoimmune disease.[37] It seems that specific production of this molecule by hepatocytes in inflammatory regions, may help to recruit T cells to the hepatic lesions in chronic viral hepatitis.[38]

On the other hand, increased CXCL10 production may shape the cytokine profile of thyroid-infiltrating T cells into an inflammatory, Th1-like pattern. It has been shown that IFN-γ, the signature cytokine of Th1 cells, in combination with TNF-α impairs the growth of thyrocytes.[39]

Moreover, the relationship between elevated plasma level of CXCL 10 and a poor outcome of antiviral therapy in patients with hepatitis C has been recognized.[40] Several lines of evidence suggest that CXCL10 may be involved the initial phases of AITD. For instance, this molecule is expressed in infiltrating inflammatory cells and in thyrocytes of patients with GD.[41] Furthermore, the serum concentrations of CXCL10 were higher in autoimmune thyroiditis than in controls.[42] and an important inverse correlation was demonstrated between circulating CXCL10 levels and disease duration in GD.[41]

In vitro stimulation of human GD thyrocytes with IFN-γ was shown to induce a large production of CXCL10.[42] This finding is in accordance with previous studies indicating an involvement mainly of Th1 cytokines in GD and GO.[43,44] The reduction of CXCL10 levels after thyroidectomy[45] or radioiodine treatment[46] in GD indicates that the intrathyroidal lymphocytes and/or thyrocytes may be the source of CXCL10.[47]

In conclusion, it seems that a complex network of cytokines, chemokines and their receptors influences the immune response in patients with hepatitis C virus infection and autoimmune thyroid disease. As a result, further studies in larger series will be required to assess the potential value of these mediators as prognostic markers of thyroiditis in the follow-up of HCV^+ patients.

Interferon-Related Autoimmune Thyroid Diseases

Interferon is the therapeutic backbone of HCV treatment. It binds to cell surface receptors and then altering cell metabolism. This biologic agent has antiviral, antiproliferative, antitumoral and immunomodulatory activity. Several studies have shown that IFN can normalize serum alanine aminotransferase (ALT), improve liver histology and reduce viral load in patients with chronic hepatitis C (CHC).[48]

Therapy of CHC has evolved from interferon alpha (IFNα) monotherapy and available published data reveal that IFNα monotherapy produces a loss of sustained virological response in <20% of CHC cases.[49] Nonetheless, results of a recent study indicate that treatment of HCV infection with pegylated interferon (peg-IFN) in combination with ribavirin can eradicate HCV infection in 40-90% of patients.[50]

In spite of its remarkable therapeutic properties, IFNα has a well-recognized adverse effects, ranging from influenza-like symptoms to hematologic effects, neuropsychiatric symptoms, and thyroid disease.[51] A link between IFNα and thyroid disease was identified as early as 1985 in patients who have been treated with IFNα for breast cancer.[52] Since then there have been a substantial number of reports on the possible association between thyroid disease and IFNα.[53] The clinical manifestations of IFN-induced thyroid autoimmunity can be divided into different types including GD, thyroiditis and profound subclinical hypothyroidism.[54] It seems that graves' hyperthyroidism is less common than the other types because only 20-25% of all patients with IFN-related thyrotoxicosis are due to Graves' disease induced by circulating thyroid receptor antibodies (TRAb).[55,56]

As a result of these side effects, the IFN therapy sometimes may need to be discontinued, depending upon the severity of symptoms.[57] In addition, hypothyroidism can escape diagnosis due to the overlap of its symptoms with those induced by IFNα therapy or hepatitis C, such as fatigue and weight increase.[51] This condition, if left unchecked, can lead to further complications. Thus, great attention must be

paid to IFN induced thyroiditis (IIT) in patients receiving IFN therapy. IIT can be divided into two main groups, autoimmune type and non-autoimmune type.[58] The former, can manifest as HT, GD and occasionally may be associated with the production of thyroid autoantibodies (TAb's) without clinical disease. In all of these disorders the presence of TAb's prior to the initiation of IFNα therapy is an important risk factor for the development of IIT. For instance, in HCV-positive individuals, the progress of HT in a TAb's positive patient who undergoing IFNα treatment is often accompanied by elevation in antibody titers.[59,60] Moreover, Prummel, *et al.* indicated that preexisting (pretreatment) of TPO autoantibodies, is a significant risk factors for the development of thyroid dysfunction (3.9 fold).[61] Several studies also indicated that there is a clear link between female sex, old age and genetic predisposition with the development of antibodies.[61,62]

Together, these observations suggest that IFN can increase the levels of TAb's in patients who were positive for TAb prior to therapy and it can exacerbate preexisting thyroid autoimmunity.[30] These lines of evidence suggest that patients who have TAb's before treatment are at higher risk for autoimmune thyroid diseases. As a result, screening for autoantibodies is proposed before, during and after IFN treatment. Furthermore, it is important that patients be well informed about the risk of thyroid dysfunction.[63]

The mechanisms for autoimmune thyroid disorders resulting from IFN therapy are not well understood. In addition to genetic susceptibility,[64,65] it is believed that IFNα induces IIT by both immune stimulatory effects and by direct effects on the thyroid. The exogenous IFN affect the immune system at different levels. Under the influence of IFN lymphocyte, macrophage and neutrophil are activated. It also enhances cytokine and chemokine production, particularly, interleukin-6 (IL-6)[66] a cytokine which has been implicated in the pathogenesis of autoimmune thyroiditis.[67]

IFNα can upregulate expression of MHC class I, MHC class II and probably CD40 molecules on thyroid cells.[68,69] Increased expression of class I antigens is accompanied by activation of cytotoxic T cells, and thus can result in tissue damage and inflammatory response.[70,71] Moreover CD40 ligation on thyrocytes causes augmented T-cell activation and overexpression of intrathyroidal IL-6. Pre-existing and circulating IL-6 together with IL-6 produced by the thyroid cell induces the development of thyroiditis within the thyroid.

Specific IL-6 binding sites have been also identified in thyroid cells,[70] which reduces TSH-mediated iodine uptake, thyroid peroxidase mRNA expression in response to TSH, and thyroid hormone release through the TSH-dependent mechanism.[70,72] Both in GD and in HT, membrane attack complexes of complement occur around thyroid follicles.[73] Formation of these complexes may result in prostaglandin E2, IL-1a, and IL-6 production, which promote infiltration of lymphocytes leading to cell destruction. In GD, proinflammatory cytokines such as IL-6 may further induce the synthesis of external thyroid-stimulating antibodies that bind to TSHR.[74] IFNα can also contribute to an autoimmune inflammatory response via a variety of mechanisms, such as reducing T regulatory cell function and alterations in immunoglobulin production.[75,76] Th1 polarization may constitute a potentially important therapeutic effect of IFNα and may contribute in the pathogenesis of IIT. This deduction depends partly on observations such as greater increase in type 1 helper T cells in hepatitis C patients who developed IIT.[77,78] However, there are some conflicts regarding these results and several studies indicated that IFNα could influence the production of type 2 cytokines.[79,80]

The HCV or its genome may act as an integral part of the thyroid dysfunction process.[64] The virus is able to induce endogenous interferon to a greater extent; this enhances thyroid auto-antibodies formation and triggers autoimmune thyroid disease in susceptible individuals. It is possible that synergy between endogenous and exogenous IFNa may exaggerate the effect on the thyroid thus causing additional hypothyroidism.[81]

As mentioned above, some studies indicate that IFN can exert a direct effect on thyrocytes.[78] This findings is supported by research from elsewhere which has identified a pattern of increased occurrence of non-autoimmune thyroiditis (about 50%) in patients with IIT.[30] Caraccio, *et al.* studied the effects of type I interferons on human thyroid follicular cells. They found that exposure of thyroid follicular cells to these cytokines inhibits TSH-induced gene expression of thyroglobulin (Tg), TPO, and sodium iodide symporter (NIS).[82] In another study, expression levels of the TSHR, Tg, and TPO genes were tested in rat thyroid cell line. The results of this study were as follows: Early elevations but a late decrease in Tg and TPO levels, increased expression of the TSHR gene in cultured thyroid cells exposed to IFNα, and enhanced induction of thyroid cell death by IFNα.[30]

Conclusion

On the basis of the data presented above, the evidence suggests that chronic HCV infection and HCV antibody seropositivity can be associated with the appearance of

thyroid autoimmunity and hypothyroidism. As a result, particular attention should be paid to verify or refute an aetiopathogenetic role of HCV in these conditions. Moreover, physician must be highly careful when examining patients presenting with above mentioned thyroid disorders. One of the standard treatments for patients with chronic hepatitis C, is the biological drug IFN-α. Although IFN therapy is generally well-tolerated, some patients may experience side effects. One of the adverse effects related to IFN therapy is thyroid disorders, and represent a main complication to sufficient treatment for patients with HCV. Therefore, the physician must be alert to the possibility of these unwanted effects and measuring the thyroid function tests and thyroid antibodies before, during, and after IFN therapy to reduce or eliminate the risk of thyroid disorders.

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