

Thyroid Dysfunction in Hepatitis C Individuals Treated With Interferon-Alpha and Ribavirin - A Review

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Hepatitis C (HCV) is now the main cause of chronic hepatic disease, cirrhosis and hepatocellular carcinoma. Several extrahepatic diseases have been associated with chronic HCV infection, and in most cases appear to be directly related to the viral infection. Thyroid disorders are common in patients with chronic HCV. Some patients with chronic hepatitis C experience thyroid problems, and thyroid dysfunction may also be a side effect of interferon-based treatment. The principal risk factor for developing thyroid disease in the course of antiviral therapy is the previous positivity for anti-thyroid antibodies (anti-thyroid peroxidase) especially in older women. Screening for autoantibodies and serum thyroid-stimulating hormone is recommended before, during and after interferon-alpha treatment, and patients should be informed of the risk of thyroid dysfunction. This review includes a summary of thyroid disease associated with chronic HCV infection, interferon-alpha and ribavirin for treatment of HCV and potential to induce thyroid dysfunction.

Key-Words: Hepatitis C, interferon-alpha, ribavirin, thyroid dysfunction, thyroiditis.

Hepatitis C (HCV) is now the main cause of chronic hepatic disease, cirrhosis and hepatocellular carcinoma. It is estimated that 170 million persons in the world are infected with HCV with a global prevalence of about 3%. Every year there are estimates of 3 to 4 million new cases of infection due to transfusion contamination, contaminated injection needles, and parenteral exposure [1]. However, the incidence of HCV has either declined or stabilized in recent years [2]. In the United States, HCV remains the most common chronic blood-borne infection [3,4].

Several extrahepatic diseases have been associated with chronic HCV infection and, in most cases, appear to be directly related to the viral infection. These include: hematologic diseases such as cryoglobulinemia and lymphoma, autoimmune disorders such as thyroiditis and the presence of autoantibodies, renal disease, dermatologic conditions such as lichen planus and porphyria cutanea tarda [5-8].

Thyroid disorders are common in patients with chronic HCV, particularly women. Anti-thyroid antibodies are present in 5% to 17% of patients with HCV infection, and thyroid disease, primarily hypothyroidism, occurs in 2% to 13% of patients and up to 25% have thyroid antibodies [9,10]. The highest prevalence of both thyroid antibodies and thyroid disease is found in older women. Most HCV patients with thyroid dysfunction are middle-aged women with asymptomatic hypothyroidism and do not require specific treatment. However, whether or not the prevalence is higher than in age and sex-matched controls is controversial [11,12].

Some patients with chronic hepatitis C experience thyroid

problems, and thyroid dysfunction may also be a side effect of interferon (IFN)-based treatment. Thyroid autoantibodies and disorders have been reported in patients with chronic hepatitis both before and after IFN-alpha treatment, but the prevalence appears greater in those with chronic HCV virus infection [13,14]. Approximately 1% to 7% of patients who are treated with chronic IFN-alpha therapy develop painless thyroiditis [14,15]. Other thyroid abnormalities can also occur, including Graves' disease and permanent hypothyroidism, or increased serum anti-thyroid antibody concentrations without thyroid dysfunction, with an estimate relative risk of 4.4% and an incidence of 5%-12% in HCV patients [16,17]. The principal risk factor for developing thyroid disease in the course of antiviral therapy is the previous positivity for antithyroid antibodies (antithyroid peroxidase) especially in older women and family [15]. Patients who develop an IFN induced thyroid disease perhaps are genetically susceptible [17,18].

The presence of low titles of autoantibodies should not be regarded as a contraindication for IFN therapy. Because most patients with increased antibody titles or thyroid dysfunction, especially hypothyroidism, under IFN therapy recover after completing therapy, interruption of IFN therapy may not always be required, although treatment must be interrupted in patients with severe symptoms. Screening for autoantibodies and serum thyroid stimulating hormone (TSH) is recommended before, during and after IFN treatment, and patients should be informed of the risk of thyroid dysfunction [19].

This review includes a summary of thyroid disease associated with chronic HCV infection, IFN and ribavirin (RIBA) for treatment of HCV and potential to induce thyroid dysfunction.

Interferon-alpha

The IFN are a group of proteins called cytokines produced by white blood cells, fibroblasts, or T cells as part of an immune response to a viral infection or other immune trigger. The name

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of the proteins comes from their ability to interfere with the production of new virus particles [20].

There are three types of IFN: alpha, beta, and gamma. IFN-alpha and -beta, which are grouped together as type I interferon, are produced by white blood cells and a type of connective tissue cell called fibroblast. IFN-gamma, or type II IFN, is produced by T cells. Production occurs when the T cells are activated such as during an infection [21].

IFN-alpha and beta share some biological activities, but also have activities that are distinct from each other. These similarities and differences reflect the common and different binding of the IFN to various receptors on the surfaces of human cells [22].

The mechanism by which IFN exerts antitumor or antiviral activity is not clearly understood. However, it is believed that direct antiproliferative action against tumor cells, inhibition of virus replication and modulation of the host immune response play important roles in antitumor and antiviral activities [23].

It has been shown that IFN has antiproliferative and immunomodulatory activities in human cells *in vitro* that are very similar to those of the mixture of IFN-alpha subtypes produced by human leukocytes. Using IFN *in vivo* has been shown to inhibit the growth of several human tumors growing in immunocompromised mice [24].

IFN-alpha is totally filtered through the glomeruli and undergoes rapid proteolytic degradation during tubular reabsorption, rendering a negligible reappearance of intact IFN-alpha in the systemic circulation. Liver metabolism and subsequent biliary excretion are considered minor pathways for elimination of IFN-alpha [25].

Conjugation of polyethylene glycol (PEG) to a pharmaceutical protein is a method that increases the lifetime blood circulation of drug. PEG-drug conjugates exhibit enhanced solubility, reduced antigenicity, reduced sensitivity to proteolysis, and reduced rate of kidney clearance. The development of PEG-IFN has significantly improved the eradication rates in patients with chronic hepatitis C. Two forms of PEG-IFN have been developed, based on two pegylation chemistries: the 12-kDa linear PEG-IFN-alpha 2b and the 40-kDa branched PEG-IFN-alpha 2a [26].

IFN-alpha is used in a number of conditions, including chronic viral hepatitis, hematological malignancies, renal cell carcinoma and melanoma.

Interrelation of Interferon on Thyroid Function

Several studies observed that IFN-alpha treatment increased the risk of thyroid dysfunction [11,27,28], whereas in most cases, thyroid dysfunction is reversed after discontinuation of IFN-alpha treatment. It is important to note that IFN-alpha treatment itself is associated with autoimmune manifestations [29]. The development of thyroid dysfunction during IFN-alpha and RIBA combination therapy has been reported to occur in 4.7% to 27.8% of patients, with a mean

incidence of 12.1%. It is higher than in those treated with IFN alone (6.6%) [18,30-34].

The clear association between autoimmune thyroid disease and IFN-alpha use suggests that high endogenous IFN-alpha levels may also be associated with naturally occurring autoimmune thyroid disease [35]. The strongest risk factors that were associated with an increased risk of development of thyroid disease during IFN-alpha therapy were female sex and the presence of thyroid autoantibodies, particularly antithyroid peroxidase antibodies, before the initiation of therapy [36].

Thyroid disease is less likely to develop in patients with chronic hepatitis B infection who are treated with IFN-alpha than in those with chronic HCV infection, this finding suggests that HCV and IFN-alpha may have a synergistic role in inducing thyroid disease during antiviral therapy [17]. It is hypothesized that HCV particles will result in an induction of IFN-alpha and -beta production in the thyroid gland as part of the innate immune response [37]. IFN can also activate natural killer cells, maturation and proliferation of dendritic cells, proliferation of memory T cells, and prevention of T cell apoptosis [38]. These will induce a rise in the thyroid auto-antibodies titer. These antibodies will, in turn, damage the thyroid gland, depending upon genetic predisposition.

The IFN-alpha induced thyroid dysfunction was reversible in 61.2% of patients, including 55.8% of patients with hypothyroidism and 69.7% of those with thyrotoxicosis [34]. The PEG form of IFN seems to have the same effects as standard IFN [39].

Ribavirin

The RIBA is a nucleoside analogue with a broad spectrum of activity against several RNA and DNA viruses, this drug probably has immunomodulatory effects, and it is possible that RIBA may stimulate the immune system alone or synergistically with IFN-alpha to cause thyroid disease via an autoimmune mechanism [40].

The RIBA is a pro-drug, meaning that it is a chemical precursor for the actual pharmacologically active molecule. The RIBA is activated by cellular kinases which change it into the 5' triphosphate nucleotide. In this form it interferes with aspects of RNA metabolism related to viral replication. A number of mechanisms have been proposed for this, but none of these is proven. More than one mechanism may be active [41]. RIBA is readily phosphorylated intracellularly by adenosine kinase to RIBA mono-, di-, and triphosphate metabolites. Ribavirin triphosphate is a potent competitive inhibitor of inosine monophosphate dehydrogenase, viral RNA polymerase and messenger RNA (mRNA) guanylyl transferase (viral). Guanylyl transferase inhibition stops the capping of mRNA. These diverse effects result in a marked reduction of intracellular guanosine triphosphate pools and inhibition of viral RNA and protein synthesis. RIBA is also incorporated into the viral genome causing lethal mutagenesis and a subsequent decrease in specific viral infectivity.

The RIBA is an inhibitor of some viral RNA guanylyl transferase and guanine-7N-methyl transferase enzymes, and this may contribute to a defective 5'-cap structure of viral mRNA transcripts and therefore inefficient viral translation for certain DNA viruses, such as vaccinia virus, a complex DNA virus. It has been suggested that incorporation of RIBA into the 5'-end of mRNA transcripts would mimic the 7-methyl guanosine endcap of cellular mRNAs, causing poor cellular translation of these. This would be a cell-toxic effect, but it does not seem to be important at therapeutic RIBA concentrations. Any difference between cellular and viral enzyme handling of RIBA-containing mRNA transcripts is a potential mechanism of differential inhibition of RIBA to translation of mRNAs from viruses [42].

However, RIBA can also enhance the non-virus-induced immune response, suggesting that this drug, as a type 1-inducing agent, could trigger autoimmune phenomena in predisposed patients. Indeed, it has been demonstrated that the Th1-like immune response is an important factor for the development and maintenance of organ-specific autoimmune diseases [43,44].

Results of *in vitro* studies using both human and rat liver microsomal preparations indicated little or no cytochrome P450 enzyme-mediated metabolism of RIBA, with minimal potential for P450 enzyme-based drug interactions. RIBA has two pathways of metabolism: a reversible phosphorylation pathway in nucleated cells; and a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite.

Interrelation of Ribavirin on Thyroid Function

Several studies have reported the development of hypothyroidism and hyperthyroidism in patients treated with IFN monotherapy, being described the incidence of thyroid dysfunction during IFN-alpha and RIBA as well as in combination therapy in men [36]. Therefore, the mean incidence of thyroid dysfunction in patients treated with IFN-alpha and RIBA combination therapy (12.1%) is higher than in those treated with IFN alone (6.6%) [34].

However, few reports have aimed to investigate the role of RIBA on the occurrence of autoimmune disorders and the data evaluating such therapy and thyroid autoimmune disorders are even more limited [18,45].

The RIBA is a guanosine analogue that plays important immunological effects *in vivo*, by a differential modulation of Th1- and Th2-like responses, with a specific shift favoring the Th1-like activity [46]. Thus, the RIBA could induce hypothyroidism by Th1-dependent activation of CD8+ T lymphocytes which induce cellular destruction predominantly by the perforin pathway [47].

Thyroid Autoimmunity in Hepatitis C Individuals Treated with IFN-alpha and RIBA

The principal risk factor for developing thyroid disease in the course of antiviral therapy is the previous positivity for

anti-thyroid antibodies especially in older women [15]. Patients who develop an IFN-induced thyroid disease are perhaps genetically susceptible [16]. It has been pointed out that IFN-related thyroid autoimmune disease may reproduce in its short-time and long-term outcome the natural history of Hashimoto's thyroiditis [48]. Therefore, it is recommended that the screening for thyroid disease to be routinely performed in all patients with HCV infection who are treated with IFN alone or in combination with RIBA [49].

IFN-alpha treatment for various conditions has been associated with thyroid autoimmunity. The incidence of interferon-induced thyroid autoimmunity has been reported to range from 2.5% to 42%, possibly depending upon dose and duration of medical therapy and patient characteristics. It is not known whether IFN-alpha initiates autoimmune thyroid disease or simply exacerbates in individuals with subclinical disease [50]. However, it is interesting to observe the thyroid in the first 24 hours of IFN-alpha therapy. The TSH levels tend to decrease while free T4 and free T3 remain unchanged. Interleukin 6 (IL-6) levels increase, and tumor necrosis factor and IL-1 levels fall [51]. The main effect of IFN-alpha on the immune system is the enhancement of cell cytotoxicity, very likely sustained by suppression of T helper (Th) 2 and an increase in Th1 immune response [52].

The IFN-alpha therapy induces thyroid autoantibodies in patients with chronic HCV infection and may precipitate thyroid dysfunction in patients with pre-existing autoantibodies [53,54].

The management of IFN-alpha-induced thyroid dysfunction in chronic HCV infection remains a matter of debate. Some patients treated with thyroid medication before IFN-alpha treatment may require increased doses during therapy and decreased doses after IFN-alpha therapy has been completed [55].

The characteristic features of thyroid dysfunction in hepatitis C individuals treated with IFN-alpha and RIBA are generally similar to post-partum or Hashimoto's thyroiditis: autoimmune process, presence of anti-TPO antibodies, variable clinical expression, biphasic presentation in some patients, heterogeneous thyroid parenchyma at ultrasound and negative scintigraphy [56].

Symptoms common in patients with thyroid disease like fatigue, decreased appetite, depression, and myalgias were common in our patients with overt hypothyroidism, whereas nervousness, irritability, fatigue, insomnia, and weight loss were prevalent in those with overt hyperthyroidism. They could easily be mistaken for adverse effects of HCV therapy and thyroid dysfunction could have remained undiagnosed if the patients did not undergo routine periodic screening of TSH levels [18]. These thyroid abnormalities resolve in more than 50% of patients six months after the discontinuation of IFN treatment [27].

Subacute thyroiditis during combination therapy with IFN-alpha and RIBA was observed, but its pathogenesis is still unknown. Four episodes of subacute thyroiditis were described,

occurring in three patients during antiviral combination therapy. All patients had symptoms compatible with hyperthyroidism, which could be misdiagnosed as IFN side-effects [57]. Silent destructive thyroiditis is seen in up to 5% of IFN-alpha treated patients. These cases are often characterized by a transient hyperthyroidism followed by a longer hypothyroid phase, which often becomes permanent [58].

The results of the review showed an association between thyroid dysfunction in hepatitis C individuals and treatment with IFN-alpha and RIBA.

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