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REVIEW

NON-HEMATOLOGIC ADVERSE EFFECTS RELATED TO INTERFERON THERAPY IN PATIENTS WITH CHRONIC HCV HEPATITIS

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Abstract. Pegylated interferon and ribavirin are mandatory in the treatment of HCV hepatitis. An early recognition of side effects related to the antiviral therapy can prevent the discontinuation of treatment and can improve the eradication of HCV infection. Hematologic side effects related to pegylated interferon and ribavirin therapy are the most studied; on the other hand it is difficult to make a correlation between a rarely reported side effect and the medication. That's why it is important to report and to recognize all these side effects in order to avoid life-threatening. This review analyses non-hematologic side effects correlated with antiviral therapy for HCV hepatitis.
Keywords: pegylated interferon, side effect, HCV hepatitis

Introduction

Infection with hepatitis C virus (HCV) is a major problem of public health, being the leading cause of severe liver disease, cirrhosis and hepatocellular carcinoma. Pegylated interferon and ribavirin remain mandatory in the treatment of HCV hepatitis, even after the introduction in clinical use of direct acting antivirals (DAA). This antiviral treatment has varying degrees of side effects (SE) such as flulike symptoms, gastrointestinal, hematologic, ophthalmologic, autoimmune and dermatologic disorders. These SE are critical factors which can lead to discontinuation of therapy and subsequently to therapeutic failure.

The main goal of antiviral therapy in HCV infection is the eradication of HCV infection and additional goals are: slowing disease progression, improvement of histological lesions and decreasing the risk of HCC.

We have at least two reasons for a correct monitoring of SE:

1. Early discover of SE in order to prevent the discontinuation of therapy
2. Avoid life-threatening SE?

The SE related to interferon therapy can be divided into three categories according to frequency and severity:

1. SE which do not impose discontinuation of therapy (90%)
2. SE which impose dose reduction or sometimes off medication (10%)
3. Severe SE, sometimes irreversible or life-threatening (0.1 - 1%)

The definition of SE related to a medication is: an undesirable or unexpected effect related to a drug administration. According to NCI Common Terminology Criteria for Adverse Effects (CTCAE) published in August 2006, the side effects grades are: 1 – mild, 2 – moderate, 3 – severe, 4 – life threatening, 5 – death related to a side effect. [1]

The main problem in front of an unexpected effect after a drug use is to assert the correlation between a SE and the drug, especially for the rarely reported SE after a certain drug. The most useful score in order to correlate a SE with a drug is Naranjo ADR probability scale (table I).

Non-hematologic SE related to pegylated interferon therapy can be divided into two groups: frequent but mild with a reported incidence greater than 25% and rare, often severe but difficult to correlate with the drug. The most frequently reported non-hematologic SE correlated with pegylated interferon and ribavirin therapy is: fatigue – 65%, headache– 47%, nausea – 37%, sleep depravation – 38%, fever – 32%, myalgia – 26%, depression – 25%, irritability – 25%, rash – 25%. The most studied non-hematologic SE related to antiviral treatment for HCV infection are: ophthalmologic SE – 19%, thyroid dysfunction – 7%, cardiovascular SE <1%,

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respiratory SE <1%, severe psychiatric disorders <2%, nervous SE < 1%, others – 5% [2].

Scoring for Naranjo's algorithm is: definite adverse drug reaction (ADR) if the score is greater than 9 points, probable ADR if the score summed up between 5 and 8 points, possible ADR if the score is between 1 and 4 points and doubtful ADR if the score is 0.

Question	yes	no	?
Are there previous conclusion reports on this reaction?	+1	0	0
Did the adverse event appear after the suspect drug was administered?	+2	-1	0
Did the AR improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the AR reappear when drug was readministered?	+2	-1	0
Are there alternate causes [other than the drug] that could solely have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Table I. Naranjo Adr Probability Scale [3]

Ophthalmologic SE related to interferon therapy

The most important ophthalmologic SE is retinopathy. At the ophthalmologic examination we can find retinal hemorrhages, cotton-wool spots and microaneurysms, with an unclear pathogenesis. Besides retinopathy, other ophthalmologic SE were described in correlation with interferon therapy: sub-conjunctival hemorrhages, choroidal neovascularization, neovascular glaucoma, ischemic optic neuropathy etc.[4]

Increasing of c5a plasma level after interferon administration seems to produce intravascular aggregation of neutrophils and platelets with infarction of retinal capillary, retinal hypoxia and blockage of axonal flow through optic nerve [5].

Other hypothesis regarding retinopathy pathogenesis is the increase of retinal blood flow because of erythrocyte count decrease (anemia produced by ribavirin); this increasing flow determines retinal endothelium dysfunction. Moreover, both HCV virus and ribavirin therapy can contribute to the occurrence of various thrombogenic antibodies [6].

The retinopathy during HCV antiviral therapy was described since 1990 and its prevalence varies for different studies between 18% and 86% (high rate if electrophysiological changes are also considered) and it is almost always reversible after the treatment cessation, without sequels. After the introduction of pegylated form of interferon, the prevalence of ophthalmologic SE seems to be lower (below 20%) [7].

The retinopathy related to interferon develops between 2 weeks and 5 months of treatment (especially between weeks 4th and 12th) and most of the cases are asymptomatic [8].

The risk factors associated with ophthalmologic SE during pegylated interferon therapy are: diabetes mellitus, arterial hypertension, anemia and the patient older than 50 years [9].

Because severe cases with visual loss were reported, some authors recommended the need of routine ophthalmologic assessments, even in the absence of symptoms. If retinopathy was diagnosed, a closely monitoring of the patient is necessary until the full resolution.

Severity of retinopathy according to CTCAE is [1]:

- Grade 1 – Asymptomatic
- Grade 2 – Symptomatic with moderate decrease in visual acuity
- Grade 3 – Symptomatic with marked decrease in visual acuity
- Grade 4 – Blindness

Severity of retinopathy related to ocular fundus appearance is [10]:

- Moderate retinopathy – less than 4 area of hemorrhage and/or fundus nodules
- Severe retinopathy – more than 5 area of hemorrhage and/or fundus nodules

Rarely, Vogt-Koyanagi-Harada- like (VKH) disease can be reported during interferon therapy for HCV hepatitis. The disease is a rare idiopathic autoimmune granulomatous disorder which affects the eyes, auditory system, skin and meninges. Modorati et al reported two cases of VKH-like disease, with bilateral uveitis and retinal detachment, without

auditory and neurologic symptoms, nor alopecia, poliosis or vitiligo. The patients were treated with oral corticosteroids, with recovery for one patient and with visual loss for the second patient. [11].

Thyroid dysfunction related to interferon therapy

One of extra- hepatic manifestations of HCV infection is thyroiditis. The most affected patients are women, especially older women. Anti-thyroid peroxidase antibodies (ATPO) were reported in 5% to 17% of patients with HCV infection, most of them without specific symptoms and with normal thyroid stimulating hormone (TSH). The prevalence of ATPO increases during antiviral treatment and seems to be linked with both interferon and ribavirin therapy. The main risk factors for interferon related thyroiditis are: genetic predisposition, age, gender, and previous positivity of ATPO [12] (figure 1).

Because thyroid disorders are less likely to occur

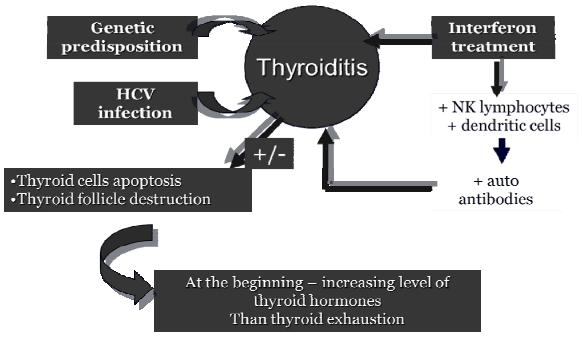

Figure 1. Thyroid dysfunction related to interferon therapy

during interferon treatment for chronic hepatitis B infection, it is hypothesized that both HCV infection and ribavirin treatment associated with interferon can be involved in the pathogenesis of the disease. High endogenous interferon alpha and beta level can increase in thyroid cells by direct HCV stimulation. Subsequently, interferon may activate natural killer cells, proliferation of dendritic cells and prevention of memory T cells apoptosis. The final result is a rise in ATPO titer [13].

Ribavirin is a type 1-inducing agent of immune response and can enhance the non-viral-induced autoimmune phenomena. This fact can explain why the incidence of thyroiditis is higher in patients receiving combination therapy than in those receiving interferon alone (12.1% vs 6.6%) [14].

It was unanimously accepted that interferon alpha therapy induces thyroid autoantibodies in HCV infected patients and may increase the thyroid dysfunction in patients with previous ATPO. For the patients receiving thyroid medication, during interferon therapy an increased dose was often necessary [15].

Four clinical entities are described for interferon induced thyroiditis:

1. Euthyroidian thyroiditis – positive ATPO but normal level of TSF and FT4
2. Thyroiditis with hypothyroidism – positive ATPO with high TSH and low FT4
3. Thyroiditis with hyperthyroidism Graves-like – positive ATPO with very low TSH (sometimes with TSH-0) and high FT4
4. Non-autoimmune thyroiditis with a biphasic evolution: first hyperthyroidism by thyroid cells destruction with high level of FT4 releasing (direct toxic effect of interferon) and then hypothyroidism which can be resolved after interferon discontinuation. Up to 50% of the patients with interferon induced thyroiditis have negative ATPO, developing a non-autoimmune thyroiditis [16].

Normalization of thyroid function seems to be around 55% for hypothyroidism and 70% for hyperthyroidism [17].

Severity of hyperthyroidism as SE and the management according to CTCAE grades is presented below [1]:

Grade 1 – Asymptomatic, intervention not indicated

Grade 2 – Symptomatic, not interfering with activities of daily living (ADL); thyroid suppression therapy indicated

Grade 3 – Symptoms interfering with ADL; hospitalization indicated

Grade 4 – Life-threatening consequences (e.g. Thyroid storm)

Grad 5 - Death

Severity of hypothyroidism as SE according to CTCAE is [1]:

Grade 1 – Asymptomatic, intervention not indicated

Grade 2 – Symptomatic, not interfering with ADL; thyroid suppression therapy indicated

Grade 3 – Symptoms interfering with ADL; hospitalization indicated

Grade 4 – Life-threatening, myxedema coma

Grade 5 – Death

The patients should be informed about the risk of thyroid disorders before antiviral treatment. All the patients must be screened for ATPO and TSH before, during and after interferon therapy. The determination of TSH and FT4 are recommended monthly – if ATPO were positive before interferon treatment and every 3 months if ATPO were negative at the beginning. It doesn't need discontinuation of the antiviral therapy [12].

Cardiac SE related to interferon therapy

Alpha interferon is the most cardiotoxic among

the known three types of interferon, followed by beta and gamma interferon. Although rarely reported (below 1%), cardiac SE related to interferon therapy can be sometimes life-threatening. The interferon determines cardiac SE by deterioration of endothelial cells with immune complex occurrence at this level. In the same time a vasopressor effect can be observed especially by release of TNF alpha, IL 2, IL 6 and IL 1. The most frequent cardiac SE during interferon therapy are: arrhythmias- 58 %, acute coronary syndrome- 21 %, cardiomiopathies-12 % and other manifestations (including pericarditis, conduction abnormalities, congestive cardiac failure, sudden death) - 9 %. These SE are not correlated with previous cardiac disease or with other predisposing factors [18, 19].

Hiramatsu et al demonstrated that interferon therapy for HCV chronic hepatitis may induce arrhythmias by ventricular late potentials occurrence; these alterations are reversible and subclinical [20].

In 2006, Condat et al reported a case of fatal cardiomyopathy associated with interferon treatment; a 45 year-old male, with HCV chronic hepatitis, without previous cardiac pathology, received interferon therapy and in the 12th month of treatment developed severe cardiomyopathy and died [21]. Before this case, 21 other cases of cardiomyopathy related to standard interferon therapy had been reported, 20 of them reversible.

Until now, seven cases of acute pericarditis related to interferon therapy for HCV chronic infection were reported [22].

Severity of acute pericarditis as SE, according to CTCAE [1] is presented below:

Grade 1 – Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis

Grade 2 – Symptomatic pericarditis (e.g., chest pain)

Grade 3 – Pericarditis with physiologic consequences (e.g., pericardial constriction)

Grade 4 – Life-threatening consequences; emergency intervention indicated

Grade 5 – death

Respiratory SE related to interferon therapy

Until now a wide spectrum of respiratory adverse events were reported related to interferon therapy for chronic HCV hepatitis: interstitial pneumonitis, bronchial asthma, pleural effusion, exacerbation of chronic bronchitis and sometimes severe disorders such as respiratory distress syndrome. The incidence of these SE was considered to be lower than 1% [23]. The most studied respiratory SE was interstitial pneumonitis (IP) with an incidence estimated of 0.01-0.3% [24].

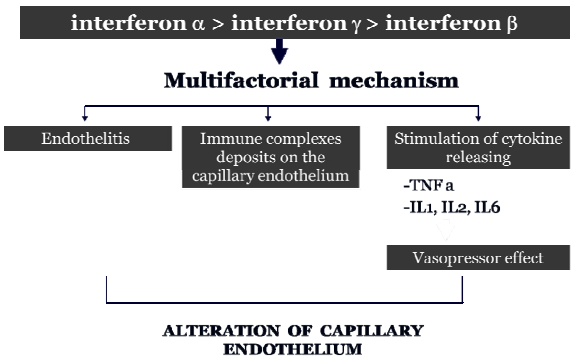

Figure 2. Cardiotoxicity of interferon - pathogenesis

The pathogenesis of interferon induced IP seems to be done by increasing cytotoxic T cells expression in the lung with concomitant inhibiting suppressor T cells. Pro-inflammatory cytokines which are released in the lung provoke lung tissue fibrosis [25].

Pegylated interferon does not seem to increase the risk of IP despite its prolonged half-life; the role of ribavirin in IP pathogenesis during antiviral treatment for HCV infection was not demonstrated [26]. Interferon induced IP can occur at any time during antiviral treatment from week 2 to week 48, usually before 12th week of therapy.

Ji FP et al published in 2010 a systematic review of 24 cases of interferon related IP reported before. Dyspnea and dry cough were the most frequent symptoms (80% and 75% respectively). In 14 of 21 cases, chest CT scan showed bilateral interstitial abnormality with ground glass opacity [27].

The management of interferon induced IP consists in the discontinuation of antiviral therapy. The use of corticosteroids is controversial. For severe cases corticosteroids may be useful. The therapy is started with high dose prednisolone and then the dosage has to be progressively decreased over the next 12 weeks [28].

According to CTCAE [1] the severity of pneumonitis is presented below:

Grade 1 - Asymptomatic, radiographic findings only

Grade 2 - Symptomatic, not interfering with ADL

Grade 3 - Symptomatic, interfering with ADL; O2 indicated

Grade 4 - Life-threatening; ventilatory support indicated

Grade 5 - Death

Neuropsychiatric SE related to interferon therapy

Pegylated interferon therapy is significantly associated with psychiatric disorders such as: depressive mood, anxiety, insomnia, irritability, difficulties of concentration and increase in the risk of suicide.

Depressive symptoms are the most studied and reported during interferon therapy. These symptoms are reported even in patients without hepatitis, who received interferon for malignant diseases such as: malignant melanoma, chronic myeloid leukemia, kidney carcinoma. The incidence of depressive disorders related to interferon therapy is high and can exceed 80% according to Center for Epidemiologic Studies Depression Scale (CES-D) criteria for depressive disorders [29]. Major depressive disorders were reported in 39% of patients who were euthymic before interferon therapy [30].

According to Pavlovic et al one third of HCV infected patients have psychiatric disorders before interferon therapy and during antiviral therapy more than 20% of the patients who developed severe depressive symptoms, required psychiatric treatment. The explanation for this high rate of depressive disorders was: neurotoxicity of HCV, psycho-social factors such as negative expectation of the outcome and insufficient information about prognosis. The only risk factor associated with depressive symptoms in HCV hepatitis is female gender [31].

Interferon leads to depression by pro-inflammatory mediators which seem to interact with neuroendocrine function and neurotransmitter metabolism. Finally, inflammation determined by interferon can contribute to the occurrence of depression [32].

Depression screening seems to be very important in order to avoid severe depressive disorders and even more, to prevent some suicide attempts in these patients.

According to CTCAE [1] the severity of mood alteration is presented below:

Grade 1 - Mild mood alteration not interfering with function

Grade 2 - Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated

Grade 3 - Severe mood alteration interfering with ADL.

Grade 4 - Suicidal ideation; danger to self or others

Grade 5 - Death

Autoimmune disorders

The expression of MHC class 1 antigens is increased during interferon alpha therapy. A large variety of autoimmune diseases can be triggered by interferon alpha. This therapeutic agent determines the increase of cytotoxic activity of NK and CD8+ and activation of CD4+ which produces IL2. In the same time, interferon inhibits the production of IL-10 and ribavirin suppresses IL-10, IL-12 and TNF-alpha [33]. Interferon also stimulates the macrophages which produce B cell activating factor belonging to the TNF-family (BAFF) involved in both rheumatoid arthritis and lupus erythematous [34]. Pegylated interferon seems to be even more involved in autoimmune diseases occurrence because of prolonged exposure due to increase in the half-life.

Among the most frequent autoimmune disorders described during pegylated interferon treatment are: autoimmune thyroiditis, rheumatoid arthritis, type 1 diabetes mellitus, lupus erythematous, sarcoidosis, psoriasis, autoimmune hepatitis [35].

a. Type 1 diabetes mellitus related to interferon therapy

Although rare, type 1 diabetes mellitus (T1DM) is a severe SE during interferon therapy, which leads to treatment discontinuation. While HCV infection is involved in type 2 diabetes mellitus (by invasion of human pancreatic beta-cells)[36], interferon therapy is involved in T1DM by occurrence of islet cells autoantibodies such as: Glutamic acid decarboxylase antibodies, Islet cell autoantibodies, Insulinoma associated antigen 2 antibodies and also by insulin autoantibodies [37]. These autoantibodies are involved in pancreatic beta cells destruction. Rarely, interferon therapy can determine the appearance of anti-insulin receptor autoantibodies which can explain the difficulties in maintaining a reasonable level of blood glucose under insulin therapy [38].

The incidence of T1DM during interferon therapy for HCV hepatitis was not analyzed until now but seems to be lower than 1% [39].

According to CTCAE [1] the severity of T1DM is presented below:

Grade 1 - Asymptomatic, intervention not indicated

Grade 2 - Symptomatic; dietary modification or oral agent indicated

Grade 3 - Symptoms interfering with ADL; insulin indicated

Grade 4 - Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

Grade 5 – Death

b. Rheumatoid arthritis (RA) related to interferon therapy

RA can be produced by HCV infection and the symptoms can be controlled by interferon therapy because of viral load decrease [40]. Sometimes, rheumatoid arthritis was reported in relation to interferon administration. The diagnosis is made by anti-cyclic citrullinated peptide (anti-CCP) antibody which can be positive before the interferon therapy, even in the absence of specific symptoms. Interferon can be a trigger for the clinical onset of

RA because of elevation of serum BAFF levels [41]. Izumi Y et al considered that the pathogenesis of RA related to interferon therapy has 2 different stages: first, anti-CCP antibodies precede the RA and second, interferon may trigger the onset of RA.

One of the important risk factor for developing RA seems to be the association between smoking and HLA-DRB1 genes [42].

According to CTCAE [1] the severity of arthritis is:

Grade 1 - Mild pain with inflammation, erythema, or joint swelling, but not interfering with function

Grade 2 - Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL

Grade 3 - Severe pain with inflammation, erythema, or joint swelling and interfering with ADL

Grade 4 – Disabling

Grade 5 – Death

Polyneuropathy related to interferon therapy

Neurological complications occurred rarely during interferon therapy. Among these SE, peripheral neuropathy is even rarer and can be: inflammatory demyelinating polyneuropathy, sensory neuropathy, autonomic neuropathy etc. The diagnosis of polyneuropathy is confirmed by electromyogram and the discontinuation of antiviral therapy is mandatory [43].

Besides cessation of interferon therapy, these patients may benefit of plasma exchange and intravenous immunoglobulin which seem to shorten the neurological symptoms [44].

According to CTCAE [1] the severity of autonomic neuropathy is:

Grade 1 - Asymptomatic, weakness on exam/testing only

Grade 2 - Symptomatic weakness interfering with function, but not interfering with ADL

Grade 3 - Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated

Grade 4 - Life-threatening; disabling (e.g., paralysis)

Grade 5 - Death

According to CTCAE [1] the severity of sensory neuropathy:

Grade 1 - Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function

Grade 2 - Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL

Grade 3 - Sensory alteration or paresthesia interfering with ADL

Grade 4 - Disabling

Grade 5 - Death

Conclusions

1. An accurate assessment is needed for patients with chronic HCV hepatitis after initiation of treatment with interferon and ribavirin for the detection of associated pathologies, often subclinical.

2. Ocular damage related to interferon treatment is relatively commonly reported; most often diagnosed late and imposes an ophthalmologic evaluation at every 3 months.

3. Heart disease although rare, is one of the most serious adverse effects, requiring cardiology evaluation every 3 months in patients treated with interferon.

4. Thyroid function monitoring is required at intervals of one or three months depending on the presence or absence of anti TPO antibodies at the start of therapy

5. Monitoring and reporting of non-hematologic adverse effects related to interferon therapy are important both for patients and for physicians who face similar situations, often difficult to interpret.

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