

# CLINICAL REVIEW

## How to manage side effects of interferon alpha therapy in Chronic Hepatitis C?

**Kamran Bagheri Lankarani**

Associate professor of gastroenterology; Department of Gastroenterology, Namazi Hospital, Shiraz University of Medical Sciences; Shiraz, I.R.Iran, Member of Study Group of Interferon in Iran (SG.IFN.IR)

### *Introduction*

Chronic hepatitis C is one of the leading indications for liver transplantation and will continue to pose a significant health and economic burden for the next 10 to 20 years.<sup>1,2</sup> Fortunately, there have been considerable advances in the treatment of this disease in recent years. Combination therapy with Interferon (IFN) and Ribavirin (RBV) has a proven efficacy in the treatment of HCV infected patients.<sup>3-8</sup>

One of the major concerns with this therapy is its adverse effects. Numerous side effects have been reported to occur with combination therapy. Most of them are mild and reversible but some of them are severe and even life threatening. There is usually a 15% rate of drug discontinuation and another 25% dose reduction during therapy with IFN & RBV.<sup>3-6</sup> Dose reduction can have adverse implications for sustained virologic response (SVR) the desired end point of treatment. Studies show that higher doses of ribavirin are associated with higher SVR rates.<sup>9-11</sup> Rates of SVR are higher in patients who receive more than 80% of their full interferon and ribavirin doses for more than 80% of the intended

duration of therapy.<sup>10</sup> Delivering the optimal dose of antiviral therapy seems to be most crucial during the first 12 weeks of antiviral therapy, the period of most frequent occurrence of side effects.<sup>9-11</sup>

Improving compliance with therapy by measures such as patient education, close follow-up, adequate treatment of side effects, and minimization of dosing changes may increase efficacy of treatment while lack of expertise of physicians in the proper management of these side effects as well as lack of education of patients may lead to higher rates of drug discontinuation or dose reduction with resultant lower efficacy.

The side effects can be categorized to five groups:

1. Constitutional symptoms
2. Injection site reactions
3. Hematological side effects including anemia, neutropenia & thrombocytopenia
4. Neuropsychiatric side effects
5. Thyroid disorders

There are also numerous reported side effects which occur rarely. This article will review these adverse effects and their proper management.

### *Constitutional Symptoms*

Fatigue, fever and myalgia the so called flu like symptom are the most frequent side effects.<sup>3-8</sup> These symptoms occur in over half of all patients within 6-8 hours after the first dose of IFN. In practice almost all patients experience at least one of these symptoms during treatment. Frequency and severity of these symptoms decrease with subsequent doses.<sup>12-13</sup>

Simple measures such as adequate hydration, light to moderate regular exercise, altering schedule of injection to days with lighter work loads are very effective but are usually neglected.<sup>13</sup> Increase intake of fruit and vegetables and reduced intake of animal fat and sugars may also help. Acetaminophen and ibuprofen before or at the time of injection may prevent these symptoms.<sup>12-13</sup> There is a concern about increased risk of bleeding in HCV infected cirrhotic patients receiving NSAID and SSRI concomitantly.<sup>12</sup> COXII inhibitors may have effect with reduced risk of bleeding but the data are scant and the drugs are more expensive.<sup>12</sup>

## *Local Injection Side Reactions*

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Up to 60% of patients may experience some reaction at the site of injection.<sup>3-8</sup> The site may be inflamed in near 25%. These local reactions seem to be more common with pegylated-Interferon PEG. They are usually mild and respond to local therapy and do not require dose reduction. There are reports of thrombophlebitis (both superficial and deep) while receiving IFN. These more severe side effects may not be distinguishable initially from common local reactions.<sup>14</sup> They should be considered in severe and/or progressive local reactions.

## *Anemia*

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Anemia is the most significant hematological side effect of combination therapy.<sup>13</sup> A pooled analysis of data from three large trials comparing pegylated-Interferon (PEG) with non-pegylated-Interferon determined that worsening of fatigue scores was a significant predictor of treatment discontinuation.<sup>15</sup> Anemia was the major determinant of fatigue in these patients. Anemia can also reduce patients' health related quality of life significantly.<sup>15</sup>

Both IFN through suppression of hematopoiesis and RBV through induction of hemolysis may contribute.<sup>13, 16, 17</sup> This adverse effect is greater with PEG-IFN.<sup>13</sup> RBV induces hemolytic anemia to some extent in almost all patients. The mechanism of RBV induced hemolysis has been described recently.<sup>16</sup> RBV is taken up by red blood cells and activated through phosphorylation to ribavirin triphosphate. This compound can not be metabolized by RBCs and is trapped within these cells. Intracellular adenosine triphosphate pool is depleted and antioxidant defense mechanisms are impaired. This leads to oxidative damage to erythrocytes' membrane with resultant extravascular hemolysis in reticuloendothelial system.<sup>16</sup>

There is usually a drop of approximately 2-3 g/dl of hemoglobin in the first 2-4 weeks.<sup>13</sup> The lowest hemoglobin level is reached in within first two months and the hemoglobin level remains stable thereafter. There is a need for dose reduction in near 25% of patients.<sup>12, 13</sup> Really in patients out of trials, anemia is the leading cause of premature discontinuation of combination therapy and 36% of all discontinuation was due to this reason in one report.<sup>18</sup> Anemia has been linked to plasma level of RBV and patients renal function. The risk is higher with doses more than 1 g/d. Asians in particular have higher risk for developing anemia.<sup>12</sup> RBV has been considered contraindicated in the presence of congenital hemolytic anemia and renal failure.<sup>12,13</sup> It should be used cautiously in patients with cardiovascular or cerebrovascular disease because of risks of anemia in these patients.

Dose of RBV should be lowered if Hb drops to less than 10g/dl and it should be discontinued if Hb is lower than 8.5g/dl and resumed later after Hb is raised.<sup>12</sup>

Two studies have evaluated the use of epoetin alfa as an adjunct for the management of anemia (defined as

hemoglobin < 12 g/dL) during combination therapy for chronic hepatitis C.<sup>19,20</sup> Dieterich et al. compared epoetin alfa therapy (40,000 units weekly) with standard-of-care anemia management in 64 patients in terms of the effects on hemoglobin levels and ribavirin dose.<sup>19</sup> They found that patients receiving epoetin alfa had increases in hemoglobin level and maintained their ribavirin dose. At 16 weeks after randomization, the patients who received epoetin alfa had significantly higher mean hemoglobin levels (14.2 vs 11.2 g/dL) and a higher mean ribavirin dose (895 vs 707 mg/d) compared with the patients who received standard anemia management. Significantly fewer patients in the epoetin alfa group had their ribavirin dose reduced (5.7% vs 33.3%). However use of erythropoietin in this situation is still experimental and more data is needed. Anemia due to RBV is usually associated with reticulocytosis. Anemia in the absence of reticulocytosis is most likely related to IFN induced marrow suppression. These subjects may be a better candidate for erythropoietin therapy.

## *Neutropenia*

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Neutropenia is a common side effect during treatment with IFN.<sup>3-8</sup> Decrease in count up to 35% of baseline level has been reported which is more marked in the first two weeks of therapy.<sup>13</sup> The white blood cell count usually stabilizes in the next 4-6 weeks. In near 5% of patients severe neutropenia (<500/ml) occurs. The event is more common with PEG-IFN compared to standard IFN. No increased instance of infections has been shown in these patients.<sup>13, 21</sup> Cirrhotic may have an increased risk of infectious complications in the presence of IFN induced neutropenia although the concept has been debated recently specially in patients with compensated cirrhosis. Decompensated cirrhosis is usually considered a contraindication of therapy due to higher risk of complications including encephalopathy, infections and liver failure.<sup>12</sup> There may be an increased risk of IFN induced neutropenia in the presence of splenomegaly.<sup>21</sup> Constitutional neutropenia should not be considered as a contraindication for treatment.<sup>13</sup>

Iranian consensus on HCV treatment has recommended dose reduction of IFN to half when neutrophil count falls below 1000/ml and discontinuation of therapy when counts fall below 750/ml. However current data indicates that neutrophil counts as low as 500/ml are usually well tolerated without any adverse event.<sup>13</sup> Neutrophil counts rapidly return to baseline when the drug is discontinued.

Regarding neutrophil kinetics it is the best to measure neutrophil count just before the injections rather than after. With this approach improper dose reduction of IFN would be avoided.<sup>13</sup>

## *Thrombocytopenia*

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The platelet count decreased by 10-50% on IFN therapy.<sup>3-8</sup> The nadir is usually reached within 8 weeks of therapy. The

counts would then be stabilized during the whole length of therapy at this low level. After discontinuation of IFN the count would return to normal within 4-8 weeks.<sup>12-13</sup> Dose reduction or drug discontinuation is usually not needed. Severe thrombocytopenia (<50,000/ml) is more common with PEG-IFN compared to standard IFN (20% vs 7%).<sup>3-8, 13</sup> As with neutropenia the incidence of thrombocytopenia is increased in cirrhotic patients specially in the presence of splenomegaly. These patients should be monitored more closely. Dose reduction to half with platelet counts below 100,000/ml and discontinuation of IFN with counts below 50,000/ml has been recommended.<sup>13</sup> Rare instance of immune mediated thrombocytopenia has been linked to IFN therapy. This complication should be managed with corticosteroids and discontinuation of IFN.<sup>13</sup>

### *Neuropsychiatric side effects*

IFN based regimens can induce a variety of neuropsychiatric adverse events including depression, irritability, emotional liability, aggressive behavior, seizures, mood disorders and panic attacks.<sup>3-8, 12-13</sup> The incidence of new onset depression has reported to be as high as 30%. Depression usually develops in the first half of treatment period. The incidence is lower with PEG-IFN. The speculative mechanism of IFN induced depression probably involves neuroendocrine system with increased cortisol level and serotonin depletion, so serotonin reuptake inhibitors (SSRI) are considered as the drug of choice in this situation.<sup>22-26</sup> Use of these drugs usually resolves depression symptoms rapidly without need to reduce IFN dose.<sup>12, 13</sup> Prophylactic use of SSRI in those with prior history of major depression seems logic but the drug should not be given to all IFN treated patients as 70-80% of these patients never develop depression.<sup>13</sup> As mentioned before there is an increased risk of bleeding complications when SSRIs are used in combination with NSAIDs specially in cirrhotic patients. Tricyclic antidepressants should be generally avoided due to their anticholinergic and sedative side effects.<sup>13</sup> If antidepressants are started they should be continued 6-12 months after discontinuation of antiviral therapy.<sup>13</sup> Use of psycho education and supportive groups were also successful in this situation. There is an increased occurrence of depression in HCV infected patients in general not related to IFN therapy. This may be related to excess fatigue, uncertainty about prognosis and higher rates of substance abuse among these patients. It is mandatory to evaluate these patients before starting antiviral therapy for the presence of psychological disturbances which may need their own management.<sup>27</sup> Suicidal thoughts or attempts and severe bipolar disorders are contraindications for IFN therapy.<sup>12, 13</sup>

Currently there is a trend in expanding eligible patients for antiviral therapy in chronic HCV infection. Active drug abusers are no longer an absolute contraindication for therapy as long as they are motivated for therapy and accept clinical follow up and monitoring during treatment. There

reports of successive therapy even in this high risk group without adverse events but there are generally more incidence of adverse neuropsychiatric events in this group while on IFN.<sup>28, 29</sup> Seizures usually grand mal occurs in 1-3% of patients receiving IFN. They usually stop after discontinuation of therapy. The risk is probably higher with higher doses of IFN.<sup>30</sup>

### *Thyroid Disease*

Some patients with chronic HCV infection have thyroid disease even before treatment. Up to 30% of women with HCV infection have autoantibodies to thyroglobin and thyroid microsomal antibody and 5-17% of them are hypothyroid.<sup>31</sup> The incidence is much lower in males. Presence of autoantibodies before treatment has been linked to the development of thyroid disease during treatment.<sup>31, 32</sup> The effect of IFN on thyroid gland is not always reversible.<sup>32</sup> A subset of patients who develop autoantibodies to thyroid proteins during IFN therapy progress to hypothyroidism even after discontinuation of therapy however measurement of these autoantibodies during therapy is not cost effective in predicting these cases,<sup>32</sup> TSH should be tested before and every 12 weeks while on therapy and once after end of treatment. There should be high index of suspicious to hypothyroidism during therapy. Subtle complaints such as fatigue may be the only clue. Hypothyroid patients should receive thyroid replacement therapy. There are also reports of hyperthyroidism on IFN therapy. This is most probably a presentation of Grave's disease or a stage of thyroiditis. Before going on with antithyroid drugs this possibility should be considered.<sup>32</sup>

### *Other Side effects*

A variety of other side effects on IFN therapy has been reported including hearing loss, retinal hemorrhage, neuropathy, photosensitivity, skin rash, interstitial pneumonitis, uncontrolled diabetes mellitus, Addison's disease, stroke and infarction.<sup>13</sup> Most of these adverse events are rare and occurred only as case reports. Uncontrolled hyperglycemia in previously controlled diabetes mellitus is not uncommon so diabetic patients on IFN need more intense monitoring.<sup>12</sup>

### *Conclusion*

Adverse events with combination therapy are not rare during treatment of HCV infection; however most of these events are mild and could be managed effectively. Drugs should not be discontinued or withheld unless severe reactions are present.

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