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Concise Review

Side effects of medical therapy for chronic hepatitis C

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Abstract

The treatment of chronic hepatitis C virus (HCV) has improved greatly over the past decade. Over half of all patients treated with the combination of peginterferon and ribavirin have the opportunity to achieve sustained virologic response. The major factors which interfere with this goal are the side effects of therapy which require that the doses of peginterferon or ribavirin be reduced or that these medications be discontinued. While some of these side effects can be overcome and treatment continued, some side effects are severe and potentially life threatening. Appropriate recognition and management of these side effects will both improve response to therapy and avoid unnecessary morbidity and mortality.

Key words: Hepatitis C virus, peginterferon ribavirin side effects.

The treatment of chronic hepatitis C virus (HCV) infection has evolved significantly over the past several years. The most effective therapy currently available is the combination of peginterferon and ribavirin. Large clinical trials have demonstrated that 42-51% of patients can achieve a sustained virologic response (SVR) following 48 weeks of combination therapy,[1,2] In patients with HCV genotypes 2 or 3 SVR approaches 80% and a recent study has suggested that this can be achieved with just 24 weeks of peginterferon and a lower dose of ribavirin.[3]

One of the major limitations of HCV therapy is that both peginterferon and ribavirin cause numerous side effects.[4] The most common of these side effects include flu-like symptoms, hematologic, neuropsychiatric and dermatologic toxicities and the development of autoimmune disorders. Most patients are able to tolerate the adverse events of treatment and complete a full course of therapy. Once treatment is discontinued these side effects typically resolve. However, about 25-33% of patients will experience severe side effects and in rare instances some adverse events may be life threatening. The standard approach to managing adverse events which are clinically significant is to reduce the dose of peginterferon and/or ribavirin. When side effects do not resolve with dose reduction or the adverse event is particularly debilitating discontinuation of therapy may be necessary. Unfortunately, an accumulating body of evidence now strongly suggests that dose reduction and particularly early discontinuation of HCV treatment is associated with a marked decline in SVR.[5] This is most pronounced in patients with HCV genotype 1 who appear to require full dose therapy to achieve the optimal virologic response. Recognizing and managing the side effects of peginterferon and ribavirin is therefore important. Proper side effect management may enable many patients to remain on therapy and this could increase the likelihood that they will achieve an SVR following treatment with peginterferon and ribavirin.

This review will summarize the major side effects associated with peginterferon and ribavirin experienced by patients with chronic HCV. Ways in which the physician and patient can both recognize and successfully manage these adverse effects will be discussed.

Flu-like and other generalized systemic side effects

Flu-like symptoms occur in nearly half of patients receiving treatment with peginterferon and ribavirin.[1,2,4] This typically includes fever, myalgias, arthralgias and headache. Flu-like symptoms are most intense following the first interferon injection and typically subside gradually with subsequent injections over several weeks to months. It is therefore recommended that the first interferon injection be administered in the evening prior to a day the patient does not have to report to work. This helps to avoid the patient developing severe flu-like symptoms at the workplace which could interfere with work performance. Administering interferon in the evening or at bedtime and pre-medicating patients with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), particu-

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larly prior to the first several interferon injections, is also very effective in limiting the severity of these symptoms and should be encouraged. Over several weeks the regular use of acetaminophen and NSAIDs can be reduced as these symptoms subside. Flu-like symptoms appear to be less severe in those patients who remain well hydrated by consuming large amounts of water, sport drinks and/or fruit juices.

Severe persistent headaches which do not respond to acetaminophen or NSAIDs occur in less than 10% of patients.[1,2,4] Use of narcotic pain medications may be necessary for these patients. In some cases interferon induced headaches have migraine features and are associated with nausea, vomiting and visual changes. Evaluation by neurology may be necessary in some cases, particularly if these symptoms do not respond to standard anti-migraine therapy.

Approximately 20% of patients will develop significant diarrhea. This typically occurs within 1-3 days following the weekly injection and is most severe for only the first several weeks. In up to 5% of patients diarrhea may persist throughout the entire week and/or throughout the entire course of therapy. Interferon induced diarrhea is typically responsive to variable doses of imodium or loperamide.

Hematologic toxicity

Anemia, neutropenia and thrombocytopenia are common during treatment with peginterferon and ribavirin. Neutropenia and thrombocytopenia are a direct result of interferon induced bone marrow suppression.[6-8] In most studies, the total neutrophil and platelet counts decline by approximately 20% from the pre-treatment baseline.[1,2,4,7] This typically occurs within the first 4-8 weeks of treatment after which time the neutrophil and platelet counts remain stable throughout the remainder of therapy. Despite this decline, the neutrophil and platelet counts remain within the limits of normal in the majority of patients receiving peginterferon.

Patients with cirrhosis frequently have a neutrophil count that is at or below the lower limits of normal and this declines further during treatment with peginterferon. In addition, many individuals of African descent have essential neutropenia and are also at risk for developing significant neutropenia during treatment with peginterferon.[9] Although it is recommended by the pharmaceutical manufacturer to reduce the dose of peginterferon if the absolute neutrophil count declines below 1,500 cells/mm^3 many physicians with significant experience utilizing this agent will tolerate an absolute neutrophil count as low as 750-500 cells/mm^3 before dose reducing or discontinuing treatment. Preliminary studies have failed to demonstrate a link between bacterial infections and interferon induced neutropenia even in patients with advanced fibrosis or stable Child class A cirrhosis.[10,11] Thus, although the use of a neutrophil stimulating factors such as granulocyte colony stimulating factor (GCSF) appears to raise the neutrophil count in patients receiving interferon therapy it is unlikely that these agents will be clinically useful even in patients with cirrhosis.[12,13] The exception is in patients with decompensated cirrhosis who appear to be at increased risk for bacterial infection in the setting of interferon induced neutropenia.[14]

Thrombocytopenia to levels associated with spontaneous bleeding rarely occur in response to peginterferon even in patients with cirrhosis.[4,7] Although it is recommended by the pharmaceutical manufacturer to dose reduce peginterferon if the platelet count falls below 75,000/mm^3 many physicians with significant experience will allow the platelet count to decline to; a value of 25,000-30,000 before they either reduce the dose or stop treatment. The only exception to this is interferon induced immune thrombocytopenia (ITP). This is characterized by a precipitous decline in the platelet count, usually to values less than 30,000/mm^3, which typically occur within 4-8 weeks after initiating interferon therapy. Antiplatelet antibodies are not detectable in all patients with interferon induced ITP.[15] If suspected, interferon must be discontinued immediately and the platelet monitored closely. In some patients, the platelet count will not increase after interferon is discontinued and corticosteroids may be need to be instituted. The development of interferon induced ITP is a contraindication to future interferon therapy, even if the initial episode resolves and the platelet count returns to the pretreatment baseline.

A decline in the hemoglobin by 2 grams or greater is observed in nearly 75% of patients treated with peginterferon and ribavirin.[1,2,4,7] This is secondary to ribavirin induced hemolysis and interferon induced marrow suppression which prevents a compensatory reticulocytosis.[16,17] Since ribavirin is excreted unmetabolized by the kidney, serum levels of ribavirin rise precipitously in patients with even mild degrees of renal insufficiency and this leads to severe hemolysis.[18] As a result, ribavirin should not be utilized in patients with significant renal dysfunction.

Anemia develops in approximately 40% of patients treated with peginterferon and ribavirin and is either symptomatic or sufficient to require that the dose of ribavirin be reduced in about 20-25%.[1,2,4,7] Although it is recommended by the pharmaceutical manufacturer to dose reduce ribavirin when the hemoglobin falls below 10 gm/dL many patients become symptomatic when the hemoglobin falls below 12 gm/dL. Both interferon and ribavirin should be discontinued if the hemoglobin falls below 8.5 gm/dL.

Neuropsychiatric toxicity

Neuropsychiatric side effects either develop de novo or worsen in patients with underlying psychiatric disease

in 30-40% of patients receiving peginterferon and ribavirin.[1,2,4,19,20] It is therefore important to both screen patients for the presence of a psychiatric disease prior to initiating treatment for chronic HCV and to monitor for the appearance of symptoms during therapy. The presence of medically treated psychiatric disease is not a contraindication to initiating interferon therapy. However, the psychiatric disorder should be well controlled and the patient should be monitored by a psychiatrist on a weekly basis during the first month of treatment and at regular intervals throughout the course of therapy.

The most common psychiatric side effects of interferon therapy include insomnia, irritability and depression. It is believed that these symptoms result from interferon induced cytokine production and inhibition in serotonin synthesis.[21] In a randomized, placebo controlled trial, the prophylactic use of the serotoin agonist paroxetine was shown to significantly reduce the incidence of major depression in patients receiving daily, high dose interferon for treatment of melanoma.[22] Since only 20-25% of patients with chronic HCV receiving peginterferon and ribavirin develop depression sufficient to warrant pharmacologic intervention, the prophylactic use of antidepressants in this population is not advocated. Treatment should be considered when irritability or depression being to interfere with work and family related activities. In many patients receiving interferon therapy depression is the result of severe insomnia. The use of anti-depressants with sedation side effects is very effective in such patients. Effective treatment of irritability and depression may alleviate the need to dose reduce peginterferon. However, if symptoms are persist the dose of peginterferon should be reduced until there is objective improvement. Patients who develop severe depression and either suicidal or homicidal thoughts should be hospitalized and discontinue treatment immediately.

Neuropathy and seizures have also been reported to be an adverse event of interferon therapy.[23,24] However, the incidence of such findings is uncommon. This is believed to be secondary to the effects of interferon on nerve conduction. Both a sensory and motor neuropathy have been reported. The appearance of such symptoms may be long lasting. Treatment should be discontinued in patients who develop neuropathy or seizures while receiving interferon therapy.

Dermatologic toxicity

Several dermatologic disorders may emerge during treatment with interferon and ribavirin. The majority of these dematologic findings are the result of immune mediated manifestations of interferon and include vitiligo, lichen planus, psoriasis and leukoclastic vasculitis.[25] Referal to a dermatologist may be helpful both in identifying the specific disorder and in instituting therapy. In many cases the dermatologic lesion can be controlled and interferon can be continued without the need for dose reduction. The only exception is leukoclastic vasculitis which in some cases may be associated with a systemic vasculitis.[26] Injection site reactions are common dermatologic findings in patients receiving interferon therapy. Such reactions typically resolve within several weeks.

Ribavirin may cause an erythematous, pruritic, papular rash which most commonly appears on chest and upper arms following significant sun exposure.[1,2,4,27] Although very pruritic, the appearance of this rash does not require that ribavirin be discontinued or dose reduced. Symptomatic treatment of pruritus with either topical or system agents is frequently successful. If the pruritus is particularly severe and therapy not helpful then reducing the dose of ribavirin is usually effective.

Autoimmune and other disorders associated with interferon treatment

Several autoimmune disorders have been reported to appear in response to interferon therapy *(Table I)*. In some cases these autoimmune disorders may be severe and life threatening. One of the most devastating of these complications is interferon induced pneumonitis which may progress rapidly to the adult respiratory distress syndrome and pulmonary failure.[28] The development of a lupus-like syndrome, rheumatoid arthritis and system vasculitis have also been observed.[26] Other uncommon findings associated with use of interferon and possibly of autoimmune etiology have included sudden hearing loss,[29] cardiac toxicity[30] and sarcoidosis.[31] Interferon should be discontinued as soon as it is recognized that treatment has precipitated a significant autoimmune disorder.

Disorders of the thyroid, both hypo- and hyperthyroidism, develop in 10-15% of patients during interferon therapy.[32] As a result, it is recommended that thyroid function studies be performed at baseline, prior to initiating interferon therapy, and a periodic intervals during therapy. Patients who develop biochemical evidence of hypothyroidism may require thyroid replacement prior to becoming overtly symptomatic but do not require that the dose of interferon be modified. It remains unclear if interferon induced hypothyroidism resolves after treatment has been completed and thyroid replacement therapy can be discontinued. Interferon induced hyperthyroidism is frequently more difficult to manage. Patients who develop symptomatic hyperthyroidism may require beta-blockade, pharmacolgic therapy or radio-iodine ablation to reduce thyroid function. However, if the symptoms of hyperthyroidism cannot be rapidly alleviated interferon should be discontinued.

Retinopathy has been reported to occur in less than 5% of patients receiving interferon therapy.[33] The etiology for this remains unclear. Retinal findings reported to occur in such patients include macular degeneration, retinal artery and vein thrombosis, retinal hemorrhages, optic neuritis,

Table I. Autoimmune disorders stimulated by interferon.

Autoimmune hepatitis
Celiac disease
Fibromyalgia
Hemolytic anemia
Hypothyroidism
Hyperthyroidism
Immune thrombocytopenia
Lichen Planus
Lupus-like syndrome
Myasthenia Gravis
Myocarditis
Pneumonitis
Rheumatoid arthritis
Vasculitis

Table II. Frequency and reasons for dose reduction of interferon and ribavirin during treatment of chronic HCV.

	Interferon	Ribavirin
Adverse side effects including:	11-15%	~20%
Depression		
Flu-like side effects		
Fatigue		
Other		
Thrombocytopenia	4%	< 1%
Neutropenia	18-20%	1%
Anemia	1%	9-22%

Data from references: 1 and 2.

Table III. Effect of dose reduction of interferon and ribavirin on early and sustained virologic response.

	Early virologic response	Sustained virologic response
Dose reduction prior to week 12:		
None	80%	62%
Peginterferon	70%	
Ribavirin	60%	
Peginterferon and ribavirin	33%	34%
Dose reduction after week 12:		
Peginterferon, ribavirin or both		51%

Data from references: 5 and 34.

and papilledema. Patients who develop significant visual changes while undergoing interferon therapy should undergo ophthamologic examination and treatment discontinued if significant abnormalities thought secondary to interferon are identified. Patients with a history of hypertension and diabetes mellitus are thought to be at increased risk for interferon induced retinal pathology. The manufacturers have recommended that persons with a history of hypertension and diabetes mellitus undergo ophthamologic examination prior to initiating interferon therapy. How this will affect the management of such patients remains undefined.

Effect of dose reduction on SVR

Reducing the dose of interferon and/or ribavirin is required in approximately 25-33% of patients who receive treatment for chronic HCV. The most common reasons for dose reduction in interferon include flu-like side effects, depression and autoimmune manefestations, neutropenia thrombocytopenia. The most common reasons for dose reducing ribavirin include anemia and rash *(Table II)*. Unfortunately, reducing the dose of peginterferon and ribavirin or discontinuing therapy before the planned course of therapy is complete has been associated with a reduction in SVR.[5,34,35] The first study in which this was demonstrated combined interferon and ribavirin dose reductions and discontinuations and did not separately evaluate the relative importance of each medication independently or of dose reduction versus discontinuation.[5] Patients who completed all therapy without dose reduction had a SVR of 61%. This declined to 50% in patients who dose reduced after week 12 and to 34% in patients who dose reduced prior to week 12 *(Table III)*. More recently, two studies have demonstrated that dose reduction of ribavirin within the first 12-20 weeks of therapy significantly reduced both early virologic response (EVR) and SVR.[34,35] In contrast, reducing the dose of peginterferon did not appear to significantly impact either EVR or SVR. More importantly, reducing the dose of peginterferon or ribavirin after patients had already become HCV RNA undetectable did not adversely affect the ability to achieve SVR.

In the original trials, where the impact of dose reduction upon SVR was first assessed, protocol mandated dose reductions for neutropenia, thrombocytopenia and amenia were the major indications for dose reduction.[1,2] In these studies the dose of peginterferon was reduced by 50% and ribavirin was reduced from either 1,000 or 12,000 mg/day to 600 mg/day. The reason for such drastic reductions was primarily related to safety in these registration trials. However, in practice many experienced physicians dose reduce by lesser amounts; peginterferon alfa-2a from 180 mcg/week to 135 mcg/week; peginterferon alfa-2b from 1.5 mcg/kg/week to 1.0 mcg/kg/week and ribavirin from either 1,200 to 1,000 mg/day or from 1000 to 800 mg/day. Since anemia is a function of both ribavirin induced hemolysis and interferon induced bone marrow suppression reducing the dose of peginterferon may instead of ribavirin may improve anemia and alleviate the need to dose reduce ribavirin. Reducing the amount by which the doses of these medications are lowered, particularly during the first 12-20 weeks of therapy, may lead to improved rates of SVR.

Role of hematologic growth factors

Anemia is the primary indication for reducing the dose of ribavirin.[1,2] As noted above, this has been associated

with a reduction in SVR, particualrly when ribavirin is reduced within the first 12-20 weeks after initiating therapy.[5,34,35] Two randomized controlled trials have now demonstrated that ribavirin induced anemia can be corrected by erythropoetin alfa.[36,37] On average the hemoglobin increased by 2 grams within 6-8 weeks after initiating erythropoetin and this alleviated the need to dose reduce ribavirin or allowed the dose of ribavirin to be increased. Quality of life and energy were both significantly improved in patients who received erythropoetin for treatment of ribavirin induced anemia. However, neither study demonstrated was designed to evaluate the effect of erythropoetin and correction of anemia on SVR. In addition, the mean time to initiate erythropoetin in the randomized, placebo controlled trial was not until after patients had received 12 weeks of HCV therapy; and that time more than half of all patients were already become HCV RNA undetectable.[37] Nevertheless, these studies do suggest that erythropoetin alfa, if instituted early, is likely to prevent a significant fall in hemoglobin during peginterferon and ribavirin therapy and could therefore prevent the need to dose reduce ribavirin and improve SVR. However, the use of erythropoetin is unlikely to be benefit in patients who do not achieve EVR despite receiving optimal doses of peginterferon and ribavirin.

Emerging data strongly suggests that dose reducing peginterferon, particularly by small amounts (ie. from 180 to 135 mcg/week for peginterferon alfa-2a and from 1.5 to 1.0 mcg/kg/week) does not impair either EVR or SVR.[38,39] In addition, the incidence of bacterial infections in patients being treated with peginterferon and ribavirin does not appear to be associated with neutropenia, particularly in patients without decompensated cirrhosis (x). As a result, the use of GCSF to prevent neutropenia does not appear to be either necessary or beneficial in the great majority of patients with chronic HCV.

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