

Expert Opinion

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Pegylated-interferon- α_{2a} in clinical practice: how to manage patients suffering from side effects

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Introduction: The goal of antiviral therapy in patients with chronic hepatitis C is to slow or halt the progression of fibrosis and prevent the development of cirrhosis. Accordingly, antiviral treatment is proposed for a large population of patients with chronic hepatitis.

Areas covered: The standard-of-care for chronic hepatitis C is the combination of pegylated IFN (PEG-IFN) and ribavirin. The use of these drugs has been correlated with a range of adverse effects, including influenza-like symptoms, hematological changes and neuropsychiatric disturbances. The effects of these adverse events associated with PEG-IFN therapy are manifold and are a major reason why patients decline or stop therapy. This review addresses the screening for adverse event risk factors and guides the patient to success with adherence strategies.

Expert opinion: Knowledge of the side effects correlated with PEG-IFN is very relevant for clinicians because it can allow them to arrange the best methods for treating these effects and avoid the discontinuation of antiviral treatment. Moreover, the use of new antiviral drugs will considerably shorten treatment periods reducing many of the above-described side effects and, thus, increase adherence to scheduled therapy.

Keywords: HCV, PEG-IFN, ribavirin, side effects

Expert Opin. Drug Saf. [Early Online]

1. Introduction

HCV infection is recognized as a global health problem, with an estimated 200 million people infected worldwide. The treatment for chronic HCV infection has evolved over the last decade from standard IFN monotherapy to combination therapy with standard IFN and ribavirin (RBV) and, more recently, pegylated (PEG)-IFN- α_{2a} or - α_{2b} and RBV combination therapy [1,2].

The use of IFN- α with or without RBV is frequently associated with a number of adverse effects, including influenza-like symptoms, hematological changes and neuropsychiatric disturbances. This is also true for PEG-IFNs, with similar side effects, dose reduction and discontinuation of treatment. Side effects are observed in almost 80% of patients receiving PEG-IFN and RBV combination therapy for chronic HCV infection. Care of patients with chronic hepatitis C depends on recognition of those at increased risk for side effects, anticipation (and prevention) of side effects and appropriate management when they occur. Furthermore, the ability to achieve a sustained virologic response (SVR) at the end of therapy depends in part on the degree of patient compliance with treatment. Dose reduction of these agents (or their discontinuation) because of side effects can potentially compromise the outcome, depending on when dose reduction has occurred.

This review summarizes the major side effects associated with PEG-IFN- α_{2a} in the treatment of chronic HCV infection, describing the best evidence derived

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Article highlights.

- The use of IFN- α with or without ribavirin in hepatitis C is frequently associated with a number of adverse effects.
- The ability to achieve a sustained virologic response depends in part on the degree of patient compliance with treatment.
- Only a minority of patients need premature discontinuation because of side effects.
- Hematologic abnormalities and depression are frequent indications for dose reductions.
- Treatment periods could be shortened adding protease inhibitors to standard-of-care therapy without significant loss of response.
- The time reduction could reduce the incidence of side effects, and thus will increase adherence to scheduled therapy.

This box summarizes key points contained in the article.

from an extensive, though not exhaustive, search of the literature (updated to the end of 2010) on the management of their occurrence.

2. Hematologic side effects

Hematologic adverse events are the most common laboratory abnormalities that lead to dose modifications or discontinuation [3-5]. Therapy with standard and PEG-IFNs is associated with rapid suppression of hematopoiesis.

2.1 Anemia

Anemia is extremely common among patients taking PEG-RBV combination therapy for chronic hepatitis C [3,6,7]. Although RBV-induced hemolysis is the major contributor to treatment-associated anemia [8-10], the etiology of anemia is multifactorial, and is also caused by IFN suppression of the normal compensatory bone marrow response. IFN is a potent suppressor of all components of the bone marrow and inhibits erythropoiesis, as evidenced by an inadequate reticulocyte response to anemia. IFN has also been associated with autoimmune hemolytic anemia [11]. As a consequence, in clinical practice special care needs to be taken in patients with a history of cardiac disease.

No studies to evaluate the use of erythropoietin (EPO) in HCV-treated patients with IFN alone have been done. The only studies to evaluate combined treatment concluded that approaches involving EPO or darbepoetin were cost-effective [9,10]. However, the cost-effectiveness was sensitive to the rates of SVR, while there was no definitive evidence that the use of these growth factors can increase SVR. Nevertheless, significant improvement of quality of life was observed by maintaining the HB above 12 g/dl. Side effects associated with the use of EPO include headache and flu-like symptoms. Pure red cell aplasia due to the

development of anti-EPO antibodies has also been reported. One case has been reported of a patient taking EPO while on PEG-RBV [9]. Red cell aplasia due to EPO is considered to be very rare, with an estimated incidence of 0.02/10,000 patient-years of exposure.

2.2 Neutropenia

The incidence of neutropenia in patients treated with PEG-IFN is greater than that seen in standard IFN regimens and is a frequent indication for dose reduction [3-5]. Rapid decrease in the neutrophil count may be seen within the first 2 weeks of therapy and usually stabilizes over the next 4 – 6 weeks as steady-state concentrations of PEG-IFN are achieved. The neutrophil count rapidly returns to baseline after therapy is discontinued [5]. A recent study of 25 patients with hepatitis C given a single high dose of standard IFN followed by regular injections of standard or PEG-IFN detailed the hematologic effects of these drugs [11]. Leukocytes were the most affected cell lineage, and PEG-IFN had a similar effect on neutrophils and lymphocytes, with a median drop of 21 and 31%, respectively, after a single dose of IFN. During daily administration of IFN, or weekly administration of PEG-IFN, the decline in the neutrophil count was larger than the drop in the lymphocyte count. PEG-IFN had a greater effect on the neutrophil count compared with standard IFN, consistent with observations in clinical trials [11].

The major concern with neutropenia is the potential risk of increased infectious complications. An analysis of 119 patients with hepatitis C who were treated with IFN and RBV showed a 34% decrease in the neutrophil count, with the steepest decline during the first 4 weeks of therapy [12]. Among 22 infections that occurred, the most common were sinusitis, pharyngitis and urinary tract infection. One patient, a 72-year-old man with cirrhosis, required hospitalization for cellulitis and lower-extremity edema. None of the patients who developed infections had pre-existing neutropenia or a neutrophil count of < 750 cells/mm³ at any point in treatment [13]. Similar analyses of databases from the registration trials of PEG-IFN also showed no significant association between neutropenia and infectious complications [3-5].

Current package insert labeling for PEG-IFN recommends dose reduction for neutrophil counts below 750 cells/mm³. Patients with neutropenia should have blood counts monitored weekly until a steady level of neutropenia is assured. Several small studies using G-CSF as an adjunctive agent have suggested that higher neutrophil counts can be maintained during IFN therapy [14-18]. Additional investigation is required before these agents can be recommended for routine use to treat neutropenia associated with PEG-IFN therapy, as G-CSF is costly and has its own unique side effect profile.

2.3 Thrombocytopenia

Thrombocytopenia is common in patients with advanced liver disease. The cause is multifactorial, and is due in part to increased sequestration in the spleen and reduced

production of thrombopoietin (a cytokine that regulates megakaryocyte maturation and platelet production) [19]. IFN also reduces the platelet count. In patients treated with PEG- α_{2a} and RBV, dose reduction is necessary in 3 – 4% of those treated with PEG-RBV versus 1% in those treated with standard IFN and RBV [3,6].

Severe thrombocytopenia is usually seen only in those with established cirrhosis or in rare patients in whom IFN induces autoimmune thrombocytopenia. Platelet counts increase in patients who have achieved an SVR to therapy possibly because of a reduction in splenomegaly, improvement in hepatic fibrosis and increased production of thrombopoietin [20,21]. Manufacturers have provided recommendations for dose reduction in patients who develop thrombocytopenia. Other than dose reduction, there are no approved therapies available to augment the platelet count in those undergoing treatment with PEG and RBV. The development and use of platelet-derived growth factors may enhance tolerability, safety and efficacy of IFN therapy in patients with HCV. Eltrombopag is a small-molecule agonist of the physiological target of thrombopoietin, and leads to increased activation and differentiation of megakaryocytes. In a study of patients with hepatitis C cirrhosis, it caused a dose-dependent increase in platelet counts, thus, allowing the initiation of antiviral therapy [22].

2.4 Flu-like symptoms

Flu-like symptoms (fatigue, headache, low-grade fever, muscle aches and arthralgia) are the most common side effects in patients treated with PEG-IFN [3-5]. Virtually all patients will experience at least one of these influenza-like side effects with the first few doses of IFN. Fortunately, these symptoms generally resolve or become less severe after the first month of therapy. Acetaminophen or ibuprofen taken at the time of injection may ameliorate the myalgias, arthralgias, headache and fever. Other drugs can be used, such as COX-2 inhibitors, but there are no data suggesting this class of medications is superior to acetaminophen or ibuprofen in this group of patients. Simple practices, such as adequate hydration, a light to moderate exercise program, and altering dosing schedules to coincide with scheduled days off from work or a lighter work load, help minimize these side effects [5].

2.5 Neuropsychiatric side effects

With improved management of anemia and other side effects associated with treatment, neuropsychiatric reactions have come to account for a progressively larger share of the overall burden associated with treatment. Indeed, neuropsychiatric side effects are increasingly recognized as a primary cause of both treatment failure and clinical decisions not to start treatment in the first place. The reasons for the high rates of depression in HCV-infected individuals are unknown but may be related to excessive fatigue or concerns about long-term prognosis [23]. In addition, some patients with chronic hepatitis C have additional risk factors for depression, including concurrent or past substance abuse. The proposed mechanisms

of IFN-induced depression, including changes in central adrenergic, serotonergic, opioid and neuroendocrine systems, have been reviewed [23,24], but remain largely speculative. A number of studies have pointed to the impact on serotonin pathways as an explanation for the neuropsychiatric effects of IFN therapy. IFN significantly increases serum kynurenine (a metabolite of tryptophan) concentrations, and significantly reduces plasma tryptophan and serum serotonin concentrations [25].

Increased serotonin turnover induced by IFN corresponds to increases in the depression scores on the Montgomery-Asberg Depression Rating Scale and the Hamilton Rating Scale for Anxiety. Decreased levels of the serotonin metabolite 5-hydroxyindolacetic acid are found in the cerebral spinal fluid of IFN-treated subjects [26]. IFN- α -induced depression has also been reported to be associated with IL-6 and hypometabolism in the prefrontal cortex as measured by positron emission tomography [27,28]. Although significant pre-existing psychiatric illness, particularly bipolar disorder, has been considered a contraindication to IFN-based medications, a recent study evaluated the effects of IFN and RBV in high-risk groups that included patients with psychiatric disorders, those on methadone maintenance, those who were former drug addicts and controls with hepatitis C, and found no contraindications [29].

Approximately 20 – 30% of patients treated with PEG-IFN and RBV will report depression during therapy, making this a frequent cause of decreased quality of life, and an indication for dose reduction or discontinuation. Underlying depression and anxiety are associated with decreased compliance, which can compromise efficacy [30]. There is growing consensus that selective serotonin reuptake inhibitors (SSRIs) may be the class of choice for treating depression associated with IFN therapy in patients with chronic hepatitis C [31]. SSRIs appear to be safe and well tolerated in patients with liver disease [32]. Conversely, the prophylactic administration of antidepressant drugs offers no advantages in the management of depression [33].

2.6 Respiratory tract symptoms

Respiratory tract symptoms, including a non-productive cough and shortness of breath, are relatively common with IFN monotherapy, and occur at a similar rate in those treated with PEG-RBV (24 vs 26%) [3]. RBV use may be associated with a persistent cough in the absence of any objective airway disease. The etiology of dyspnea is usually related to the severity of anemia. However, interstitial lung disease, alveolar disease and sarcoidosis have been reported in hepatitis C therapy treated with IFN [34-37]. In a series of five patients, bronchiolitis obliterans organizing pneumonia and interstitial pneumonitis were reported in patients treated with PEG-IFN or IFN- α_{2b} [34,35]. Some of these patients presented with persistent cough and underwent lung biopsy, showing bronchiolitis obliterans organizing pneumonia or interstitial pneumonitis. Thus, persistent dyspnea and persistent cough should be investigated, and therapy may need to be discontinued.

Interstitial pneumonitis associated with IFN can be severe and life-threatening, though it is usually reversible on discontinuation of IFN [38,39]. Reports of sarcoidosis with significant dyspnea and dependency on steroids have been published [36,37]. The presence of pulmonary or systemic sarcoidosis is generally considered a contraindication to therapy with IFN-based medications.

2.7 Ophthalmologic disorders

Ophthalmologic disorders (retinal hemorrhages, cotton wool spots, loss of color vision and, rarely, retinal artery or vein obstruction) can occur during IFN therapy. The most common ocular complication is the development of a mild-to-moderate ischemic retinopathy. On fundoscopy, the two most common signs with IFN-related retinopathy are cotton wool spots and retinal hemorrhages that resemble diabetic retinopathy. They are usually found at the posterior pole around the optic nerve head, and typically occur within 1 – 3 months of treatment, which makes it important to see patients for a baseline examination at the beginning of IFN treatment. Cotton wool spots and retinal hemorrhages normally resolve spontaneously during or after treatment [40,41]. The incidence of this retinopathy varies greatly in different reports (ranging from 2 to 86%), though in most cases it was not associated with significant visual loss. The risk may be greater in patients with a history of hypertension or diabetes mellitus.

Several cases of glaucoma have also been reported in association with IFN therapy, but a causative association remains unproven [42]. Case reports have also described a toxic effect of IFN on the optic nerve, in which patients presented with blurred vision similar to that seen with optic neuritis [43,44].

Patients should be cautioned about the possibility of visual disturbance when they are treated with IFN therapy. We suggest a baseline retinal examination performed by an ophthalmologist in patients who have diabetes or hypertension prior to treatment, followed by a regular fundoscopic examination during treatment. In addition, we refer patients for prompt ophthalmologic examination for any new ophthalmologic complaints, particularly changes in visual acuity.

2.8 Thyroid dysfunction

The development of thyroid dysfunction is common in patients treated with IFN [45-50]. The most common IFN- α -associated thyroid abnormality is the development of antithyroid antibodies with no clinical disease (5 – 15% of patients). Approximately 5 – 10% of patients develop one of three autoimmune thyroid diseases. Patients can develop hyperthyroidism associated with Graves' disease, painless thyroiditis (a variant of Hashimoto's thyroiditis) with a triphasic course of transient hyperthyroidism followed by transient hypothyroidism with a return to euthyroidism, or hypothyroidism associated with Hashimoto's thyroiditis. More rarely, patients may develop hypothyroidism that does not appear to be related to underlying autoimmunity.

All patients receiving IFN- α should be monitored for thyroid disease, particularly women and patients with pre-existing antithyroid antibodies. We suggest measuring TSH and antithyroid antibodies before treatment and every 12 weeks during treatment. IFN therapy can usually be continued while hypothyroidism is being treated. Asymptomatic biochemical hyperthyroidism due to Graves' disease or painless thyroiditis that is picked up on scheduled thyroid testing can be observed closely and, if symptoms are minimal, low dose propranolol can be instituted. If clinically apparent hyperthyroidism develops, we stop PEG-RBV and get specialist endocrinology assistance with further management. Following IFN withdrawal, spontaneous normalization of thyroid function can be expected in many, but not all, patients with hypothyroidism, though not in those who develop Graves' disease. Persistent antithyroglobulin and antithyroid peroxidase antibodies after cessation of IFN therapy predict the later development of thyroid dysfunction.

2.9 Autoimmune disease exacerbation

A variety of other autoimmune diseases can develop or be exacerbated during IFN therapy, including psoriasis, vitiligo, rheumatoid arthritis, lichen planus, dermatitis herpetiformis and type 1 diabetes mellitus [51-55]. Thus, IFN should be used with caution in patients with known autoimmune disease and is contraindicated in patients with known autoimmune hepatitis.

2.10 Dermatologic complications

HCV has been associated with multiple dermatologic complications, including leukocytoclastic vasculitis, porphyria cutanea tarda, lichen planus, erythema nodosum, urticaria, erythema multiforme and polyarteritis nodosa [51-54]. Both IFN and RBV have been associated with rashes. The most common is a nonspecific, pruritic rash associated with flaky dry skin. Although the rash has been attributed to RBV, it appears to be more common in those treated with PEG-RBV combination therapy. The rash resolves over time in many patients, but may require a reduction in the dose of RBV (or discontinuation) if it is severe. All patients are advised to avoid powerful skin detergents and to use regular, non-perfumed skin moisturizers in addition to sunblock. In cases of persistent symptoms, we also suggest a low-potency steroid cream (1% hydrocortisone) and non-sedating antihistamine (loratadine 10 mg/day). The administration of systemic steroids may be useful in patients with severe pruritus in order to avoid discontinuation of treatment in patients with virological response.

Erythema and induration are practically constant at the IFN injection site, and may occasionally deteriorate to painful nodules, though they rarely ulcerate. If severe injection site reactions occur, we immediately assess injection technique and avoid further injections in that region.

2.11 Hair loss

Reversible hair loss occurs in ~ 20% of patients, probably due to telogen effluvium, as a result of IFN [56]. While it resolves

on discontinuation of therapy, it can be distressing to patients. Anecdotal experience suggests hair loss may be reduced by using silk/satin pillow cases, avoiding high pressure showers and cutting long hair. Topical minoxidil has also been used, though its efficacy is unclear. Normal hair growth resumes within 3 – 6 months following discontinuation of treatment. Irreversible alopecia associated with RBV and PEG-IFN therapy [57] and autoimmune alopecia areata have also been reported with IFN, but are rare [58].

2.12 Hearing loss

Though extremely rare, sudden hearing loss and tinnitus have been described with IFN and PEG-IFN plus RBV combination therapy [59]. The mechanism is unclear but may be related to direct ototoxicity of IFN, autoimmunity or hematologic changes. Hearing loss does not fully resolve in all patients after discontinuing therapy. On the other hand, continuation of therapy may not worsen symptoms.

3. Conclusion

Most of the patients treated with PEG-IFN experience some adverse events during therapy. However, most adverse events can be managed properly so that only a minority of patients will require premature discontinuation because of side effects. Hematologic abnormalities and depression are frequent indications for dose reductions. The use of hematopoietic growth factors may improve the quality of life and the management of adverse events during IFN-based antiviral therapy. Further studies are required on the mechanisms of IFN-induced depression, which will facilitate the development of new therapeutic approaches.

At present, several direct-acting antiviral drugs are under clinical assessment. Recent clinical trials evaluating the most advanced compounds, telaprevir and boceprevir, indicate that the addition of these protease inhibitors to standard-of-care therapy considerably increases the rate of SVR in treatment-naïve patients, as well as in relapsers, and nonresponders to standard therapy [60,61]. The clear evidence

that overall treatment periods can be shortened considerably with no significant loss of response could reduce many of the above-described side effects of PEG-IFN, and thus increase adherence to scheduled therapy.

4. Expert opinion

The relevant clinical benefits of IFN-based treatment encourage clinicians to propose the therapy to a majority of patients with chronic hepatitis C. The side effects of the standard-of-care therapy discussed in this paper could affect a large number of patients, but mounting knowledge of these complications and increased physician experience may allow for correct management and avoidance of treatment discontinuation in the majority of cases.

Growth factor therapy, used mostly for anemia and neutropenia, has an important role in the management of hematologic adverse events during antiviral treatment. A prospective study performed in a large cohort of patients would be useful in assessing their impact on patient compliance and, consequently, on the rate of SVR. Furthermore, a definitive collection of guidelines for the correct management of the different kinds of side effects should be undertaken and studied in order to improve the treatment of these patients and diminish dose reductions or treatment discontinuation.

Future treatment with protease inhibitors will change the current approach to the treatment of HCV infection. New therapeutic protocols would ideally include a combination of PEG-IFN, RBV and protease and/or polymerase inhibitors, and so it is possible that patients will experience side effects that are different from those previously reported. However, combined therapy can result in a shortened treatment period, and this should improve patient compliance.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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