

Interferon and Ribavirin Treatment Side Effects

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Summary Points

- Treatment-related side effects are nearly universal
- Most common:
 - fatigue (interferon and ribavirin)
 - flulike symptoms: fever, headache, muscle ache (interferon and ribavirin)
 - mild anxiety (interferon)
 - skin rash (ribavirin)
 - depression (interferon)
 - gastrointestinal symptoms: nausea, diarrhea (interferon and ribavirin)
- Monitoring for severe side effects (eg, marked anemia) is an important part of treatment follow-up
- Management of symptoms due to side effects is critical to completion of therapy

Introduction

Alpha interferons, which are given as subcutaneous injections, have been used since the late 1980s in the treatment of chronic hepatitis C.(1) Refinement of their use, pegylation to make them long-acting, and the addition of oral ribavirin to them, has brought their rate of long-term viral clearance (or sustained virological response) from <5% to now approximately 50% in patients who have never before received treatment.(2,3,4) The use of alpha interferons is currently a very important part of the management of chronic hepatitis C infection.

Side effects of treatment, however, are essentially universal. These led to modification of the dosage of interferon and/or ribavirin in 35-42% of patients treated with pegylated interferon in large, randomized clinical trials and discontinuation of therapy in 14-19% of these patients.(3,4) The most common side effects and their prevalence in these clinical trials are listed in [Table 1](#).

Practitioners caring for patients who develop these side effects can take management steps to help them with each one. Patient behavior modification and the administration of routine medical therapy is often the first step in management. Administration of more complicated medications is often a second step.

Dose reduction or discontinuation of interferon or ribavirin is another extremely important step in side-effect management, indicated immediately if severe side effects of therapy develop. Dose reduction should be done judiciously, however, particularly early in therapy, as it has been shown to be associated with a decreased rate of sustained virological response in some settings. Standard recommendations for dose reduction of interferon or ribavirin and the use of growth factors erythropoietin and filgrastim are described below in the [Laboratory](#) section.

Table 1. Common Side Effects of Interferons and Ribavirin in Large, Randomized Clinical Trials (% of Patients Affected)

Adverse Event (%)	PEG-alfa 2b + Ribavirin 800 mg/day Manns et al.(3) n = 511	PEG-alfa 2a + Ribavirin 1,000-1,200 mg/day Fried et al.(4) n = 453	Interferon-alfa 2b+ Ribavirin 1,000-1,200 mg/day McHutchison et al.(2) n = 228
Constitutional			
Fatigue	64	54	70
Headache	62	47	66
Fever	46	43	41
Myalgias	56	42	64
Gastrointestinal			
Nausea	43	29	46
Anorexia	32	21	25
Diarrhea	22		22
Psychiatric			
Insomnia	40	37	39
Irritability	35	24	32
Depression	31	22	36
Dermatological			
Alopecia	36	28	32
Skin rash	24	21	28
Laboratory			
Anemia	9	23	8
Neutropenia	18	21	

Constitutional

Fatigue

Fatigue is the principal side effect of interferon and ribavirin therapy in each trial listed in Table 1. This is partly a direct side effect of interferon-alpha, with its stimulation of the immune response giving the release of cytokines and other factors that cause fatigue, and is partly related to the anemia caused by ribavirin. Ribavirin is directly toxic to red blood cells, causing them to break down, giving a median decline in hemoglobin of approximately 3 g/dL,^(3,4) which will cause most patients to feel fatigued. Fatigue also can clearly be multifactorial, with *insomnia*, dehydration, and *anorexia* contributing in individual patients.

Management

1. Encourage patients to get plenty of sleep, keep well-hydrated, and eat well-balanced meals to maintain their weight if possible.
2. Acetaminophen (Tylenol) <2 gm per day orally in divided doses, also can be very helpful in combating fatigue, particularly with 325-1,000 mg as a premedication prior to an interferon dose if the fatigue is worse 1-2 days after an interferon injection.

Headache

Headache is very common and can be a direct side effect of interferon. It also can result from the development of anemia.

Management

1. Steps outlined for *fatigue*.
2. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen also may be helpful, but generally should not be used in patients with significant liver scarring or cirrhosis, who are at risk for gastrointestinal bleeding or renal failure due to NSAIDs.
3. Antimigraine medications such as Imitrex may be helpful for patients who have a history of migraines.

Fever

Fever is principally a side effect of interferon, and tends to be worse with the first few injections. Fever $>101^{\circ}\text{F}$ (38.5°C) for more than 24-48 hours, or not following an interferon injection, should prompt a medical evaluation for an infectious source of the fever.

Management

1. Steps outlined for **fatigue**, as well as the use of NSAIDs, as described for **headache**.

Myalgias

Myalgias are principally a side effect of interferon. The precise mechanism for them is unknown, but they seem to be related to the systemic inflammation and dehydration brought about by therapy.

Management

1. Steps outlined for **fatigue**, as well as the use of NSAIDs, as described for **headache**.
2. A hot bath or use of a hot tub may be helpful.

Gastrointestinal

Nausea

Nausea is the most common gastrointestinal side effect of interferon and ribavirin therapy, linked at times to each medication.

Management

1. Particularly for nausea linked to ribavirin dose, taking the ribavirin with food or eating smaller, more frequent meals may be helpful.
2. Ginger may be helpful for nausea and can be found in tea, ale, and ginger snap cookies.
3. Avoid smells and foods that trigger nausea
4. Prochlorperazine (Compazine) 5 mg tablet, 1-2 every 8-12 hours when nausea occurs. Precautions: Do not use in patients with a history of phenothiazine allergy; beware of side effects of tardive dyskinesia; beware of interactions with other medications.

Anorexia

Anorexia is common, with most patients losing weight, even 10-15 lbs or more, during therapy.

Management

1. Eating smaller, more frequent meals may be helpful.
2. Nutritional supplements (Ensure, nutrient bars) may be helpful.
3. Eat snacks with protein (eg, cheese, peanut butter, eggs).
4. If taste sensation is altered, try lemon drops or zinc lozenges.

Diarrhea

Diarrhea is present in 20% or so of patients on therapy, but can be a significant side effect. It tends to be episodic, and will often improve even with continued therapy. If persistent and significant, adequate hydration needs to be assured, and a workup for general causes of diarrhea, including taking a full patient history and obtaining stool studies, should be done.

Management

1. Once other causes of diarrhea are deemed unlikely, oral antidiarrheal agents can be used, eg, loperamide (Imodium) 2 mg capsules, 2 initially then 1 after each loose stool to a maximum of 4 per 24 hours; or diphenoxylate/atropine (Lomotil) 2.5 mg/0.025 mg, 2 tablets up to 4 times daily.
2. Avoid or limit caffeine-containing beverages (such as coffee and cola) and high-sugar soft drinks.
3. Limiting of lactose-containing foods may be helpful in some patients.
4. Boiled rice, apples or applesauce, bananas, oatmeal, and bulking agents such as Metamucil can help solidify stool.

Psychiatric Side Effects

Insomnia

The most common psychiatric side effect of therapy, insomnia is present to some degree in 40% or so of patients. Insomnia can contribute to fatigue, headache, irritability, depression, and other side effects.

Management

1. Improvement in sleep habits to the degree possible, with sleeping principally at night, not reading or watching television in bed.
2. Limit fluid intake at night to avoid having to get up to go to the bathroom.
3. Avoid stimulants, such as caffeine, at night.
4. Medication sleep aids may be helpful in some patients. Patients always should be aware that these medicines may impair driving or work performance and should not be used in combination with other sedatives, including alcohol. The non-habit-forming diphenhydramine (Benadryl), 25-50 mg orally at bedtime as needed, can be helpful. Precautions: can cause headache, dry mouth, difficulty urinating, and weakness. Desyrel (Trazodone), 50-100 mg at bedtime, and zolpidem (Ambien), 5-10 mg orally at bedtime, are among the medications that have been helpful, but they should be used only after consulting manufacturer guidelines.

Irritability

Another very common side effect, irritability is documented in clinical trials in 30% or so of patients, but may be present to a lesser degree in most patients.

Management

1. Educating patients (and their spouses or close friends, if possible) that they will likely have a quicker temper and be less understanding during treatment is very important. If patients are aware that the medications predispose them to temper flares, they can anticipate them and control them more

- effectively.
2. Patients should be aware that job circumstances may exacerbate these symptoms and that making arrangements for maximal job flexibility and limitation of stress at work can be extremely helpful.
 3. Encourage patients to try relaxation techniques (eg, take a deep breath and count to 10).
 4. Encourage patients to share their feelings with friends and family. Consider joining a support group.
 5. Managing other symptoms such as **insomnia**, **fatigue**, and **depression** is also very important.

Depression

Depression develops in 20-35% of patients treated with interferon and ribavirin. This can be one of the major morbidities associated with treatment, and practitioner screening for the development of suicidal or other destructive ideation is essential when patients develop symptoms of depression. Comanagement of patients with a prior history of depression or other mental illness by mental health professionals, with appropriate therapy before treatment, is very important.⁽⁶⁾

Management

1. Patient education, close monitoring during therapy, reassurance, and treatment of other symptoms as outlined above.
2. Selective serotonin reuptake inhibitors (SSRIs) have been found to be effective in treating the depression associated with interferon therapy,⁽⁶⁾ with typical dosage of fluoxetine (20 mg orally daily), paroxetine (20 mg orally daily), sertraline (50 mg orally daily), and other agents being options for individual patients. Manufacturer recommendations regarding side effects and treatment guidelines for each medicine should be consulted.

Dermatological

Alopecia

Approximately one third of patients develop noticeable hair loss while on therapy. When present, the hair loss tends to be gradual, not patchy as with systemic chemotherapy. Subtle hair loss is even more common.

Management

1. Factors which may help include not pulling on the hair, not braiding it, and avoiding vigorous combing. Using a wide-tooth comb may be helpful.
2. Use of harsh hair products may also contribute to hair loss, and should be avoided.
3. Patient should be reassured that hair tends to grow back gradually to essentially pre-treatment levels after interferon is stopped.

Skin Rash

20-25% of patients develop a skin rash, which is generally due to ribavirin. It is a fine, red, petechial or reticular rash, and tends to be seen over the arms and trunk, although it may be present diffusely. It tends to improve and recur spontaneously during treatment.

Management

1. Topical therapies, starting with moisturizing lotions and then low-dose steroid creams (eg, 1% hydrocortisone or triamcinolone), are often very helpful in improving the rash and its associated pruritus.
2. Oral medications such as diphenhydramine may be helpful if topical therapies do not relieve symptoms.
3. In severe cases, dosage reduction or even discontinuation of ribavirin tends to be helpful, with reintroduction as symptoms improve.
4. For skin rash developing at injection sites, changing sites is often helpful.

Laboratory

Anemia

Ribavirin causes a dosage-dependent, hemolytic anemia, and interferon can suppress bone marrow production of red blood cells. This results in anemia, likely in >20% of patients treated with a pegylated interferon and ribavirin at 1,000-1,200 mg/day.(4) Anemia can be one of the most clinically significant side effects of therapy, and patients with conditions that can be exacerbated by anemia, such as coronary artery disease or chronic obstructive pulmonary disease, should be monitored particularly closely. Patients coinfecting with HIV may be even more susceptible to developing anemia due to treatment.(7) Complete blood counts should be checked every 2-4 weeks while a patient is on therapy.

Management

1. Dosage reduction in ribavirin likely should be the first step in managing symptomatic anemia. The efficacy of ribavirin may be dosage related in part, however,(3) and doses therefore should be maintained at 800 mg/day or more if possible. Manufacturer guidelines recommend reducing ribavirin dosage (to 600 mg/day for Copegus, and by 200 mg/day for Rebetol) with hemoglobin <10 g/dL, and discontinuing ribavirin with hemoglobin <8.5 g/dL.(8,9)
2. Subcutaneous injections of recombinant erythropoietin (eg, epoetin alfa 20,000-40,000 units weekly or darbepoetin 200-300 mcg every other week), can be used to treat anemia due to ribavirin. Its use has not yet been shown to improve the rate of sustained virological response to treatment.

Neutropenia

Interferon suppresses bone marrow production of leukocytes, which leads to neutropenia in approximately 20% of treated patients.

Management

1. Manufacturer guidelines recommend reducing interferon dosage (to 135 mcg peginterferon alfa-2a or to 50% of

peginterferon alfa-2b) when the absolute neutrophil count falls below $750/\mu\text{L}$, and suspending interferon for neutrophil counts below $500/\mu\text{L}$.(8,9)

2. Subcutaneous injections of filgrastim can be used to treat neutropenia due to interferon. Similar to erythropoietin, its use has not yet been shown to improve the rate of sustained virological response to treatment.

Thrombocytopenia

Platelet counts often drop in the setting of interferon and ribavirin therapy, due at least in part to interferon suppression of platelet production in the bone marrow. Patients with cirrhosis, who may begin treatment with low platelet counts due to portal hypertension, can be particularly affected.

Management

1. Manufacturer guidelines recommend reducing interferon dosage (to $135 \mu\text{g}$ peginterferon alfa-2a or to 50% of peginterferon alfa-2b) when the platelet count falls below $80,000/\mu\text{L}$, and suspending interferon for platelet counts below $50,000/\mu\text{L}$.(8,9)

Other Side Effects

Dyspnea (Shortness of Breath)

While the incidence rate of dyspnea was not uniformly reported in clinical trials, this is a common side effect of therapy, and it is often linked to the severity of **anemia**, with its accompanying decreased oxygen-carrying capacity leading to dyspnea on exertion.

Management

1. Dyspnea should be evaluated by a clinician to ensure that it does not have a serious cardiac, pulmonary, or other origin which needs to be managed specifically.

Chest Pain

Chest pain is another fairly common side effect of therapy.

Management

1. For any symptomatic chest pain that develops during therapy, a clinician should be involved in assessing whether the chest pain could be cardiac in origin. Appropriate studies, including electrocardiograms, medical therapy (including dosage reduction of interferon and/or ribavirin), and monitoring, should be instituted as clinically indicated.

Visual Changes

Visual changes are fairly common, but the exact incidence is unknown.⁽¹⁰⁾ The most commonly documented eye complications are “cotton wool spots” and retinal hemorrhages, but most interferon-related retinopathy is asymptomatic and reversible.

Management

1. It is reasonable to perform a baseline eye exam in any patient with diseases associated with the retina (eg, diabetes, hypertension) to establish a pretreatment baseline. Any patient who develops visual changes while on interferon should be evaluated by an ophthalmologist. Treatment changes can then

be made in consultation with the ophthalmologist based on the findings observed. Patients should know that there have been instances of serious eye injury (eg, optic neuritis, visual loss, retinal detachment) in patients taking interferon, although these are rare and may improve with discontinuation of the medication.

Thyroid Dysfunction

Interferon therapy can be associated with changes in thyroid function, with both hypothyroidism and hyperthyroidism occurring. Such changes are more common in patients with a history of thyroid dysfunction.

Management

1. Serum thyroid stimulating hormone (TSH) levels should be checked before, during, and after therapy. Free thyroid levels (“free T4”) also should be assessed if changes in TSH values are noted. Patients should be evaluated by a clinician if biochemical thyroid abnormalities are noted, and should be aware that prolonged thyroid dysfunction is a rare side effect of therapy.
2. Therapy can be stopped and thyroid hormone replacement can be initiated if indicated.

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