



Pharmacy

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Update

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor-in-Chief
Karim Anton Calis, Pharm.D., M.P.H.
Coordinator, Drug Information
Service, and Endocrinology Clinical
Pharmacy Specialist
kcalis@nih.gov

Associate Editor
Maryam R. Mohassel, Pharm.D.
Specialized Resident in Drug
Information Practice and
Pharmacotherapy
mmohassel@nih.gov

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Influenza Vaccination: 1998-1999

Each year, infections due to the influenza virus result in substantial morbidity and mortality worldwide. Vaccination offers appreciable protection against the influenza virus for individuals and contributes to improved overall public health.

A new trivalent vaccine is now available for the 1998-1999 influenza season. The vaccine is recommended for patients with chronic medical disorders, children with asthma, residents of long-term care facilities, and the elderly. Health-care workers and household contacts of elderly and high-risk patients are also strongly encouraged to receive the vaccine.

Protection conferred by the influenza vaccine typically begins two weeks after vaccination and may last for six months or longer. Serum antibodies in some elderly patients can diminish more rapidly to non-protective levels. Because large outbreaks in the United States usually occur between December and early March, the optimal time to receive the vaccination is between October and November. However, administration of the vaccine is appropriate anytime from September to the end of the influenza season.

The vaccine formulation is changed annually because of the antigenic variability of the influenza virus. Antigens in the current vaccine are derived from A/Sydney/05/97-like (H3N2), A/Beijing/262/95-like (H1N1), and B/Beijing/184/93-like viruses.

Influenza vaccine is produced from inactivated virus grown in chicken eggs. Individuals who have experienced severe hypersensitivity reactions to eggs or egg products should not receive the vaccine. An intramuscular dose of 0.5 mL of the split-virus formulation can be administered (in the deltoid) to adults and children at least three years of age. Recipients of the vaccine may experience soreness at the site of injection, fever, and malaise that may persist for one or two days.

Questions about influenza or the vaccine should be directed to the Hospital Epidemiology Service at 6-2209 or the NIH Drug Information Service at 6-2407. For questions about the vaccination schedule, contact the Occupational Medical Service at 6-4411.

Interferon alpha-2b/Ribavirin (Rebetron®): A Brief Review

Chronic hepatitis C infection is considered the single most common cause of cirrhosis, hepatic carcinoma, and chronic liver disease. Patients with this infection typically present with elevations in serum aminotransferase concentrations (specifically alanine aminotransferase) and positive serum HCV-RNA. Interferon alpha is the principal treatment available to patients with chronic hepatitis C. Interferon alpha-2b, given subcutaneously (SQ) three times a week (TIW) for 12 months, can decrease serum aminotransferase concentrations and render serum HCV-RNA undetectable. Once treatment is discontinued, however, the majority of patients relapse, and only 20% maintain a sustained response. Ribavirin, a nucleoside analog administered orally, has been used in combination with interferon alpha-2b to improve the overall response rate. Previously, ribavirin was available in the United States only in an aerosol form for the treatment of respiratory syncytial virus infections in infants and young children.¹

Description:

Intron-A® is Schering Corporation's brand name for interferon alpha-2b, a purified sterile recombinant interferon product. Intron-A® injection is a clear, colorless solution which is available as a 3-MU single-dose vial (3 MU/0.5 ML), an 18-MU multi-dose vial (3 MU/0.5 ML), and an 18-MU multi-dose pen (3 MU/0.2 ML). Rebetol® is Schering Corporation's brand name for ribavirin, a nucleoside analog with antiviral activity. Rebetol® capsules consist of a white powder in a white-opaque gelatin capsule. Each capsule contains 200 mg of ribavirin. The combination of interferon and ribavirin is marketed as a package containing a two-week supply of both medications.²

Indication:

The combination therapy of oral ribavirin and recombinant interferon alpha-2b injection is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed following alpha interferon therapy alone.²

Pharmacology:

Ribavirin is a nucleoside analog that inhibits the replication of many different RNA and DNA viruses, including some related to HCV.^{1,2} Interferon alpha-2b is a recombinant alpha interferon with both antiviral and immunomodulatory effects. It blocks viral replication and inhibits viral activity by reducing entry of viruses into cells, impairing viral uncoating, and inhibiting viral mRNA and protein synthesis.³ Approximately 60% of patients with chronic hepatitis C have normalization of serum aminotransferase concentrations during treatment with interferon. Nearly 40% of these patients show undetectable serum HCV-RNA levels. However, the majority of these patients relapse once interferon treatment is discontinued.⁴

Pharmacokinetics:

Single- and multiple-dose pharmacokinetic properties of interferon alpha-2b and ribavirin are summarized in Table 1.²

Ribavirin is rapidly and extensively absorbed following oral administration. However, the absolute bioavailability is decreased due to first pass metabolism. Both AUC and C_{max} are increased by 70% when ribavirin is administered with high-fat meals. Ribavirin is metabolized via two pathways: a reversible phosphorylation pathway in nucleated cells and

a degradative pathway involving deribosylation and amide hydrolysis, yielding a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. Following oral administration, approximately 61% of the ribavirin dose is excreted in the urine, and 12% in the feces. In vitro studies suggest little or no cytochrome P-450 enzyme-mediated metabolism of ribavirin. No pharmacokinetic interactions between ribavirin and interferon alpha-2b have been noted.²

Selected Clinical Trials:

Several clinical trials have investigated the efficacy of interferon/ribavirin combination therapy in the management of chronic hepatitis C. Most of these studies involved patients who have failed to respond or maintain a sustained response to interferon monotherapy. The efficacy of interferon combination therapy has also been compared to that of interferon therapy alone in a number of randomized, double-blind, placebo-controlled clinical trials which included interferon-naive patients.

In a Swedish clinical trial, twenty patients with chronic hepatitis C (10 with a history of non-sustained response to interferon, and 10 with no response at all) were started on the interferon alpha-2b (3 MU SQ TIW) and ribavirin (1000-1200 mg/day PO) combination.⁵ All patients had positive HCV-RNA tests and elevated aminotransferase levels for at least six months prior to enrollment. The duration of treatment was 24 weeks, and all patients were monitored for an additional 24 weeks after discontinuation of therapy. All 10 patients who had previously experienced a non-sustained response with interferon, experienced a sustained response with the combination. These patients developed negative HCV-RNA tests and normal aminotransferase levels upon completion of treatment, with nine maintaining a negative HCV-RNA test at the 24-week follow-up. Of the 10 patients who had experienced no response with interferon, five developed normal aminotransferase levels by the end of therapy, and four had a negative HCV-RNA test. At follow-up, three of these 10 patients continued to have negative HCV-RNA tests and normal aminotransferase levels. Reductions in leukocyte counts and hemoglobin concentrations were the most common adverse effects reported. However, none of the patients discontinued therapy due to adverse reactions. This study was limited by a small sample size (n=20) and the lack of clear inclu-

Table 1. Mean Pharmacokinetic Parameters for Interferon alpha-2b and Ribavirin

Parameter	Interferon alpha-2b		Ribavirin	
	Single Dose 3 MU	Multiple Dose 3 MU TIW	Single Dose 600 mg	Multiple Dose 600 mg BID
T _{max} (h)	7	5	1.7	3
C _{max} *	13.9	29.7	782	3680
AUC **	142	333	13400	228000
T _{1/2} (h)	6.8	6.5	43.6	298

* U/mL for interferon alpha-2b and ng/mL for ribavirin

** U.h/mL for interferon alpha-2b and ng.h/mL for ribavirin

sion/exclusion criteria. Additionally, patients enrolled in this study had varying degrees of disease severity, including a few with severe liver cirrhosis.

Combination therapy with interferon and ribavirin was also evaluated in a clinical trial enrolling 10 patients with chronic hepatitis C (six with a non-sustained response to previous interferon therapy and four with no response).⁶ Patients were given interferon alpha-2b (3 MU SQ TIW) and ribavirin (1000-1200 mg/day PO) for 24 weeks and were monitored for 24 weeks after discontinuation of therapy. All four non-sustained responders had normal aminotransferase levels at the end of therapy and at follow-up. Among the non-responders, three out of six had normal aminotransferase levels at the end of therapy, but only one at follow-up. All four non-sustained responders developed negative HCV-RNA tests, with three remaining negative at follow-up. In the non-responder group, two patients became HCV-RNA negative and remained negative at follow-up. All patients completed the study. Common adverse drug reactions included mild reductions in hemoglobin, and decreased white blood cell and platelet counts. This study was limited by a small sample size and the lack of clear exclusion criteria. Additionally, it was unclear if all patients enrolled in this study had the same degree of disease severity.

The use of interferon/ribavirin combination therapy in interferon-naive patients has also been evaluated. One study compared the efficacy of interferon alpha-2b/ribavirin combination therapy to that of interferon with a placebo capsule.⁷ This was a randomized, double-blind, placebo-controlled study enrolling 100 patients with chronic hepatitis C. Patients were randomly assigned to treatment with interferon alpha-2b (3 MU SQ TIW) and ribavirin (1000-1200 mg/day PO) or interferon (3 MU SQ TIW) and placebo. The duration of treatment was 24 weeks, with an additional 24-week follow-up period. An additional follow-up was performed one year after discontinuation of therapy. Thirty-six percent (18/50) in the interferon/ribavirin group had a sustained response vs. 18% (9/50) in the interferon/placebo group. At one-year follow up, 42% of the patients in the interferon/ribavirin group maintained a sustained response vs. 20% of those in the interferon/placebo arm ($p=0.03$). Common adverse reactions experienced included fatigue, nausea, headache, alopecia, and anemia. A total of seven patients discontinued treatment due to adverse drug effects. This study included a relatively large sample size, and the inclusion/exclusion criteria were clear. In addition, complete patient demographics, including the degree of disease severity, were provided.

The use of ribavirin/interferon combination therapy has also been studied in liver transplant recipients with hepatitis C infection.⁸ Mazzaferro et al. studied the effects of interferon/ribavirin combination therapy in 21 patients following liver transplant. Combination interferon alpha-2b (3 MU SQ TIW) and ribavirin (10 mg/kg/d PO) therapy was started three weeks after liver transplant in all HCV-RNA positive patients discharged from the ICU on an oral diet. These patients continued on the combination therapy for one year and were followed every two weeks. After the first month and

a half of therapy, all patients had normal alanine aminotransferase serum concentrations. At the one-year follow-up, 20 of the 21 patients were alive, and 8 of these 20 were HCV-RNA negative. Common adverse reactions reported were anemia and asthenia, but none of the patients discontinued treatment because of adverse effects. However, 43% experienced adverse drug reactions (primarily anemia) and required dosage reduction. This study was poorly reported, and limited patient demographics and baseline data were presented.

Adverse Effects:

The most common adverse effects seen during combination therapy with interferon alpha-2b and ribavirin included flu-like symptoms, headache, fatigue, fever, and myalgia. Other commonly reported side effects were nausea, anorexia, insomnia, alopecia, and irritability. Neutropenia, elevated uric acid levels, and thyroid abnormalities were also reported.² Ribavirin induces a dose-related hemolysis, and most patients experience a decrease in hemoglobin levels of 1-2 g/dL.

Drug Interaction:

Co-administration of ribavirin with an antacid preparation containing magnesium, aluminum, and simethicone resulted in a 14% decrease in mean ribavirin area under the time-concentration curve. The clinical relevance of this interaction is unknown.²

Precautions and Contraindications:

Combination interferon/ribavirin therapy is categorized by the FDA as pregnancy category X. This combination must be avoided in women who are or may become pregnant. Therapy should not be started until pregnancy is ruled out. Interferon/ribavirin combination therapy is contraindicated in patients with autoimmune hepatitis or those with a history of hypersensitivity to interferon or ribavirin. In addition, patients with a history of unstable cardiac disease should not be started on this combination therapy, since anemia associated with this treatment can result in further deterioration of cardiac function. Interferon/ribavirin therapy must also be used with extreme caution in patients with a history of preexisting psychiatric disorders. Severe psychiatric adverse effects including depression and suicidal behavior have been reported with the use of this combination. Because patients have complained of loss of visual acuity while on this therapy, a visual exam is recommended prior to initiation. Combination interferon/ribavirin therapy should be used with caution in patients with creatinine clearance measurements less than 50 mL/min.²

Dosage and Administration:

The recommended dosing guidelines for ribavirin and interferon alpha-2b are provided in Table 2. Since the long-term safety and efficacy of this combination therapy has not been evaluated, treatment should be limited to a period of six months.

Table 2. Recommended Dosage Guidelines

Body Weight	Interferon alpha-2b	Ribavirin
< 75 Kg	3 MU SQ TIW	2x200 mg caps AM (PO) 3x200 mg caps PM (PO)
> 75 Kg	3 MU SQ TIW	3x200 mg caps AM (PO) 3x200 mg caps PM (PO)

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if hemoglobin levels decrease by more than 2 g/dL during any four-week period. The dose of ribavirin must be decreased to 600 mg/day in patients with hemoglobin levels less than 10 g/dL. If hemoglobin falls below 8.5 g/dL, therapy must be discontinued.²

Cost:**Table 3. Cost of Rebetron®**

Patient's Weight	Monthly Cost of Therapy
> 75 Kg	\$ 910*
< 75 Kg	\$ 815*

*Federal Supply Schedule

Conclusion:

The combination of interferon alpha-2b and ribavirin appears to be effective in patients who have failed to respond or maintain a sustained response to interferon monotherapy.

Additional long-term studies and studies in interferon-naïve patients are warranted.

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Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196