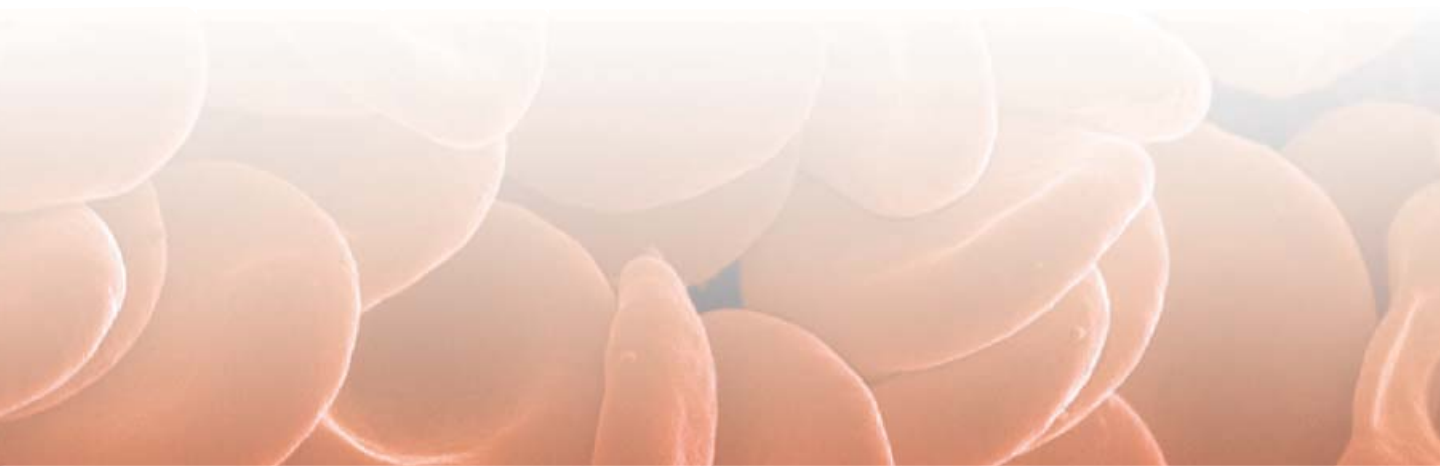


“While combined-therapy dose reduction or treatment discontinuation has been shown to alleviate hemolytic anemia in some patients, the use of erythropoietin may achieve the same goal.”

IX Anemia & Hepatitis C

Key Points

- Hemolytic anemia is a major side effect of ribavirin therapy in patients with hepatitis C.
- Pernicious anemia may be induced in patients with hepatitis C by long-term interferon therapy.
- Erythropoietin therapy may be useful in managing anemia in patients with hepatitis C.



HCV Infection Common

Hepatitis C virus (HCV) infection is the most common chronic blood borne infection in the United States. Although the incidence of HCV infection has declined to 36,000 new infections per year since 1996,¹ an estimated 3.9 million Americans are or have been infected.¹ Of those, 2.7 million are chronically infected.²

HCV is primarily transmitted by large or repeated direct percutaneous exposures to blood, such as by injection drug use, which currently accounts for most HCV transmission in the United States.¹ Coinfection of HIV patients with HCV is a serious clinical problem, occurring in approximately one quarter of HIV patients.³ Other risk factors associated with transmission of HCV include employment in patient care or clinical laboratories, exposure to an infected sex partner or multiple sex partners, and low socioeconomic level.

Before the 1990s, transfusions contributed substantially to the incidence of HCV infections, but improved screening practices have lowered the incidence to a negligible rate of about 1 in 100,000 per unit transfused.⁴ In dialysis patients, however, infections are common, with the prevalence of HCV infection ranging from 10% to 30%.⁵

Treatment for HCV Infection

Two regimens have been approved for the treatment of HCV infection in the United States: monotherapy with alpha interferon and combination therapy of alpha interferon and the oral antiviral agent ribavirin.⁶ Studies of patients treated with combination therapy have demonstrated a substantial increase in

sustained response rates, about 40% to 50%, compared with response rates of 15% to 25% with alpha interferon alone.⁷ Pegylated forms of interferon, which have a prolonged half-life and a lower rate of clearance compared to unmodified interferon, are now being used with ribavirin, and this combination is becoming the standard of care.⁸

Ribavirin-induced Hemolytic Anemia

While combined therapy has proven more effective than monotherapy for patients with HCV infection, hemolytic anemia is a major side effect of therapy with ribavirin. Hct values generally reach their lowest values within 2 to 3 weeks after therapy has commenced.⁸

Anemia associated with ribavirin treatment has been attributed to the accumulation of ribavirin triphosphate in erythrocytes, which interferes with cells' function.⁹ Ribavirin causes red cell hemolysis to a variable degree in almost all patients⁶ and necessitates dose reduction in an estimated 7% to 9% of patients receiving combination therapy.^{10,11} Consequently, patients with preexisting hemolysis or anemia (Hb <11 g/dL or Hct <33%) should not receive ribavirin. Similarly, neither should patients who have significant coronary or cerebral vascular disease, since anemia caused by treatment can trigger significant ischemia.⁶

Little is known about the variables influencing hemolytic anemia in patients treated for HCV infection, but a recent study of 244 chronically infected HCV patients indicates that ribavirin-induced hemolysis is significantly influenced by three factors: pretreatment platelet level ($P = 0.01$), the amount of

alpha interferon administered ($P = 0.001$), and the haptoglobin phenotype ($P = 0.01$).¹² Haptoglobins bind to Hb and are present in three phenotypes that have differing binding properties. In this study, Van Vlierbergh and colleagues found that anemia occurred in 67% of the patients. Patients who began therapy with lower platelet counts had a significantly higher drop in Hb level with treatment than those with higher counts. Low platelet counts were especially common in older male patients with cirrhosis, which appeared to be a risk factor for ribavirin-induced anemia. Alpha interferon, known to be myelosuppressive when given in higher doses, also contributed to anemia in patients receiving high doses.¹³ As a potential explanation for the third factor influencing anemia in these patients, haptoglobin phenotype, the researchers suggest that there are differences in uptake or competition in uptake of ribavirin between the different haptoglobin phenotypes.¹¹

Pernicious Anemia in Patients with HCV

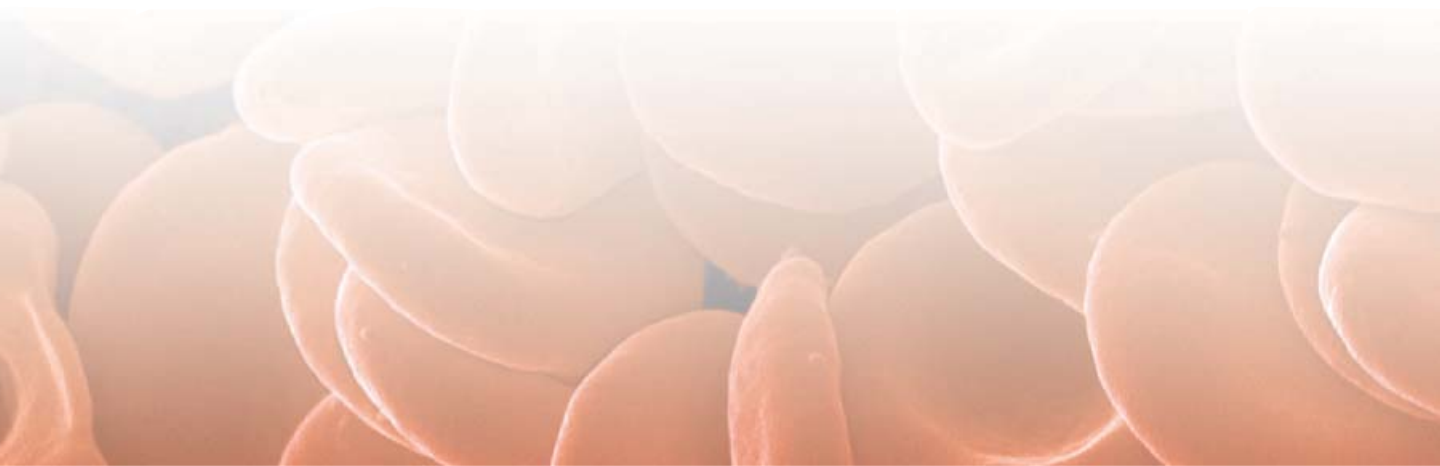
The immunomodulatory effects of interferon therapy may induce pernicious anemia.¹⁴ Although the association between HCV infection and pernicious anemia has not been well studied, reports indicate that the longer-term schedules of interferon, used for treatment of cancer, induced pernicious anemia in some patients.¹³ Careful monitoring of these effects in long-term HCV maintenance therapy appears to be necessary, whether interferon is used alone or in combina-

tion with ribavirin, as the drugs may contribute to pernicious anemia.

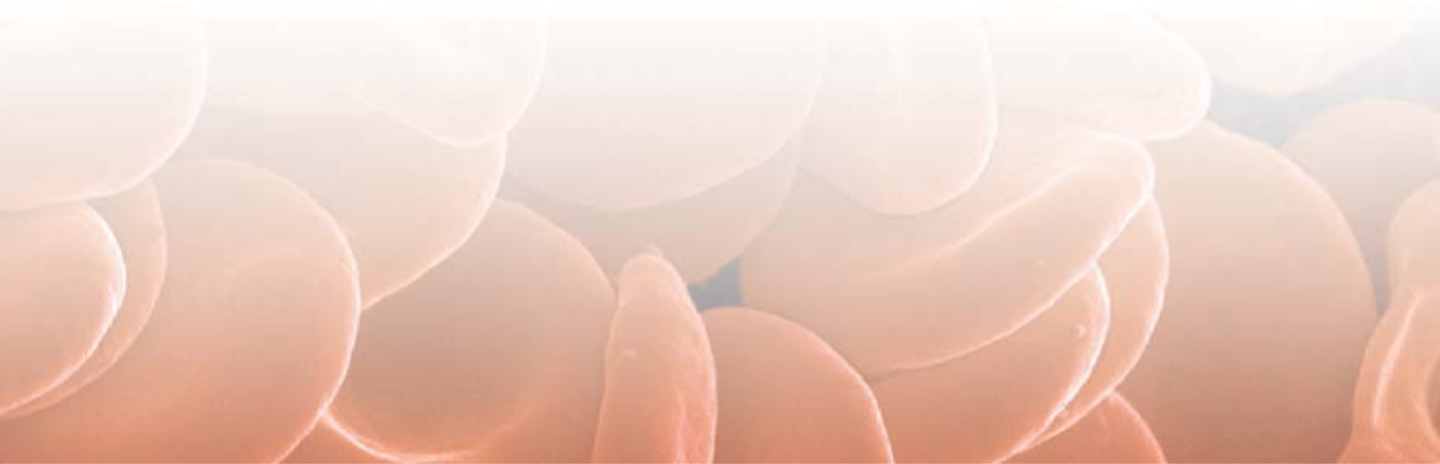
Management of Anemia in Patients with HCV

While combined-therapy dose reduction or treatment discontinuation has been shown to alleviate hemolytic anemia in some patients,¹⁰ the use of erythropoietin may achieve the same goal. A few clinicians have explored the use of epoetin, primarily in patients undergoing liver transplants.¹⁴⁻¹⁷ A recent Swedish pilot study investigated epoetin's use in dialysis patients undergoing combined interferon-ribavirin therapy. The study was conducted in patients with chronic HCV infection, of whom five were receiving hemodialysis and one was receiving peritoneal dialysis. The results showed that ribavirin-induced hemolytic anemia could be managed with high doses of epoetin (20,000 to 30,000 IU/week), and close monitoring of plasma ribavirin and Hb concentrations.¹⁵

The direct cost of treating clinically significant ribavirin-induced hemolytic anemia is low in comparison to the cost of treatment with combination therapy. In a review of the literature, Devine and colleagues estimated the costs at 1% of total drug treatment costs.¹⁶ In their review of 26 studies, they included three studies¹⁷⁻¹⁹ in which epoetin was used 11% of the time, mainly in patients undergoing liver transplants. In these patients, the erythropoietin therapy increased the average cost slightly, but it still accounted for only 1.7% of the total drug treatment costs.



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