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Management of Antiviral Induced Anemia in HCV Infected Patients

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Introduction

Hepatitis C virus (HCV) infection affects more than 170 million people worldwide[1, 2]. Approximately 80% of patients with acute infection will subsequently develop chronic disease, and an estimated 20% to 30% will develop cirrhosis and hepatocellular carcinoma[3]. The maost effective therapeutic regimen for chronic hepatitis C is the combination of pegylated interferon alpha and ribavirin, which yields a sustained virologic response (SVR) in up to 56% of patients[4, 5]. However, combination therapy is also associated with significant adverse events and is contraindicated in certain patient populations. Development of side effects, particularly hematologic ones, may result in suboptimal dosing or discontinuation of therapy that can reduce the likelihood of SVR.

Incidence

In clinical trials, significant anemia (hemoglobin < 10 g/dL) has been observed in 9-13% of patients[4]. Moderate anemia (hemoglobin < 11 g/dL) may be seen in 30% of cases[6]. The mean maximal reduction in hemoglobin can be as high as 3.7 g/dL within the first 2 to 4 weeks of combination therapy[5]. In the "real world", anemia may be the leading cause of premature discontinuation of combination therapy, accounting for 36% of all discontinuations (ie, 8.8% of all patients)[7]. Certain patient populations appear more susceptible to anemia such as cirrhotic patients, HIV coinfected patients, and liver transplant recipients[8].

Impact

Ribavirin is a nucleoside analog which has a broad-spectrum of antiviral activity. It has been shown to inhibit the replication of RNA viruses in cell culture. Ribavirin monotherapy is associated with a decline in serum aminotransferase levels during therapy and may lead to histologic improvement in those in whom the aminotransferases become normal. However, ribavirin is ineffective in eliminating HCV RNA although it may reduce HCV RNA levels in some patients[9]. Ribavirin improves the rate of sustained virologic clearance when given in combination with standard or pegylated interferon alpha[10-12].

The enhanced response to combination therapy was first demonstrated in two small uncontrolled studies[10-11]. In both, the rate of sustained virologic clearance was higher in subjects treated with interferon and ribavirin than those treated with interferon alone.

Ribavirin-related anemia in patients with chronic hepatitis C may alter adherence to treatment, increase the frequency of adverse events, and require ribavirin dose reduction or discontinuation[4, 13-15]. This results in a significant decrease in the chance of achieving SVR. More than 50% of patients

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receiving pegylated interferon plus ribavirin will complain of fatigue[4, 5, 14]. Anemia can lead to symptoms of fatigue or dyspnea and may exacerbate underlying heart disease or chronic obstructive pulmonary disease[8]. Impairment of quality of life may be the main consequence of anemia-related fatigue[16]. Analysis of data from 3 large trials of interferon and ribavirin found that worsening of fatigue scores was predictive of treatment discontinuation[17]. Results from pivotal studies suggest that ribavirin doses < 10.6 mg/kg/d are associated with lower SVR[14]. The SVR rate for patients receiving peginterferon alfa-2b (1.5 mg/kg/wk) plus ribavirin dosages> 10.6 mg/kg/d is 65% compared with a rate of 50% for those receiving peginterferon alfa-2b plus ribavirin at dosages of 10.6 mg/kg/d or less.

It has been shown that SVR rates are significantly higher in patients who receive more than 80% of their full interferon alfa-2b plus ribavirin doses for more than 80% of the time for more than 80% of the intended duration of therapy[14]. In the Hepatitis C Long-term Treatment Against Cirrhosis (HALT-C) trial, a trial involving patients who were previous nonresponders to or relapsers after therapy, reduction of ribavirin dose from> 80% to < 60% of the starting dose during the first 20 weeks of treatment was associated with a decline in SVR from 21% to 11% ($P < .05$)[18]. In a recent prospective study, patients with genotype 1 who were randomized to receive peginterferon alfa-2a (180 g/wk) plus ribavirin 1000 to 1200 mg/d achieved a higher SVR rate than patients who received peginterferon alfa-2a plus ribavirin 800 mg/d[19].

Thus, reduction of the ribavirin dosage to < 10.6 mg/kg/d may clearly affect the SVR rate. It is particularly important to maintain the appropriate ribavirin dosage during the first 12 weeks of therapy in order to decide to continue or stop HCV combination therapy based on the early virologic response.

Mechanism

Both ribavirin and interferon contribute to the development of anemia. Hemolytic anemia is a nearly universal event associated with ribavirin therapy although the extent of hemoglobin reduction can vary considerably among individuals. The mechanism of ribavirin induced anemia has been recently described[20]. After entering red blood cells, ribavirin is phosphorylated into its active form, leading to depletion of adenosine triphosphate. Ribavirin triphosphate cannot be metabolized further in erythrocytes, so it accumulates to levels 60-fold greater than plasma concentrations. This leads to impaired antioxidant mechanisms, resulting in membrane oxidative damage. The erythrocyte is therefore highly susceptible to oxidative stress by the reticuloendothelial system, resulting in extravascular hemolysis. However, additional factors contribute to anemia. Ribavirin also induces anemia through the suppression of erythropoiesis, possibly as a result of erythropoietin receptor regulation[20, 21].

The current recommended dosages for ribavirin are based on body weight. Ribavirin is mainly cleared by the kidneys, and plasma concentrations are determined by renal function[22]. A recent study of patients receiving HCV therapy showed that the decrease in hemoglobin level did not correlate with the dose of ribavirin per kg of body weight but with the ribavirin plasma concentration[23]. This finding suggests that ribavirin should be dosed according to renal function.

Hemolysis typically becomes an issue only in patients who have preexisting anemia, renal insufficiency, or coronary artery disease[24]. In addition, chronic hemolysis induced by prolonged therapy with ribavirin can lead to increased deposition of iron in the liver. In one report, for example, the average rate of hepatic iron accumulation in six patients who had received ribavirin for 6 to 12 months was 1500 g/year[25]. The authors predicted that hepatic iron concentrations might enter the range clearly associated with hepatic fibrosis after approximately 15 years of continuous therapy. Other possible long term complications of hemolysis, including the development of gallstones, were not addressed.

As a result of hemolysis, ribavirin treatment may be associated with a mild reversible increase in serum bilirubin and uric acid. Neither condition requires modification of treatment.

Interferon alpha contributes to anemia through inhibition of progenitor proliferation in bone marrow. Interferon may also accelerate apoptosis of erythroid progenitor cells, induce immune hemolysis, and impair renal function[15]. These effects do not generally result in significant symptoms, dose reduction, or treatment discontinuation.

Management

There are widely variable approaches to the management of anemia during combination therapy. The ideal objective of management is to correct or prevent decreases in the hemoglobin level while maintaining the optimal ribavirin dose> 10.6 mg/kg/d. The standard-of-care management of

ribavirin induced anemia has been dose reduction to 600 mg/d when the hemoglobin level decreases to < 10 g/dL and discontinuation when it decreases to < 8.5 g/dL with transfusion as necessary (**Table 1**)[6]. However, as previously noted, such an approach can have adverse implications for SVR.

Table 1: Guidelines for Ribavirin Dose Modification

Patient group	Reduce ribavirin dose to 600 mg/day if:	Discontinue ribavirin if:
Hemoglobin level in patients with no cardiac disease	<10g/dL	<8.5 g/dL
Hemoglobin level in patients with history of stable cardiac disease	>=2g/dL decrease in hemoglobin during any 4-week treatment period	12g/dL despite 4 weeks at reduced dose

Recombinant human erythropoietin therapy in the HCV-infected patient who becomes anemic during antiviral therapy represents an alternative to ribavirin dose reduction or discontinuation. Erythropoietin is mainly produced by the kidney in adults in response to tissue hypoxia, and it increases the number of erythroid cells in bone marrow by acting as a mitogen, and through the inhibition of apoptosis. Erythropoietin has been used successfully to treat anemia in a variety of diseases. Commercially available as epoetin alfa, this drug is used to treat anemia associated with chronic renal failure, zidovudine therapy for HIV, and cancer chemotherapy.

Two studies have evaluated the use of epoetin alfa for the management of anemia (defined as hemoglobin< 12 g/dL) during HCV combination therapy[26, 27]. The first study compared epoetin alfa (40,000 units/wk) with standard-of-care anemia management in 64 patients in terms of the effect on ribavirin dose and hemoglobin level[26]. Patients who received epoetin alfa had increases in hemoglobin and maintained their ribavirin dose. For example, at week 16 after randomization, patients treated with epoetin alfa had a significantly higher mean hemoglobin level (14.2 vs 11.2 g/dL) and a higher mean ribavirin dose (805 vs 707 mg/d) compared to patients managed for anemia according to the standard of care. The proportion of patients who had their ribavirin dose reduced was significantly lower in the epoetin alfa group (5.7% vs 33.3%).

The second study involved 185 HCV patients undergoing pegylated interferon and ribavirin therapy[27]. Patients who developed anemia were randomized to receive epoetin alfa (initially 40,000 units/wk) or placebo. The study design included an 8-week double-blind phase followed by an 8-week open-label phase during which patients were crossed over to epoetin alfa. At the end of the double-blind phase, ribavirin doses were maintained in 88% of patients receiving epoetin alfa vs. 60% of patients on placebo ($P < .001$). During the double-blind phase, the mean increase in hemoglobin was 2.2+/-1.3 in the epoetin group vs. 0.1+/-1.0 g/dL in the placebo group. Similar results were obtained during the open-label phase. Furthermore, quality-of-life was significantly superior in the epoetin group[27, 28]. Quality-of-life significantly improved in all mental and physical categories assessed by the SF-36v2 questionnaire. Improvement in hemoglobin was an independent predictor of SF-36v2 improvement[27, 28].

Epoetin alfa did not adversely affect HCV clearance. It was well tolerated, with the most common side effects being nausea and headache. These studies suggest that addition of epoetin alfa to maintain ribavirin dose could be an option, particularly for patients with progressive fibrosis, who are difficult to treat.

These data may give hope to many patients who have experienced treatment failure as a result of suboptimal ribavirin dosing. However, several questions need to be answered before this approach becomes standard practice. Does epoetin alfa lead to a higher SVR rate? The study by Afdhal and colleagues[27], unfortunately, did not provide SVR rates. Should epoetin alfa be used as preemptive therapy or as curative therapy? Would all HCV patients benefit from epoetin alfa to a similar extent (cirrhosis vs. mild fibrosis)? Finally, the cost-effectiveness of the use of epoetin alfa needs to be considered. Do the benefits of this treatment outweigh the cost of treating a large proportion of patients? Further studies with this drug are warranted before making strong general recommendations.

Conclusions

Hematologic abnormalities, particularly anemia, are common during combination antiviral therapy for chronic hepatitis C[29]. Ribavirin-related anemia is associated with fatigue, impaired quality of life, and poorer adherence to therapy. Although dose reduction or discontinuation of ribavirin can easily treat these adverse events, this option may also adversely affect the efficacy of combination therapy. Recent data suggest that epoetin alfa may be a

therapeutic option for the management of ribavirin-induced anemia. However, the current data are limited, and further studies are needed in order to evaluate the potential impact on SVR and cost-effectiveness.

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