

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Management of Anemia in Patients Receiving Triple Therapy for Hepatitis C



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G&H What effect does treatment-related anemia have on overall outcomes?

AB Anemia contributes to patients feeling poorly and accentuates fatigue, but, fortunately, findings from phase III clinical trials suggest that dose reduction of ribavirin in the presence of anemia does not impact overall sustained virologic response (SVR) rates when triple therapy includes either boceprevir (Victrelis, Merck) or telaprevir (Incivek, Vertex).

G&H What are the mechanisms behind treatment-related anemia?

AB Ribavirin is the major player in regard to anemia. Ribavirin is thought to induce a reversible dose-dependent hemolytic anemia by infiltrating and massively accumulating in erythrocytes, which are unable to hydrolyze its metabolite, which is ribavirin triphosphate. Depletion of adenosine triphosphate (ATP) results. This, in turn, ultimately results in extravascular hemolysis.

Although anemia is also seen with boceprevir and telaprevir, these protease inhibitors induce an anemia that is additive to that caused by ribavirin. On average, hemoglobin levels drop by an extra gram of the drop in levels caused by ribavirin. The mechanisms are poorly understood, probably multifactorial, and probably associated with ribavirin-induced hemolysis and some degree of bone marrow suppression.

Many patients, especially patients with advanced fibrosis or cirrhosis, are going to be more sensitive to bone marrow suppression or hemolysis. It has been observed in our practice that patients with cirrhosis are more sus-

ceptible to the development of anemia than, for instance, patients without significant fibrosis. Whether anemia develops also depends on the patient population that is being treated. Older patients (ie, age 60 years or older) are at greater risk for development of anemia than younger patients. Anemia also commonly develops in frail patients with low body mass indices.

Treatment-related anemia is multifactorial; however, ribavirin is the most significant driver because improvement is seen when the ribavirin dose is reduced. Ribavirin-induced hemolysis is likely the major culprit, although other agents, as mentioned, are additive.

G&H When should dose reductions or other treatment modifications be considered in patients receiving triple therapy?

AB Although ribavirin is the most problematic among the agents used in triple therapy in terms of its association with the development of anemia, it remains an indispensable component of current triple therapy and, as mentioned, its adverse effects can be managed with dose reduction without compromising SVR rates when used in a boceprevir- or telaprevir-based regimen. Only the ribavirin dose can be reduced, however. Protease inhibitors, due to their low barrier to resistance, cannot be dose reduced. Strategies about when and how ribavirin should be reduced have been studied.

Most patients should be started on ribavirin at a dosage of 1,000–1,200 mg per day. (Patients on peginterferon alfa-2b who are >105 kg may be started at a dosage of 1,400 mg/day.) If a 1.5 g drop in hemoglobin level occurs, only then should dose reductions be considered. The aim

of management with triple therapy, in part, is to keep the hemoglobin levels from falling below 10 g/dL. Hemoglobin levels should be checked 2 weeks into therapy because a drop at this time is predictive of more significant anemia later during therapy.

We have learned a bit about ribavirin dose reduction from the SPRINT 1 and 2 trials, which were trials of boceprevir-based therapy. In the second phase of the SPRINT 1 trial, 75 patients were randomly assigned to receive 48 weeks of either boceprevir at a dosage of 800 mg 3 times daily with 1.5 µg/kg of peginterferon alfa-2b plus 800–1,400 mg of ribavirin daily (n=16) or boceprevir and peginterferon alfa-2b plus low-dose (400–1,000 mg) ribavirin (n=59). The administration of reduced-dose ribavirin at baseline resulted in reduced efficacy of triple therapy, so dose reductions should not be made until signs of anemia develop. At that time, the ribavirin dose can be reduced without compromising efficacy. The SPRINT 2 and RESPOND 2 trial results suggest that the dosage of ribavirin can be reduced by 200–400 mg per day.

A much more significant dose reduction was studied in the phase III telaprevir trials in which ribavirin was reduced by 600 mg for a dosage of 600 mg per day. Pooled data from 2 of these trials—the ADVANCE and ILLUMINATE trials—showed an SVR rate of 76% in those patients receiving reduced-dose ribavirin, compared with a rate of 72% in patients whose ribavirin dose was not reduced.

G&H What, in your opinion, would be an optimal protocol for erythropoietic growth factor use in this setting?

AB Growth factor use, specifically use of epoetin alfa, can be considered a second-line strategy in the face of significant anemia in which hemoglobin levels drop to 10 g/dL or lower even after ribavirin dose reduction. Epoetin alfa, in contrast to darbepoetin (Aranesp, Amgen), allows for more frequent dosing (ie, weekly instead of every 2 weeks) and greater dosing flexibility such that, if the hemoglobin level increases to more than 10 g/dL through a combination of ribavirin dose reduction and growth factor support, then epoetin alfa can be administered on an as-needed basis.

For practical purposes, epoetin alfa should not be administered unless the patient's hemoglobin level is less than 10 g/dL, but the clinician should consider ordering the growth factor if he or she has good clinical suspicion that the patient's hemoglobin level may fall below the 10 g/dL cutoff. For example, if a patient presents with a hemoglobin level of 10.8 g/dL, there is a good likelihood that the level will coast downward. In preparation, I will order the epoetin alfa but instruct the patient not to take it until the hemoglobin level drops to 10 g/dL or lower.

Ordering epoetin alfa in anticipation of anemia is a logistic strategy. Epoetin alfa must be ordered from a specialty pharmacy—at least in our patient population. Prescription of epoetin alfa also requires insurance approval. This means that a 7–10-day delay may elapse between the time an order for the agent is placed and the time a patient receives it. Therefore, it makes sense to anticipate the occurrence of anemia and the need for epoetin alfa and instruct the patient to take the epoetin alfa when and if the hemoglobin level drops below 10 g/dL.

G&H Is testing patients with chronic hepatitis C for inosine triphosphatase deficiency useful?

AB The role of inosine triphosphatase (ITPase) in relation to why ribavirin causes anemia is interesting. Some of the mechanisms are explained in an article by Hitomi and colleagues, which was published in 2011 in *Gastroenterology*. The research shows that inosine triphosphate (ITP) protects against ribavirin-induced ATP reduction by acting as a substitute for erythrocyte guanosine triphosphate (GTP) in ATP biosynthesis. Ribavirin can cause depletion of GTP. It has been observed by Hitomi and coauthors that patients with excess ITP are generally protected from development of anemia.

The accumulation of ITPase in erythrocytes, which is a function of ITP deficiency (a heritable condition), is protective against ribavirin-induced anemia. Although it is of great interest in prospectively determining in whom anemia may develop, ITPase accumulation does not impact strategies to manage anemia because, as mentioned, based on the current data, a patient would not be started on a reduced dose of ribavirin. All patients, whether or not they have ITP deficiency, are going to be monitored closely. In addition, the laboratory test for detection of ITP deficiency is not widely available, so the clinician practicing outside a tertiary academic center is not going to have easy access to diagnostic information about ITP deficiency.

From a more practical point of view, my colleagues and I begin dose reductions based on the patient's response. If an early 1.5 g drop in hemoglobin level is seen in the first 2 weeks of therapy, it is predictive of severe anemia. This drop in hemoglobin level is a much more practical sign of anemia and a signal that intervention—namely, dose reduction of ribavirin—should be initiated.

G&H How does renal dysfunction figure into the problem of anemia in regard to drug clearance? How should that be managed?

AB This is a challenge because a lot of patients have renal dysfunction that develops from a variety of reasons, whether the reason is related to hypertension, diabetes,

or the standard problems that can cause renal dysfunction. Hepatitis C–related renal dysfunction, whether it is cryoglobulinemia or membranoproliferative glomerulonephritis (MPGN), is also common. This mounts a challenge to therapy because these patients do not tolerate ribavirin and are more susceptible to anemia. Patients in this specific situation should be started on reduced-dose ribavirin according to their creatinine clearance.

In more challenging cases, such as in patients with significant cryoglobulinemia or MPGN, the best approach is to try to cure the hepatitis C, although patients with severe cryoglobulinemia should first be treated with monoclonal antibodies, such as rituximab (Rituxan, Genentech), and with plasmapheresis to try to improve their renal function so that triple therapy can be initiated.

Beyond that, telaprevir should be used with caution. Associated renal tubular acidosis has been reported in the literature and in my clinical practice as well. Renal function should be monitored throughout therapy even

in patients with normal function because a decrement in renal function can occur even in these patients while on triple therapy.

Suggested Reading

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