Management of Anemia in Patients Receiving Protease Inhibitors

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G&H How frequently does anemia occur in patients who are receiving protease inhibitor–based therapy?

SAH Anemia occurs frequently in these patients—certainly more frequently than it does in patients receiving only pegylated interferon and ribavirin. In a pooled analysis of the clinical safety data from trials of telaprevir (Incivek, Vertex), hemoglobin values less than 10 g/dL were found to occur in approximately 36% of patients receiving telaprevir-based triple therapy. More severe anemia, defined as hemoglobin values less than 8.5 g/dL, was observed in about 14% of patients. Among patients treated with pegylated interferon and ribavirin alone, only 17% had hemoglobin values less than 10 g/dL, and 5% had hemoglobin values less than 8.5 g/dL.

Similar rates of anemia were seen in trials of boceprevir (Victrelis, Merck). Pooled data from SPRINT-1 and SPRINT-2 showed that approximately 49% of patients had hemoglobin values less than 10 g/dL, and approximately 6% of patients had hemoglobin values less than 8.5 g/dL. Similar rates of anemia were observed in RESPOND-2, a trial that evaluated boceprevir-based triple therapy in interferon-experienced patients: Approximately 49% of these patients had hemoglobin values less than 10 g/dL, and approximately 10% of patients had hemoglobin values less than 8.5 g/dL. Among patients in the control group, who were treated with pegylated interferon and ribavirin alone, approximately 30% of patients showed a hemoglobin value less than 10 g/dL, and only approximately 3% of patients had a hemoglobin value less than 8.5 g/dL. Overall, there is a significantly higher rate of clinically significant anemia when therapy includes either boceprevir or telaprevir compared to treatment with pegylated interferon and ribavirin alone.

G&H Are rates of anemia similar between these 2 protease inhibitors?

SAH Yes, rates of anemia seem to be fairly similar with both telaprevir and boceprevir. While the pooled registration data suggest that telaprevir has higher rates of grade 3/4 anemia (hemoglobin levels <8.5 g/dL; 14% with telaprevir vs 6–10% with boceprevir), the boceprevir studies allowed the use of erythropoietin at the investigator’s discretion. While prospective, randomized, head-to-head trials assessing both frequency and severity of anemia are lacking, interim data from an ongoing French study (presented as an abstract at HepDART 2011) found on preliminary analysis that moderate, grade 2 anemia (hemoglobin level of 8–10 g/dL) occurred in 33% of telaprevir-treated patients and 31% of boceprevir-treated patients. Grade 3/4 anemia (hemoglobin level <8 g/dL) occurred in 13% of telaprevir-treated patients and 6% of boceprevir-treated patients. The transfusion rate was 18% for telaprevir-treated patients and 6% for boceprevir-treated patients. Overall, these findings correlate with clinicians’ anecdotal clinical experience, which shows significant anemia with both drugs.

G&H How frequently does anemia lead to either dose reduction or discontinuation of therapy?

SAH Dose reductions occur roughly twice as often when a protease inhibitor is added to the treatment regimen. According to the registration trial data, dose reductions occur in approximately 26% of patients treated with boceprevir.
Similarly, data from the telaprevir registration trials show that dose reductions occur in approximately 32% of patients. In terms of treatment discontinuation, data show that boceprevir-based therapy is discontinued in approximately 1% of patients, and telaprevir-based therapy is discontinued in 3–4% of patients. Again, both drugs show roughly similar rates of dose reductions and discontinuation.

G&H What are the clinical consequences of anemia?

SAH The presence of anemia does not negatively impact sustained virologic response (SVR) rates. However, it is well known that quality of life is certainly affected, which can lead to potential compliance or adherence issues. Recent data with the protease inhibitors suggest that clinicians can dose-reduce ribavirin fairly significantly in the setting of anemia and still achieve high SVR rates. Treatment discontinuation obviously has a more significant effect on clinical outcomes, but discontinuation is rare. Nonetheless, more data are needed to clearly show how quickly ribavirin dose reductions can occur (before virus negativity) and how long ribavirin can be stopped without affecting overall SVR rates. In the meantime, I advocate dose reduction instead of drug discontinuation for anemia, especially given that clinicians can probably get by with lower doses of ribavirin in the era of direct-acting antiviral drugs than they could when treating patients with pegylated interferon and ribavirin alone. If clinicians must discontinue ribavirin, they should do so for a short period of time (2–3 days) and then restart ribavirin at a lower dose.

In addition to necessitating dose reductions or discontinuations, anemia can significantly affect patients’ quality of life in terms of fatigue, inability to go to work and/or be productive at work, and difficulty in performing activities of daily living. As a result, compliance with therapy can become an issue. Thus, the effects of anemia extend beyond the possible impact on SVR rates to include compliance and quality-of-life issues as well.

G&H Have any studies compared SVR rates in patients with and without anemia?

SAH Yes. There are 2 large studies in genotype 1 hepatitis C virus (HCV)-infected patients treated with pegylated interferon and ribavirin (IDEAL, n=3,070; CHARIOT, n=871) showing that patients who developed anemia (hemoglobin level <10 g/dL) were significantly more likely to obtain SVR than those without anemia. Post–hoc, retrospective studies with telaprevir and boceprevir have also been conducted, but to date, these results remain in abstract form. Data from the REALIZE trial and combined data from ADVANCE and ILLUMINATE (with telaprevir) demonstrate that anemia is not a significant predictor of SVR. However, a retrospective review of the SPRINT-2 and RESPOND-2 trials (with boceprevir) did find a positive association with anemia and SVR.

G&H Are there any factors that predict the likelihood of anemia in patients receiving protease inhibitor–based therapy?

SAH Patients who had significant anemia during prior treatment with pegylated interferon and ribavirin and are re-treated with boceprevir- or telaprevir-based triple therapy are likely to develop anemia again, and anemia may be more severe given the addition of the protease inhibitor. Retrospective data from the telaprevir registration trials show on multivariate analysis that older age, lower body mass index, lower baseline hemoglobin level, more advanced fibrosis, and genotype 1b HCV are all significantly associated with anemia. Retrospective data from the boceprevir registration trials show on multivariate analysis that baseline hemoglobin level, gender, age greater than 40 years, statin use, and race were associated with anemia.

G&H Can clinicians address some of these factors before starting treatment?

SAH Clinicians need to do due diligence and look at the patient’s past treatment. Was there significant anemia? Are patients starting out with lower hemoglobin levels? Are they cirrhotic? Are they older? Do they have any renal impairment issues? If any of these factors are identified ahead of time, then clinicians should be quicker to dose-reduce or add an agent like erythropoietin if hemoglobin levels begin to drop.

G&H How effective is erythropoietin for the management of anemia in patients who are receiving a protease inhibitor plus pegylated interferon and ribavirin?

SAH We lack good, clear-cut data regarding the effect of erythropoietin on SVR rates in patients treated with direct-acting antiviral drugs. Erythropoietin was not allowed in the telaprevir registration trials. In the boceprevir registration trials, erythropoietin was allowed at the discretion of the investigator, but these studies were not designed to evaluate the effect of erythropoietin on SVR rates. The results of a recently completed prospective trial assessing the benefits of concomitant erythropoietin use for anemia in boceprevir-based therapy are anxiously awaited.

Prior to the advent of direct-acting antiviral drugs, a prospective, randomized, placebo-controlled trial showed that the use of erythropoietin for anemia related to treatment with pegylated interferon and ribavirin resulted in maintenance of the ribavirin dose, stabilization of the hemoglobin decline, and improvement in quality of life compared to ribavirin dose reduction alone.
When do you consider adding erythropoietin to a patient's treatment regimen?

SAH This decision should be made at the discretion of the individual clinician, as there are no guidelines regarding the use of erythropoietin. If a patient experiences anemia, I personally prefer to try ribavirin dose reduction of 400–600 mg as a first-line measure, depending on the initial severity of the anemia. Then, if the hemoglobin level has not stabilized, I will add erythropoietin before further dose-reducing ribavirin or withholding ribavirin. While adding erythropoietin is not my first-line treatment for anemia, it is an option if a patient's hemoglobin level is not stabilizing. Consideration can also be given to pegylated interferon dose reduction, as this may also help anemia. Data from the previously mentioned IDEAL trial show that with conventional pegylated interferon and ribavirin therapy, dose reductions from 1.5 mcg/kg/week to 1.0 mcg/kg/week did not adversely affect SVR.

In which patients is erythropoietin contraindicated?

SAH The black box warning for erythropoietin states that this drug should not be used in patients with hemoglobin values greater than 12 g/dL. Thus, clinicians should not start erythropoietin until the patient's hemoglobin level falls below 12 g/dL, and erythropoietin should be discontinued once the hemoglobin level rises back above 12 g/dL. Caution should be used when treating patients with end-stage renal disease as well. Clinicians should also be aware of the relatively rare, but significant, complication of pure red cell aplasia that has been reported with the use of recombinant erythropoietin.

What further research do you hope to see in this area over the next couple of years?

SAH Telaprevir and boceprevir, both of which are now approved by the US Food and Drug Administration, are the first direct-acting antiviral agents to come onto the market. Unfortunately, these drugs are associated with significant anemia; in general, patients who are receiving either of these drugs experience an additional hemoglobin decline of approximately 1 g/dL beyond the hemoglobin decline caused by pegylated interferon and ribavirin alone. The good news is that the second-generation direct-acting antiviral agents currently in development will probably cause less anemia than the 2 drugs that are currently available.

In addition to new drugs, we need further research regarding treatment of anemia in patients receiving telaprevir or boceprevir, including studies assessing how quickly we can dose-reduce ribavirin and by how much. The use of erythropoietin for anemia and its effect on SVR should be assessed. Finally, data suggest that polymorphisms in the inosine triphosphate pyrophosphatase (ITPA) gene may help to predict ribavirin-associated anemia during antiviral treatment, and further research is needed regarding the utility of this test. Should we be testing for this gene mutation in the same way that we now test for interleukin-28B (IL-28B) mutations prior to initiating antiviral therapy? More data are needed to determine whether this information would positively impact outcomes.

How might such information help clinicians prevent treatment-induced anemia?

SAH If I had information suggesting that a patient was at increased risk for anemia, then I would probably check for anemia more frequently at the start of therapy. My preferred strategy—especially in patients who I feel are at risk for developing anemia—is to obtain complete blood counts at Week 1 and Week 2. If these tests show that the patient is doing well, then I may wait until Week 4 before performing follow-up testing. However, if testing at Week 1 and Week 2 shows that the patient’s hemoglobin level has dropped significantly, then I would adjust the ribavirin dose and obtain another complete blood count at Week 3. The key for treating anemia in the setting of HCV therapy is to address anemia very quickly, because it is much harder to bring hemoglobin levels back up after they have declined than it is to mitigate the rate of decline.

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