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Conflicts of interest
The authors disclose no conflicts.

Does Eltrombopag Really ENABLE SVR?

> See "Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infection and cirrhosis, allowing for effective antiviral therapy," by Afdhal NH, Dusheiko GM, Giannini EG, et al, on page 442.

Patients with hepatitis C (HCV) cirrhosis and thrombocytopenia represent a particularly high-risk group for future liver decompensation, death, and hepatocellular carcinoma.[1] These patients are among those who most desperately require therapy and cannot afford to wait for new treatment developments. However, these are also the patients for whom current therapies pose the highest risk of complications.[2] Bone marrow suppression is a well-known complication of interferon treatment, with falling blood counts during therapy often leading to dose reductions, dose interruptions, and early cessation of treatment, all of which may lower the likelihood of attaining a sustained virologic response (SVR).[3] Cirrhotic patients with significant thrombocytopenia are largely excluded from clinical trials of promising new therapies and therefore must rely on existing interferon-based regimens. Strategies to enhance rates of treatment initiation and completion have the potential to maximize SVR in this difficult-to-treat population.

Eltrombopag is a new oral platelet growth factor that acts as a thrombopoietin (TPO) receptor agonist, resulting in differentiation and proliferation of megakaryocytes. It acts in an additive fashion with endogenous TPO by binding and activating the TPO receptor through an alternate binding site.[4] Eltrombopag has been studied in patients with immune thrombocytopenia purpura, cirrhosis (from any cause), and in those undergoing interferon-based therapy for HCV. To clarify whether eltrombopag would enhance rates of SVR in patients with HCV and thrombocytopenia, the ENABLE 1 and ENABLE 2 trials (Eltrombopag to initiate and maintain interferon antiviral treatment to benefit subjects with HCV-related liver disease) were carried out in North America and Europe, the results of which are published together in this edition of *Gastroenterology*.[5]

Before the ENABLE study, McHutchison et al[6] evaluated the use of eltrombopag in 74 patients with HCV-related cirrhosis and platelet counts between 20,000 and 70,000/μL. Patients were randomized to increasing doses of eltrombopag (30, 50, and 75 mg) for 4 weeks before initiation of interferon and then for 12 weeks during interferon-based therapy. Between 75% and 95% of treated patients achieved the primary endpoint of an increase in platelet count to 100,000/μL during the initiation phase. Higher rates were seen in those treated with higher doses of eltrombopag. Between 36% and 65% of patients treated with eltrombopag maintained a platelet count >50,000/μL and were able to complete 12 weeks of interferon therapy compared with only 6% in the placebo group. Interestingly, no thromboembolic events were seen in this small study.

The ENABLE 1 and ENABLE 2 studies were thus undertaken to assess the effect of eltrombopag on rates of SVR in patients with HCV cirrhosis undergoing interferon-based antiviral therapy. The studies differed only in the pegylated interferon used and the corresponding platelet threshold set for initiation of treatment. Both trials recruited patients with chronic HCV with platelet counts <75,000/μL. Before starting antiviral therapy, all patients received open-label eltrombopag during the study initiation phase. Eltrombopag was initiated at a dose of 25 mg/d and increased gradually to a maximum of 100 mg/d until platelet levels crossed the recommended thresholds for initiating interferon-based therapy according to the peginterferon product label. Only patients who responded to eltrombopag were eligible for randomization in a 2:1 ratio to eltrombopag maintenance treatment during antiviral therapy or placebo (ie, antiviral therapy alone). The primary endpoint of the study was the effect of eltrombopag on the

attainment of SVR. Adverse events were recorded as safety endpoints.

The patient population consisted mainly of middle-aged Caucasian men with genotype 1 infection and Child–Pugh A cirrhosis. The median platelet count at trial enrollment was 59,000/μL. Patient characteristics, including interleukin (IL)-28B status, were similar in all groups. During the initiation phase, 96%–97% of patients achieved the required platelet levels to proceed with therapy, with 86% doing so on 25 or 50 mg of eltrombopag. Adverse events were minor and included headache, nausea, and diarrhea. During the antiviral phase of the trial, a significantly higher proportion of eltrombopag-treated patients attained SVR (ENABLE 1, 23% vs 14% [$P = .0064$]; ENABLE 2, 19% vs 13% [$P = .02$]) and the treatment effect remained consistent across HCV genotypes. Patients treated with eltrombopag required fewer peginterferon dose reductions and were maintained on full-dose peginterferon for a longer amount of time. Notably, however, portal vein thrombosis (PVT) occurred more frequently in the eltrombopag-treated patients (n = 12 for eltrombopag vs n = 2 for placebo). Rates of thromboembolic complications did not correlate with platelet count or eltrombopag dose. Hepatic decompensation, specifically ascites and hepatic encephalopathy, were also more frequently seen in the eltrombopag-treated group (10% eltrombopag vs 5% placebo).

The ENABLE study was an ambitious effort to improve SVR rates in a very difficult-to-cure population. Although the study nicely confirmed that eltrombopag has potent platelet stimulatory effects, it is difficult to determine whether the improved rates of SVR seen in the trial will translate to better outcomes in general clinical practice. Study investigators were required to lower peginterferon doses according to the product labels rather than clinical judgment. Most seasoned clinicians do not strictly adhere to the thresholds in the label because clinical experience has shown that maximizing medication exposure is important and clinically significant bleeding events with moderate degrees of thrombocytopenia are very rare.[7,8] The differences in SVR were owing to greater peginterferon exposure in the eltrombopag arms. Had investigators had the freedom to adjust the peginterferon dose, it is likely that patients in the placebo arm would have received more cumulative peginterferon, which may have improved their rates of SVR. The trial design clearly favored the eltrombopag arms. The authors acknowledge this limitation in the discussion; however, it is difficult to overstate the importance of this issue in interpreting the effect of eltrombopag on treatment outcome and the overall significance of the study.

Predicting the risk of bleeding in patients with cirrhosis is complex because end-stage liver disease reduces both procoagulant and anticoagulant factors. In cirrhosis, the cause of thrombocytopenia is multifactorial. In addition to splenic sequestration resulting from portal hypertension, coating of platelets by circulating immunoglobulins may lead to increased platelet destruction by the reticuloendothelial system.[9] Platelet production may also be impaired owing to reduced levels of endogenous TPO[4]

and HCV-related bone marrow suppression.[5] However, despite the low platelet counts seen, which can fall significantly further during interferon treatment, data suggest that clinically significant bleeding is uncommon in patients with liver disease–related thrombocytopenia. This may be partially explained by effects on platelet function. In patients with cirrhosis, platelet function may be enhanced due to a decrease in production of ADAMTS13, a plasma metalloprotease that normally limits the effect of von Willebrand factor on platelets.[10] Furthermore, high levels of von Willebrand factor, a common finding in patients with cirrhosis, enhance platelet adhesion to the subendothelium at sites of vascular injury.[9] Other studies in patients with cirrhosis, have found that platelet counts as low as 60,000/μL are able to generate thrombin levels in the normal range.[10] All of these factors enhance platelet function and may limit bleeding, even with low absolute platelet counts. Roomer et al[8] recorded bleeding events in a cohort of HCV patients with and without cirrhosis treated with peginterferon and ribavirin. Although epistaxis and gingival bleeding were relatively common in patients with platelet counts of <50,000/μL, only 1 major bleeding event was recorded, which occurred at a platelet level of 65,000/μL.[8] Hence, a clinically relevant platelet threshold for interferon dose reduction or cessation is not known and accurately predicting the bleeding risk of an individual patient in the office is currently very difficult. However, it is fair to say that the peginterferon product labels are relatively conservative and most clinicians would be comfortable maintaining full-dose peginterferon at platelet counts well below those recommended for dose reduction.

Even if we may be comfortable with lower platelet counts than in the product labels, there is no doubt that clinicians would sleep easier if they did not have to worry about thrombocytopenia during interferon-based therapy—but at what cost? The major concern with eltrombopag in patients with cirrhosis is the potential for an increased risk of thromboembolic complications. This was borne out in the ENABLE study with a higher number of thromboembolic events in the eltrombopag-treated group compared with those who received placebo. This phenomenon has been observed in previous studies[11,12] and is biologically plausible. Interestingly, a high absolute platelet count or high dose of eltrombopag was not correlated with thromboembolic events, making it difficult to predict who is at highest risk. A post hoc analysis of a previous study[11] identified a platelet counts of >200,000/μL as a risk factor for thrombotic events. The most common thromboembolic event in the ENABLE study was PVT, which is a well-known complication of advanced cirrhosis. The prevalence of PVT in a large, retrospective, Italian study of 701 patients with cirrhosis was 11%[13] and PVT occurs more frequently in those with more advanced disease.[14] The effect of PVT on the natural history of cirrhosis is not entirely clear, with studies coming to varying conclusions. A large, retrospective study of 3295 patients awaiting liver transplantation found that the presence of PVT was an independent factor associated with death,[15] whereas a prospective study of 290 patients

awaiting liver transplantation did not show a significant effect of PVT on mortality.[16] The effect of PVT post liver transplantation is more evident. In a recent, large, systematic review by Rodriguez-Castro et al,[17] the presence of an occlusive PVT was associated with an increased 30-day and 1-year mortality post liver transplantation. This finding may be particularly relevant in the ENABLE cohort of patients, whose advanced liver disease and poor response to treatment may necessitate a future liver transplant.

Beyond PVT, there was a higher rate of hepatic decompensation among eltrombopag-treated patients. The reasons for this are not entirely clear, because it was not directly correlated with PVT or other obvious thrombotic events. Interferon-based therapy is associated with a risk of decompensation; therefore, it is conceivable that the greater cumulative exposure to interferon pushed some patients to develop hepatic complications. This study confirmed what we already knew; interferon is relatively ineffective and potentially very dangerous in patients with advanced cirrhosis.[2] We were reminded of this with the introduction of first-generation protease inhibitors, for which thrombocytopenia and low albumin have been recognized as predictors of serious complications, presumably because of greater exposure to interferon in patients who might otherwise have stopped therapy earlier owing to virologic failure.[18] Another intriguing possibility is that decompensation itself may be a thrombotic complication. Recently, Villa et al[19] showed that low-dose enoxaparin treatment in patients with cirrhosis reduced not only PVT but also lowered the rate of hepatic decompensation and improved survival. It has been proposed that the benefits of enoxaparin may relate to prevention of microthrombi in the intrahepatic circulation. Fortunately, the rates of decompensation with eltrombopag were low, but it is conceivable that increased platelet counts may promote microthrombosis, which may be clinically relevant in a very cirrhotic liver.

Eltrombopag has also been evaluated for other treatment indications in cirrhosis. The ELEVATE study (Eltrombopag Evaluated for Its Ability to Overcome Thrombocytopenia and Enable Procedures) assessed the short-term use of eltrombopag in patients with cirrhosis and thrombocytopenia (platelet count <50,000/mm^3) who required an invasive procedure.[11] The primary endpoint was avoidance of platelet transfusion, and a key secondary endpoint was the occurrence of bleeding. The study demonstrated that patients treated with eltrombopag were significantly less likely to require a platelet transfusion compared with patients receiving placebo (72% vs 19%), but the rate of bleeding was not different between the 2 groups. Thromboembolic events, predominantly PVT, were more common in the treated group (odds ratio, 3.04). The ELEVATE study again confirms the potent physiologic effect of eltrombopag on platelet production but it also demonstrates that the risk of thromboembolic events is present even after short-term use. Although no clear dose or platelet level was associated with thrombosis, if one elects to use eltrombopag, it would seem prudent to use the lowest dose possible to maintain a safe platelet level.

Eltrombopag is a potentially useful tool for treating clinically relevant thrombocytopenia in patients with advanced liver disease. The ENABLE study provides further evidence that eltrombopag is effective at increasing the number of eligible patients for interferon-based therapy, as well as decreasing the number of interferon dose reductions and interruptions. However, owing to the likely difference between the very conservative study protocol and routine clinical practice for platelet count–based initiation and continuation of interferon therapy, the true effect of eltrombopag on SVR rates is uncertain. The widespread use of eltrombopag should further be tempered by the increased rates of thromboembolic events associated with its use. At present, no tools are available to accurately predict the risk of bleeding or thrombosis in an individual cirrhotic patient with thrombocytopenia or to identify in whom the benefit of eltrombopag would likely outweigh the risk. It is important to note that even with eltrombopag, the absolute rates of SVR were very low (19%–23%) and the rates of serious adverse events were high (20%) in this difficult-to-cure population. It would seem, therefore, that eltrombopag should be reserved for a carefully selected subset of patients with severe thrombocytopenia who cannot wait for new therapies and are under the care of clinicians with experience treating patients with advanced cirrhosis. If one opts to use eltrombopag, the minimum effective dose should be used. In this case, rather than a randomized, controlled trial, real-world data will *ENABLE* us to understand the true effect of eltrombopag on SVR, but hopefully by the time such data emerge, interferon and the need for support with eltrombopag will be a thing of the past.

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