ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Current Treatment of Thrombocytopenia in Chronic Liver Disease

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G&H How common is thrombocytopenia in the setting of chronic liver disease?

SS Thrombocytopenia is the most common hematologic complication in patients with chronic liver disease. The prevalence of this complication is directly proportional to the severity of the liver disease. Thus, the sicker a patient's liver is, the higher the likelihood of the patient having thrombocytopenia. Overall, it is believed that 15% to 30% of patients with chronic liver disease have some degree of thrombocytopenia.

G&H What platelet count is typically used to define thrombocytopenia?

SS Thrombocytopenia is defined by a platelet count below 150,000/μL. The spectrum of thrombocytopenia ranges from mild to severe. Severe thrombocytopenia, which is defined by a platelet count of less than 50,000/μL, is associated with an increased risk of bleeding from invasive procedures.

G&H Under which circumstances should prophylactic measures be used in patients with thrombocytopenia and chronic liver disease who are undergoing an invasive procedure?

SS Any time a potential invasive procedure is being considered, whether it is a biopsy, banding, or an aspiration, prophylactic measures are required if the patient has chronic liver disease and has a platelet count below 50,000/μL. For patients with chronic liver disease, the most common invasive procedures are upper endoscopy and band ligation of esophageal varices.

G&H What are the roles of avatrombopag and lusutrombopag in this setting?

SS Avatrombopag (Doptelet, Dova Pharmaceuticals) and lusutrombopag (Mulpleta, Shionogi) were approved by the US Food and Drug Administration (FDA) in May and July 2018, respectively, for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. These agents belong to the thrombopoietin receptor agonist class and have very similar mechanisms of action. Avatrombopag and lusutrombopag activate thrombopoietin receptors

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located on megakaryocytes, which are located in the bone marrow, resulting in the production of more platelets. There are a number of reasons that patients with chronic liver disease develop thrombocytopenia. One is because of splenic sequestration of platelets. Another is decreased production of thrombopoietin. Thus, platelet counts can increase by administering a thrombopoietin agonist to stimulate megakaryocytes.

G&H What were the key clinical trial findings regarding the use of avatrombopag or lusutrombopag in patients with chronic liver disease and thrombocytopenia?

SS Patients in the key clinical trials were randomized to either placebo or the study drug to determine what proportion of patients could avoid a platelet transfusion before an invasive procedure. Both avatrombopag and lusutrombopag met the endpoint of patients needing significantly less platelet transfusion vs placebo. The authors examined the need for platelet transfusion because it would be unethical to withhold this intervention and compare the risk of bleeding.

G&H How do the dosing schedules of avatrombopag and lusutrombopag affect the current procedure planning processes in clinical practice?

SS The use of platelet transfusion is limited by availability, logistics of administration, a short half-life, and potential adverse effects. On the other hand, thrombopoietin receptor agonists are effective in increasing platelet counts, have no drug-drug interactions, and are well tolerated. Both avatrombopag and lusutrombopag have to be administered days before an invasive procedure (10-13 days and 8-14 days, respectively), and, thus, there is a window of time in which the procedure should be performed. This represents a paradigm shift, as doctors have historically relied on platelet transfusions given on the day of the procedure for prophylaxis. Therefore, the use of these oral medications requires coordination regarding the timing of the procedure.

G&H How important is the duration of time that platelets remain over 50,000/µL after treatment, particularly when clinicians perform invasive procedures?

SS When patients with chronic liver disease have a platelet count less than 50,000/µL and undergo an invasive procedure, they have an increased risk of immediate bleeding as well as delayed bleeding (ie, several days after the procedure). Therefore, when the platelet count is raised above 50,000/µL, it is important for that elevation to persist for at least several days to provide protection from the risk of delayed bleeding.

G&H When avatrombopag and lusutrombopag are used, how long do the effects usually last?

SS Procedures should be completed 5 to 8 days after the completion of avatrombopag treatment, and 2 to 8 days after the last dose of lusutrombopag. Platelet values increase because of these thrombopoietin receptor agonists but return to baseline levels 30 days after the first dose.

> … there should be no hesitation to use avatrombopag or lusutrombopag.

G&H How important is it to consider the risk of drug-drug interactions and food effect in patients with chronic liver disease?

SS Patients with chronic liver disease are generally on multiple medications with the potential for drug-drug interactions as well as food-drug interactions. Fortunately, there are no drug-drug interactions with avatrombopag or lusutrombopag, and these 2 agents are very well tolerated. According to package inserts, avatrombopag needs to be taken with food, whereas lusutrombopag can be taken with or without food.

G&H Are these agents associated with any significant side effects?

SS In addition to having no significant drug-drug interactions, avatrombopag and lusutrombopag also have no signature adverse events. The side-effect profiles of both of these agents are no different from placebo. This may be a virtue of the short duration that these agents are taken (5-7 days).

G&H Are there any contraindications?

SS Avatrombopag and lusutrombopag do not have contraindications stated in their FDA-approved labels.

However, these agents should be used with caution in patients who are already known to have a hypercoagulable state. This is because taking these agents may lead to an increase in hypercoagulation and runs the risk of forming clots in the body.

G&H Is a patient evaluation always required before these agents can be used?

SS Not necessarily. However, as mentioned above, it is important to be cautious when using thrombopoietin receptor agonists in patients with a known hypercoagulable state. Safety and efficacy are also not well understood in patients with known portal vein thrombosis. Because there are no drug-drug interactions or signature adverse events, an extensive evaluation is not required.

G&H Do you have any advice for doctors using avatrombopag and lusutrombopag?

SS These agents are very effective, safe, and tolerable. They have been shown to significantly increase platelet counts, which reduces the need for platelet transfusion. Therefore, there should be no hesitation to use avatrombopag or lusutrombopag. Now that these agents are available in clinical practice, doctors should not take any chances with the risk of bleeding in patients with chronic liver disease who are undergoing an invasive procedure and have a low platelet count, and should readily use avatrombopag and lusutrombopag.

In addition, it is important for all providers to be aware that there is an increased risk of bleeding in patients with chronic liver disease who undergo an invasive procedure and have a platelet count below 50,000/μL. Some providers were trained before platelet thresholds were appreciated.

G&H What are the next steps in research in this area?

SS A next step is to see if chronic use of a medication can raise platelet counts, not to normal levels, but perhaps to above 50,000/μL, which would allow patients to undergo repeat invasive procedures over a period of time, if needed, instead of treating the patients episodically. My colleagues and I have published an article looking at repeated use of thrombopoietin receptor agonists, and found that there was no associated loss of efficacy or emergence of signature adverse events. More research is needed on repeat doses or chronic low doses in patients with chronic liver disease.

Dr Saab has been on the speakers bureau and has been an advisor for both Dova Pharmaceuticals and Shionogi.

Suggested Reading

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