Brief Report

Efficacy of repeat doses of avatrombopag: a case series

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Abstract: Thrombocytopenia is a common hematologic complication in patients with chronic liver disease. Thrombocytopenia places these patients at risk who undergo invasive procedures. Patients with cirrhosis often require repeat procedures. Patients with chronic liver disease and platelet counts below 50,000/μL who underwent repeat doses of avatrombopag (AVA) prior to multiple invasive procedures. Changes in platelet count were measured with each course of AVA. The need for platelet transfusion and adverse events from AVA were noted. Four patients underwent repeat AVA dosing. The mean [± standard deviation (SD)] age of the patients who underwent repeat dosing was 65 (±29) years. The mean (± SD) platelet count prior to the procedure was 38,250 (±5,679)/μL, and the mean increase of platelets was 52,000 (±33,000)/μL. Similarly, the mean (± SD) increase after the repeat administration was 51,000 (±31,000)/μL. No patient required platelet transfusion or rescue therapy. No adverse effects were reported. Repeat use of AVA continues to be an effective tool to minimize the use of platelet transfusions in patients undergoing invasive procedures who have chronic liver disease. Repeat dosing does not appear to reduce AVA efficacy.

Keywords: Thrombocytopenia; cirrhosis; avatrombopag (AVA)

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Introduction

Thrombocytopenia is an important common hematologic complication of cirrhosis with approximately three-quarters of patients having some degree of thrombocytopenia; its values inversely relate to the severity of liver disease (1-3). Not only is the platelet count employed for laboratory estimates of fibrosis, low platelet count is associated with risks of bleeding (4-6). The degree of thrombocytopenia is stratified to mild, moderate and severe if the platelet count is: >75,000–<150,000/μL; 50,000–75,000/μL, and <50,000/μL, respectively (7).

Medical societies recommend a threshold platelet value of least 50,000 μL before most invasive procedures (1,8-11). Until recently, the only reliable treatment for increasing platelet count was a platelet transfusion. However, the use of transfusions is limited by administration logistics, short half-life, and potential adverse reactions (10,12-15). Two thrombopoietin (TPO) receptor agonists, avatrombopag (AVA) and lusutrombopag, are currently approved for adult patients with chronic liver disease who are scheduled to undergo a procedure (6,16-18). Typically, these TPO receptor agonists increase the platelet count and significantly reduce the need for platelet transfusion.

Patients with cirrhosis often require repeat invasive procedures (19,20). However, we are not aware of studies assessing efficacy of AVA with repeated use. The aim of this study is to describe the efficacy of TPO receptor agonists in increasing platelet count with recurrent uses.

Methods

We identified all patients who underwent repeat AVA dosing at the University of California Los Angeles Pfleger Liver Institute, Los Angeles, California (*Table 1*). Patients were prescribed AVA according to recommended dosing (17). Procedures were performed between 9 and 13 days after starting AVA, and the dose of AVA was dependent on baseline platelet count. Repeat dosing was performed no sooner than 30 days from completing the

Table 1 Demographic and indications for AVA

Patient	Age (years)	Gender	Cause of cirrhosis	Platelet (first) baseline/post AVA	Indication for AVA	Platelet (repeat) baseline/post AVA	Indication for AVA
R	71	Male	Autoimmune cholangiopathy	42,000/131,000	EGD with banding	N/A/105,000	EGD with banding
H	59	Male	Alcohol	44,000/68,000	EGD with banding	47,000/67,000	EGD/dental extractions
C	69	Female	HCV	32,000/75,000	EGD with banding	36,000/80,000	EGD with banding
D	60	Female	NASH	35,000/87,000	EGD with banding	35,000/111,000	Radiofrequency ablation

AVA, avatrombopag; EGD, esophagogastroduodenoscopy; N/A, not available; HCV, hepatitis C; NASH, nonalcoholic steatohepatitis.

initial AVA dose. Three of the four patients had baseline platelet drawn before the repeat dosing. His repeat baseline platelet count was assumed to be the same as his original for analysis (Patient R).

Results

Patient 1

Mr. R is a 71-year-old gentleman with well compensated cirrhosis from autoimmune cholangiopathy. He was found to have non-bleeding esophageal varices on screening esophagogastroduodenoscopy (EGD). Banding was deferred because his platelet count was below 50,000/μL. Mr. R underwent a repeat EGD with banding after being treated with a course of AVA. AVA 40 mg was administered by mouth daily for 5 days and an EGD was performed 10 days after starting AVA. His platelet count increased from 42,000/μL at baseline to 131,000/μL the day of EGD. He received a second course of AVA for a repeat EGD with banding 2 months later. He received 40 mg of AVA for 5 days. His platelet count increased to 105,000/μL at the time of his second procedure. Mr. R had no adverse effects from AVA, and did not require platelet transfusions or rescue therapy after the endoscopies.

Patient 2

Mr. H is a 59-year-old gentleman with cirrhosis from alcohol consumption. He required hospitalization and treatment for esophageal variceal bleeding. Follow up outpatient EGD was recommended. Several weeks after discharge, he was treated with a course of AVA 40 mg by mouth daily for 5 days prior to his repeat EGD because of severe thrombocytopenia. His platelet count increased from 44,000/μL before AVA to 68,000/μL the day of EGD. A month later he required dental extraction and a repeat EGD. He received a second course of AVA for another EGD and dental extraction procedures. His platelet count increased from 47,000/μL before his second dose of AVA to 67,000/μL. He underwent Argon plasma coagulation on the second outpatient EGD for gastric antral vascular ectasia. He had no adverse effects from AVA and did not require platelet transfusions or rescue therapy after the endoscopies and dental extraction.

Patient 3

Mrs. C is a 69-year-old-woman with decompensated liver cirrhosis from hepatitis C (HCV). She was found to have large non-bleeding esophageal varices on follow-up EGD for previous esophageal varices bleeding in 2017. She received a course of AVA 60 mg by mouth daily for 5 days for an EGD procedure. Her EGD was performed 10 days after starting AVA. Her platelet count increased from 32,000/μL before AVA to 75,000/μL the day of EGD. She underwent banding ligation. She then received a second course of AVA for another EGD (When/what was the time frame?). Her platelet count increased from 36,000/μL to 80,000/μL the day of EGD. She also required band ligation on the follow up EGD. She had no adverse effects on AVA and did not require platelet transfusions or rescue therapy after the endoscopies.

Patient 4

Mrs. D is a 60-year-old-woman with well-compensated liver cirrhosis from cryptogenic cirrhosis. She received a course of AVA 60 mg by mouth daily for 5 days prior to a screening EGD. Her platelet count increased from 35,000/μL before AVA to 87,000/μL 4 days prior to EGD. Banding was not required. A diagnosis of a 2.6 cm hepatocellular carcinoma (HCC) was subsequently made during surveillance. She

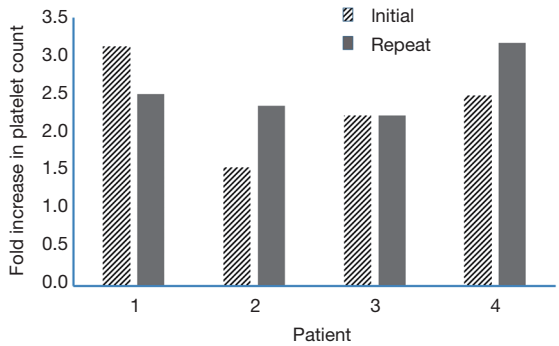

Figure 1 Fold change in platelet after initial and repeat avatrombopag administration.

received second course of AVA prior to radiofrequency ablation of HCC (when/what was the time frame?). Her platelet count increased from 35,000/μL to 111,000/μL the day of ablation. She had no adverse effects on AVA. She did not require platelet transfusion or rescue therapy on either procedure.

Discussion

The mechanism of action of TPO receptor agonists is to stimulate megakaryocytes in the bone marrow, which will lead to the production of platelets. AVA does not have homology to native TPO and although AVA increases platelet count, it is not believed to cause platelet activation (21). There are now several TPO receptor agonists available but only 2 are specifically approved by the FDA for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure (6,16-18).

The greater the severity of liver disease, the more likely the degree of thrombocytopenia and likelihood of repeated invasive procedures. AVA has been shown to be effective—irrespective of disease severity and etiology (22). The results of our case series demonstrate not only the continual safety and tolerability of AVA with repeated use, but its continual efficacy. We found no evidence of tachyphylaxis with the second administration of AVA. The mean increase in platelet count was 2.3 folds after the first administration, and 2.6 folds after the second administration (*Figure 1*).

A limitation of our study is the few patients followed. However, our proof of concept is consistent with observations from other commonly used growth factors such as filgrastim and erythropoietin where no loss of efficacy is demonstrated after repeated uses (23,24). What is unclear is the optimal timing of repeated dosing of AVA. The results of a pharmacokinetic modeling study suggested that AVA can be redosed as early as 12 days after completion of the first dosing regimen without excessively increasing platelet counts (25). We chose to dose after 35 days when the platelet count returned to baseline to avoid excessive platelet elevation that may increase the risk of thrombosis.

Repeat use of AVA continues to be an effective tool to minimize the use of platelet transfusions in adult patients scheduled to undergo a procedure who have chronic liver disease. The effect of repeat dosing dose does not appear to reduce its efficacy. Patients with cirrhosis and thrombocytopenia can be treated with repeated dosing of AVA.

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Footnote

Conflicts of Interest: Author S Saab has received a speaker honorarium from Dova, Inc., and also a consultant for Dova, Inc. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Informed consent was not obtained because of the retrospective nature of the study.

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