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Do we have to worry for thrombocytopenia during treatment of hepatitis C

Afdhal NH, Dusheiko GM, Giannini EG, et al. Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infection and cirrhosis, allowing for effective antiviral therapy. Gastroenterology 2014; 146: 442-52.

Thrombocytopenia is defined as platelet count being <150.000 cells/μL. A platelet count of 50.000 to 75.000/μL means moderate thrombocytopenia and a platelet count below 50.000 indicates severe thrombocytopenia. It is common among individuals with HCV-associated chronic hepatic conditions and a significant problem, which requires dose reduction in or discontinuation of antiviral treatment and reduces sustained viral response to therapy. The prevalence of thrombocytopenia was reported as 0.16% to 45.4% (24% in average) in chronic hepatitis C (HCV) (1). In chronic HCV, thrombocytopenia may develop due to bone marrow inhibition, platelet sequestration in splenomegaly, reduced hepatic thrombopoietin production, as well as autoimmune causes. In addition, antiviral (AV) therapy (particularly pegylated interferon (PEG) + ribavirin (RBV)) induces bone marrow suppression, further reducing platelet counts (2). To initiate AV therapy, platelet count should be above the minimal threshold count (PEG-2a; >90.000, PEG-2b; >100.000), and, where platelet count is ≤50.000, a reduction in the dose will be necessary (3). In HCV and secondary cirrhosis, platelet infusion, splenic artery embolisation, splenectomy and TIPS have been used in the treatment of thrombocytopenia. Apart from these, thrombopoietin receptor agonists (Eltrombopag, AKR-501, MG 531, NIP-004, Peg-TPOmp, agonist antibodies) and some cytokines (Recombinant thrombopoietin, rhTPO and PEG-rHuMGDF, IL-1, IL-3, IL-6, GM-CSF, IL-11, Promegapoietin) can also stimulate thrombopoiesis. In a phase II study published in 2007, 30-75mg of eltrombopag given as a single daily dose for the commencement of PEG-based therapies was shown to increase platelet counts in 71-91% of the patients with HCV-associated hepatic cirrhosis plus thrombocytopenia (4). Eltrombopag (Promacta; GlaxoSmithKline, Research Triangle Park, NC) is a FDA-approved non-peptide thrombopoietin receptor agonist which corrects thrombocytopenia and thereby facilitates initiation and maintenance of INF-based treatments in HCV.

In this study published in the February 2014 issue of the Gastroenterology journal, Afdhal et al. (5) have reported that eltrombopag elevated platelet counts and thus contributed to the efficacy of antiviral therapy in patients with HCV and HCV-associated cirrhosis. Patients with HCV and thrombocytopenia (<75,000/μL) from 23 countries and 150 centres joined this study by receiving ≤9 weeks of treatment with eltrombopag (25-100mg/day) as per ENABLE-1 (Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C-Related Liver Disease) (n ¼ 715, PEG-2a) and ENABLE-2 (n ¼ 805, PEG-2b) protocols. Patients who attained 95% and 94% of the threshold platelet count in ENABLE-1 and ENABLE-2, respectively, were randomized in a double-blind fashion and with a ratio of 2:1 to receive AV treatment (24 or 48 weeks based on genotype) plus eltrombopag or to placebo. In the eltrombopag group, the dose of the medication was reduced if platelet was >200.000/μL, and reduced or withdrawn if ≥400.000/μL. The primary endpoint of the study was sustained viral response after 24 weeks of AV treatment cessation, while the secondary endpoints were platelet count, dose reduction/discontinuation of AV treatment, rapid virological response (RVR), early virological response (EVR), complete early viral response (EVR) and end-of-therapy response (ETR). The groups were compared within individual studies and between the studies. The mean platelet count was 59.000/μl in both ENABLE trials. The subjects were of the genotype 1 (62-65%) and had compensated liver disease (Child-Pugh: 5-6). During the initial phase, 97% and 96% of the subjects in ENABLE-1 and 2, respectively, reached the sufficient threshold by week 2 in average (86% on eltrombopag 25-50mg/day).

Adverse effects (AEs) with eltrombopag use were investigated separately: the most common side effects were

headache (7/4% in ENABLE-1/2), nausea and diarrhoea (3% in ENABLE-1/2); no thromboembolic event was noted and decompensation occurred in less than 1% of the patients in this study. In ENABLE-2, two subjects died with no causal relationship with eltrombopag (hepatorenal syndrome and hepatocellular carcinoma). During the AV phase, SVR was more common in eltrombopag subjects compared to the placebo group (ENABLE-1: 23/14%, p:¼ .0064; ENABLE-2: 19/13%, p:¼ .0202). Excluding RVR, eltrombopag was superior to placebo for all measures of virological response. The therapeutic effect observed in the overall population with univariate analysis was comparable between genotype 2/3 and other genotypes. Mean platelet count in the eltrombopag group was above the threshold necessary for AV dose reduction. Platelet counts were ≥50,000/μL in 9/81% of the subjects in ENABLE-1/2 and in 15/23% of those in placebo arms. In ENABLE-1 and 2, fewer subjects in the eltrombopag group required PEG dose reduction (57/59%). Cumulative mean of PEG use was greater in ENABLE-1/2 compared to placebo (60/69%). AEs were comparable between the two studies (ENABLE-1: eltrombopag, 31.71/100 patient-years; placebo, 28.45/100 patient-years, ENABLE-2: eltrombopag, 31.25/100 patient-years; placebo, 29.06/100 patient-years). There were more AE-related treatment discontinuations in the placebo group (ENABLE-1: 17% vs. 28%; ENABLE-2: 21% vs. 26%). Cataract was more common in ENABLE-1/eltrombopag group; (8% vs. 3%) and was similar in both arms of ENABLE-2 (7% vs. 6%). HCC-associated mortality was similar between the two arms of the study. Thromboembolism occurred in 3% of the patients in the eltrombopag group and in 1% of the placebo subjects. Portal vein thrombosis was common in both treatment arms (eltrombopag: 12 subjects (1%); placebo: 2 patients (<1%)). Thromboembolism occurred most commonly during the AV phase of ENABLE-2 - 4% in the eltrombopag group and 0.4% in the placebo group (2.5% and 1.7% in ENABLE-1). Hepatic failure was more frequent in the eltrombopag group (10% and 5% in the two studies), the primary causes of which were ascites and encephalopathy; ascites occurred in 6% of the subjects on eltrombopag and 3% of those on placebo while encephalopathy occurred in 3% and <1% of the subjects on eltrombopag and placebo, respectively. Hyperbilirubinemia occurred in 55-53% of the subjects in the eltrombopag group and in 24-25% in the placebo group.

These results of ENABLE-1 and 2 demonstrated that eltrombopag can be used safely in HCV-associated hepatic disease and thrombocytopenia. Eltrombopag increased SVR clinically and statistically significantly by allowing initiation and maintenance of INF-based AV therapy. Eltrombopag should be reassessed for new triple and quadruple therapies in patients with cirrhosis and thrombocytopenia.

The risk of thromboembolism requires utmost caution during treatment with eltrombopag and, as stated in the drug's prescribing information, it is recommended that the drug is administered by specialists experienced in hepatitis C treatment when initiating treatment with eltrombopag.

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