

Stable Liver Function during Long-Term Administration of Eltrombopag, a Thrombopoietin Receptor Agonist, in Patients with Chronic Liver Disease

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Liver cirrhosis is the end stage of chronic liver disease, but no definitive pharmacological treatment is currently available. It has been reported that thrombopoietin (TPO) promotes liver regeneration and improves liver cirrhosis by increasing platelet count. We have shown the direct effect of platelet transfusion on the improvement of liver function in patients with chronic liver disease. However, platelet transfusion often causes adverse events, such as platelet transfusion refractoriness and pruritus. Therefore, we conducted an exploratory clinical trial and administered eltrombopag, an orally bioavailable, small-molecule, non-peptide TPO receptor agonist that has been approved for the treatment of chronic idiopathic thrombocytopenic purpura. The study included five male patients, aged from 49 to 75 years (57.6 ± 10.4 years), with both chronic liver disease and hepatitis C virus infection, who presented with thrombocytopenia but without cancer. Eltrombopag, ranged from 6.25 to 50 mg/day (18.75 ± 18.22 mg/day), was administered to the five patients during six months. All of the patients maintained platelet counts between 10 and $15 \times 10^{10}/L$ during the study. The indicators of liver function in patients were stable throughout the clinical trial, although we had predicted the same degree of the improvement of liver function, compared to platelet transfusion. Importantly, the liver volumes were also stable, and no cancerous lesions were observed. These results indicate the safety of long-term eltrombopag administration for patients with chronic liver disease and hepatitis C virus infection.

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Introduction

Chronic liver disease (CLD) is a progressive disease of destruction and regeneration of the liver leading to liver cirrhosis (LC). LC is the end stage of CLD and a major life threatening health problem worldwide. In addition to thrombocytopenia, patients with CLD suffer from several serious symptoms leading to liver failure. When medications fail to control CLD, the only effective therapy is liver transplantation (Neuberger 2016). However, liver transplantation is associated with serious problems, such as donor shortage, surgical complications, organ rejection, and high cost.

Platelets contain various trophic factors, such as platelet-derived growth factor, insulin-like growth factor-1, vascular endothelial growth factor, and serotonin. Platelets promote hepatocyte proliferation (Matsuo et al. 2008) and exert anti-fibrotic effects *in vitro* (Ikeda et al. 2012), and thrombocytosis promotes liver regeneration and reduces

liver fibrosis *in vivo* (Murata et al. 2007; Watanabe et al. 2009). We hypothesized that platelet transfusion therapy would improve liver function in humans (Murata et al. 2007). In a previous clinical study, we revealed the direct effect of platelet transfusion on the improvement of indicators of liver function, i.e., albumin and cholinesterase, in patients with CLD and LC (Maruyama et al. 2013). The platelet counts in the transfused patients returned to the pre-dose counts one week after the transfusion. However, platelet transfusion often causes adverse events, such as platelet transfusion refractoriness (PTR) and pruritus.

Eltrombopag (EP; GlaxoSmithKline, Ware, UK) is an orally bioavailable, small-molecule, non-peptide thrombopoietin (TPO) receptor agonist that is approved for the treatment of chronic idiopathic thrombocytopenic purpura (ITP) but not for CLD. ENABLE-1 and 2 are the largest phase 3 randomized controlled trials of chronic hepatitis C patients with LC, thrombocytopenia (platelet count $< 75 \times 10^9/L$) and portal hypertension (Afdhal et al. 2014). Both

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studies evaluated the ability of EP, as a supportive treatment, to increase platelets to a level sufficient to initiate and maintain PEG-IFN/ribavirin antiviral therapy. In other words, EP increases platelet numbers in thrombocytopenic patients with hepatitis C virus (HCV) and advanced fibrosis and cirrhosis, allowing otherwise ineligible or marginal patients to begin and maintain antiviral therapy, leading to significantly increased rates of sustained virologic response. Therefore, to increase platelets in a continuous manner and avoid PTR, we conducted an exploratory clinical trial and administered EP for six months.

Materials and Methods

We performed a clinical trial from July 2012 until February 2015. This exploratory clinical trial was approved by the institutional review board of Tsukuba University Hospital and was performed in accordance with the Declaration of Helsinki. This trial was registered in the UMIN Clinical Trials Registry system (<http://www.umin.ac.jp/NO.UMIN000008289>). Inclusion criteria were as follows: participants who gave written informed consent; outpatients; chronic hepatitis C and LC patients with liver dysfunction under sustained virologic response after treatment with PEG-IFN plus Ribavirin; chronic hepatitis C and LC patients who had no response to PEG-IFN plus Ribavirin and who passed four weeks after the treatment; chronic hepatitis C and LC patients who could not receive PEG-IFN treatment due to thrombocytopenia; platelet counts, ranged from 30 to 70 thousands/microl; serum albumin, ranged from 2.5 to 4.0 g/dl; chronic hepatitis C and LC patient with liver dysfunction in previous half year; Child-Pugh score (8 or under). Exclusion criteria were as follows: patients with acute hepatitis; patients with severe liver dysfunction whose serum liver function test is 5-fold higher than normal range, especially, 2-fold higher levels of aspartate transaminase (AST) or alanine transaminase (ALT); HIV patients; patients with shunt from portal vein to inferior vena cava; serum total bilirubin concentration (> 3.0 mg/dl); past history of severe stroke or severe heart disease; bone marrow transplantation recipients or patients with immunodeficiency; patients with IgA or other plasma protein deficiency; patients with severe pulmonary, renal, gastroenterology, hematology or psycho-neurologic disease; serum HbA1c (> 8.0%); patients with hepatocellular carcinoma (HCC) or another malignancy; women with pregnancy or willing to get pregnant; patients who received platelet

transfusion in previous two weeks; patients who are administered albumin preparation in previous six months; past history of splenectomy or partial splenic embolization; past history of drug allergies; past history of thromboembolism; patients whose doctor determined as inadequate for the study. Based on the above criteria, five male patients were selected, aged from 49 to 75 years (57.6 ± 10.4 years).

All data are shown as the mean \pm standard deviation. Statistical analyses were carried out with one-way ANOVA. In all cases, $P < 0.05$ was considered significant.

Results

The study included five patients with both CLD and HCV infection (Child-Pugh class A) who presented with thrombocytopenia (average platelet count was $54 \times 10^9/L$). They received EP, ranged from 6.25 to 50 mg/day (18.75 ± 18.22 mg/day), during six months. All of the patients administered EP maintained platelet counts between 10.0 and $15.0 \times 10^{10}/L$ during the 6-month study. The indicators for liver function were stable throughout the clinical trial, including serum albumin, cholinesterase, hyaluronic acid, type IV collagen, AST, ALT, γ -glutamyltransferase (γ GTP), total bilirubin, and prothrombin time (Table 1). Importantly, the liver volumes calculated by computed tomography were also stable during the clinical trial, and no cancerous lesions were observed.

Discussion

Currently, liver transplantation is still the only curative approach for end-stage cirrhosis. We have reported that platelets could improve liver fibrosis (Murata et al. 2007; Watanabe et al. 2009) and accelerate liver regeneration (Matsuo et al. 2008). However, platelet increment therapies, such as splenectomy and platelet transfusion, have been reported to have adverse effects, although they have ameliorating effects for CLD and cirrhosis. In a previous clinical study, we revealed the direct effect of platelet transfusion on the improvement of indicators of liver function (Maruyama et al. 2013). However, platelet transfusion often causes adverse events, such as PTR and pruritus. Therefore, we performed this clinical trial.

Table 1. Platelet counts and liver function data of five patients during this study.

Factor	pretreatment	0w	6w	12w	18w	24w	posttreatment
platelet($10^9/L$)	54.4 ± 12.1	$110.2 \pm 7.1^*$	$136 \pm 17.3^*$	$127 \pm 24.2^*$	$137.6 \pm 20.9^*$	$123.2 \pm 16.1^*$	47.3 ± 26.0
albumin(g/dL)	3.54 ± 0.09	3.44 ± 0.27	3.42 ± 0.29	4.52 ± 0.13	3.4 ± 0.19	3.36 ± 0.22	3.32 ± 0.09
CHE(U/L)	173.2 ± 19.2	166.8 ± 29.6	165.2 ± 0.29	166.8 ± 16.39	157 ± 22.08	157.8 ± 27.7	159.2 ± 18.38
HA(ng/mL)	287.8 ± 107.2	357.2 ± 180.8	443.4 ± 268.8	391.4 ± 214.2	423.2 ± 160.6	471.2 ± 461.1	354.6 ± 108.1
IV col(ng/mL)	301 ± 100.8	315.2 ± 116.6	306.4 ± 79.8	288.2 ± 123.8	305.2 ± 1260.4	318.2 ± 122.8	305 ± 102.6
AST(U/L)	48 ± 11.7	47 ± 15.0	51 ± 12.2	50.8 ± 11.6	49.2 ± 11.3	59.2 ± 18.3	61.4 ± 31.4
ALT(U/L)	30.6 ± 8.4	29.2 ± 8.6	30.8 ± 12.5	35 ± 6.7	29.6 ± 5.5	38.4 ± 20.3	43.6 ± 29.9
γ GTP(U/L)	34.8 ± 19.9	35 ± 21.9	33.8 ± 20.3	36.6 ± 17.6	34 ± 15.2	34.6 ± 14.4	33 ± 12.7
T-Bil(mg/dl)	1.24 ± 0.43	1.18 ± 0.30	1.2 ± 0.47	1.38 ± 0.53	1.22 ± 0.41	1.28 ± 0.32	1.3 ± 0.77
PT%(%)	75.3 ± 20.1	73.9 ± 19.46	79.1 ± 24.6	78.7 ± 24.7	74.5 ± 19.7	67.9 ± 12.3	71.7 ± 21.1

The data are expressed as the mean \pm standard deviation. * $p < 0.05$ compared with the pre-treatment levels. CHE, cholinesterase; HA, hyaluronic acid; IV col, type IV collagen, γ -glutamyltransferase (γ GTP), total bilirubin (T-Bil), and prothrombin time (PT%).

Compared with platelet transfusion, the degree of the improvement in the liver function was small, although adverse events did not occur. A recent report stated that the aging of platelets controls the production of TPO (Grozovsky et al. 2015); thus, the aging and activation of platelets are involved in liver regeneration. During this clinical trial, no cancerous lesions were observed, which may ensure the safety of EP concerning cancer in patients with hepatitis and LC. In other words, we have shown the safety of long-term administration of EP in patients with CLD and HCV infection. Therefore, together with the anti-tumor effects of EP on HCC (Kurokawa et al. 2015), we are planning the EP clinical trials for HCC patients with unmet medical needs who cannot use sorafenib.

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Conflict of Interest

The authors declare no conflict of interest.

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