

# Telaprevir-based triple therapy following partial splenic arterial embolization for chronic hepatitis C with thrombocytopenia can reduce carcinogenesis and improve hepatic function reserve

TORU ISHIKAWA, SATOSHI ABE, YUICHI KOJIMA, RYOKO Horigome, TOMOE SANO,  
AKITO IWANAGA, KEIICHI SEKI, TERASU HONMA and TOSHIAKI YOSHIDA

Department of Gastroenterology and Hepatology, Saiseikai Niigata Daini Hospital, Niigata 950-1104, Japan

Received September 3, 2014; Accepted June 11, 2015

DOI: 10.3892/etm.2015.2674

**Abstract.** Thrombocytopenia in patients with chronic hepatitis C negatively impacts interferon (IFN)-based treatment. The aim of this study was to evaluate the efficacy and safety of telaprevir (TVR)-based triple therapy including IFN for patients who have undergone partial splenic arterial embolization (PSE). Ten patients with thrombocytopenia who were infected with hepatitis C virus (HCV) genotype 1b received 12 weeks of TVR in combination with 24 weeks of pegylated interferon (PEG-IFN) $\alpha$ 2b and ribavirin following PSE. A sustained virological response (SVR) was seen in 9 of the 10 patients who could be assessed. Early relapse was seen in 1 patient who had the IL-28B minor allele and a null response to pretreatment. The  $\alpha$ -fetoprotein levels of the patients decreased from  $17.94 \pm 7.30$  ng/ml prior to PSE to  $4.33 \pm 2.41$  ng/ml at 6 months after triple therapy ( $P=0.08$ ). Furthermore, serum albumin levels improved significantly from  $3.68 \pm 0.49$  g/dl pre-PSE to  $4.13 \pm 0.34$  g/dl at 12 months after triple therapy ( $P=0.043$ ). PSE contributed to the treatment success of triple therapy, particularly for patients who were either treatment-naïve, had a history of relapse or the IL28B major allele. This strategy can reduce carcinogenesis and improve hepatic function reserve.

## Introduction

Treatment outcomes for patients with chronic hepatitis C and thrombocytopenia are typically poor due to the difficulty of providing adequate interferon (IFN) therapy (1). Patients with thrombocytopenia may be ineligible for antiviral treatment or, if able to start therapy, may require a dose reduction

or even discontinuation due to the hematological adverse effects. Therefore, splenectomy and partial splenic arterial embolization (PSE) are attracting attention for the treatment of thrombocytopenia with the aim of boosting the efficacy of IFN therapy (2,3). However, the indications for these procedures should be examined carefully only after considering the outcomes of IFN therapy.

Triple therapy with pegylated interferon (PEG-IFN), ribavirin (RBV) and telaprevir (TVR) has emerged as a treatment for patients with chronic hepatitis C genotype 1 and a high viral load, and it has been reported to achieve a high sustained virological response (SVR) (4-7). Nevertheless, there are few published studies concerning the outcomes of this triple therapy subsequent to PSE.

The present study was conducted to determine whether PSE is effective for patients given telaprevir-based triple therapy.

## Materials and methods

**PSE procedure.** The present study targeted 10 patients with chronic hepatitis C and thrombocytopenia who had a platelet count of  $\leq 10 \times 10^4$ /ml, and who underwent PSE using the Seldinger technique at Saiseikai Niigata Daini Hospital (Niigata, Japan) prior to receiving PEG-IFN/RBV/TVR triple therapy. In this study, thrombocytopenia was defined as a platelet count of  $< 10 \times 10^4$ /ml (8). To perform PSE, a hook-shaped 4-Fr catheter (Seiya; Medikit Co., Ltd., Tokyo, Japan) was inserted near to the splenic hilum, and following splenic arteriography, each branch was identified from the intrasplenic artery map that was obtained. A microcatheter (Sniper 2; Terumo Clinical Supply Co. Ltd., Tokyo, Japan) was selectively inserted into each of these vessels, and embolization using coils and 2-mm<sup>2</sup> gelatin sponges soaked with 20 mg gentamicin (Gentacin; Merck & Co., Inc., Whitehouse Station, NJ, USA) was performed, as previously described (9). To prevent complication, superselective angiography was performed to accurately estimate the areas of infarction and a sterile technique was cautiously practiced during the PSE. Furthermore, broad-spectrum antibiotics were administered by peripheral intravenous infusion for 5 days after the procedure, and oral non-steroidal anti-inflammatory drugs were

**Correspondence to:** Dr Toru Ishikawa, Department of Gastroenterology and Hepatology, Saiseikai Niigata Daini Hospital, 280-7 Teraji, Niigata 950-1104, Japan  
E-mail: toruishi@ngt.saiseikai.or.jp

**Key words:** partial splenic arterial embolization, telaprevir-based triple therapy, thrombocytopenia

Table I. Clinical features of patients with thrombocytopenia and chronic hepatitis C.

Case no.	Age (years)	Gender	Treatment history	IL-28	Spleen volume (ml)	Infarction volume (ml)	Non-infarction volume (ml)	Infarction rate (%)
1	49	F	Naïve	Major	268.6	131.3	137.3	48.9
2	69	M	Relapse	Major	217.1	167.4	49.7	77.1
3	44	M	Relapse	Major	1,028.2	364.8	663.4	35.4
4	56	F	Relapse	Minor	117.4	112.4	5.0	95.6
5	67	M	Naïve	Major	114.1	79.6	34.5	69.2
6	71	M	Relapse	Major	215.6	31.9	183.7	14.8
7	71	M	Naïve	Major	210.9	106.6	104.3	50.6
8	46	M	Naïve	Major	338.2	248.4	89.8	73.3
9	55	M	Naïve	Major	283.4	117.8	165.6	41.6
10	61	M	Null	Minor	482.2	373.3	108.9	46.5

M, male; F, female.

given as required for fever  $\geq 38^{\circ}\text{C}$ . The splenic infarction rate of PSE was measured immediately following the procedure by computed tomography angiography.

After confirming an increase in platelet counts, treatment with PEG-IFN/RBV/TVR was initiated, and viral variation and shifts over time in  $\alpha$ -fetoprotein (AFP) and serum albumin (Alb) values were investigated.

Mean integration values of Alb and AFP in each patient were calculated prior to and following IFN therapy in order to evaluate the effect on hepatocarcinogenesis of changes in serum Alb and AFP levels during IFN therapy.

Written informed consent was obtained from all patients prior to starting the study, and the Ethics Committee of Saiseikai Niigata Daini Hospital approved the study, which was conducted in accordance with the 1975 Declaration of Helsinki.

**Antiviral treatment.** Each patient received a combination treatment comprising TVR (Telavie; Mitsubishi Tanabe Pharma, Osaka, Japan) at a dose of 750 mg every 8 h in combination with PEG-IFN $\alpha$ 2b (PegIntron; MSD, Tokyo, Japan) and RBV (Rebetol; MSD) for 12 weeks, followed by an additional 12 weeks of treatment with only PEG-IFN $\alpha$ 2b and RBV. PEG-IFN $\alpha$ 2b was injected subcutaneously once weekly at a dose of 1.5  $\mu\text{g}/\text{kg}$ . RBV was given orally at a daily dose of 600–800 mg based on body weight. If marked anorexia, an elevation of serum creatinine level or severe anemia developed, the TVR dose was reduced to 1,500 mg/day (750 mg at 12-h intervals after a meal). The method of RBV/TVR dose reduction in the case of anemia was conducted as previously reported (10).

**Virological assessment and definition of viral response.** Serum hepatitis C virus (HCV) RNA level was quantified with the COBAS® TaqMan® HCV test, version 2.0 (detection range 1.2–7.8 log IU/ml; Roche Diagnostics, Branchburg, NJ, USA). The serum HCV RNA level of each patient was assessed prior to treatment, every 4 weeks during treatment and 24 weeks after the therapy.

A rapid virological response was defined as undetectable serum HCV RNA at week 4, and early virologic response as

undetectable serum HCV RNA at week 12. SVR was defined as undetectable serum HCV RNA at 24 weeks after the discontinuation of treatment.

**Statistical analysis.** Statistical processing was performed using StatView version 5.0 software (SAS Institute, Cary, NC, USA). All reported P-values are 2-sided, with P<0.05 considered statistically significant. A P-value of <0.05 was considered to indicate a statistically significant difference.

## Results

**Patient characteristics.** The mean age of the patients was  $58.67 \pm 9.91$  years (range, 44–71 years), and the male-female ratio was 8:2. Five patients were pretreatment-naïve, four had relapsed and one was a null responder. Eight patients had the IL-28 major allele, and two patients had the IL-28 minor allele (Table I).

**Effects of PSE.** The mean spleen volume was  $329.94 \pm 254.78$  ml (range, 114.07–1,028.28 ml), the mean infarction volume was  $172.55 \pm 111.44$  ml (range, 31.9–373.3 ml) and the mean splenic infarction rate was  $57.32 \pm 23.31\%$  (range, 14.8–95.6%; Table I). The mean platelet count increased from 85,600/ml pre-PSE to 152,700/ml post-PSE.

**Treatment efficacy.** SVR was observed in 9 of the 10 patients who could be assessed. Early relapse was seen in 1 patient who had the IL-28B minor allele and a null response to pretreatment (Table II).

The mean AFP level of the patients decreased from  $17.94 \pm 7.30$  ng/ml prior to PSE to  $4.33 \pm 2.41$  ng/ml at 6 months after the triple therapy (P=0.08; Fig. 1).

The mean serum albumin level of the patients improved from  $3.68 \pm 0.49$  g/dl prior to PSE to  $3.88 \pm 0.57$  g/dl at 6 months after the triple therapy (P=0.41). Furthermore, the mean serum albumin level improved significantly at 12 months after triple therapy from  $3.68 \pm 0.49$  g/dl pre-PSE to  $4.13 \pm 0.34$  g/dl (P=0.043; Fig. 2).

**Clinical adverse effects.** No patients were withdrawn from the study due to adverse reactions to the triple therapy. Four

Table II. Virological response of telaprevir-based triple therapy after partial splenic arterial embolization.

Case no.	HCV RNA (Log IU/ml)				
	Pre treatment	4 weeks	12 weeks	EOT	SVR
1	7.3	-	-	-	Yes
2	7.1	-	-	-	Yes
3	6.6	-	-	-	Yes
4	5.6	-	-	-	Yes
5	6.2	-	-	-	Yes
6	7.3	-	-	-	Yes
7	6.8	-	-	-	Yes
8	6.2	-	-	-	Yes
9	5.4	-	-	-	Yes
10	5.6	-	-	-	Relapse <sup>a</sup>

<sup>a</sup>Relapse at 4 weeks. Antiviral response after 4, 12, and 24 weeks (end of treatment, EOT). A dash (-) indicates undetectable levels. HCV, hepatitis C virus; SVR, sustained virological response.

of the 10 patients exhibited thrombocytopenia during the study period, but none had to be withdrawn as a result. A rash occurred in 4 patients, but all cases were Grade 2 or lower.

## Discussion

In patients with advanced hepatitis, thrombocytopenia can be caused by shifts of platelet distribution to an enlarged spleen (11), platelet destruction due to an immunological mechanism (12,13) and decreased production of thrombopoietin (14,15). These patients are at a high risk of hepatocellular carcinoma (HCC). HCC, in particular, is a frequent complication of cirrhosis. IFN therapy is essential in such patients deemed to be at high risk of HCC, and the risk of HCC is expected to decline significantly in those who show a SVR. However, thrombocytopenia represents a major obstacle to IFN therapy. In patients with marked thrombocytopenia with hypersplenism, combination therapy with PEG-IFN or RBV is difficult due to IFN-accelerated thrombocytopenia, and triple therapy is likely to be inadequate.

Splenectomy and PSE have attracted interest for the treatment of portal hypertension with thrombocytopenia (16,17). Splenectomy is considered to be superior to PSE with regard to its ability to increase platelet counts; however, portal vein thrombosis and overwhelming postsplenectomy infection (OPSI) due to pneumococcus are problems (18). OPSI has a high mortality rate and poor prognosis (19,20), and these risks are expected to rise further in patients with progressive liver fibrosis.

Maddison first reported splenic embolization as a treatment for hypersplenectomy in 1973 (21); however, the indications were initially limited by severe complications such as splenic abscess and pneumonia with sepsis. Subsequently, Spigos *et al* reported PSE limited to the area of infarction (22).

As the safety of PSE has improved, the technique has come into wide clinical use. PSE, in a similar manner to

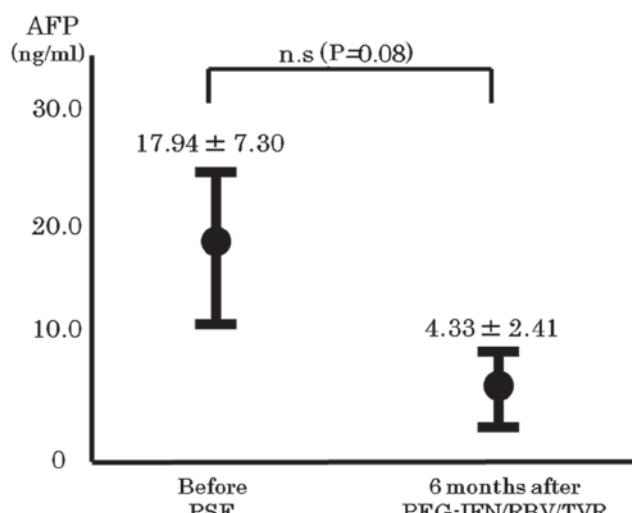


Figure 1. Changes of AFP levels prior to PSE and at 6 months after PEG-IFN/RBV/TVR. AFP,  $\alpha$ -fetoprotein; PSE, partial splenic arterial embolization; PEG-IFN, pegylated interferon; RBV, ribavirin; TVR, telaprevir; n.s., not significant.

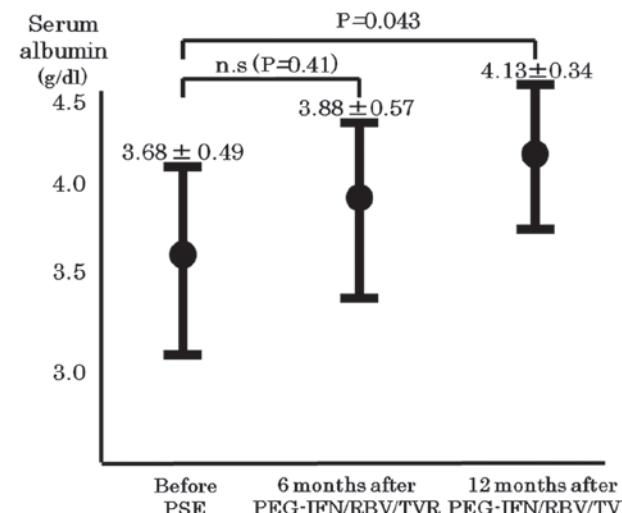


Figure 2. Changes of albumin levels prior to PSE, and at 6 and 12 months after triple therapy. PSE, partial splenic arterial embolization; PEG-IFN, pegylated interferon; RBV, ribavirin; TVR, telaprevir; n.s., not significant.

splenectomy, increases platelet count, improves hepatic function, hypersplenism, portal hypertension and gastroesophageal varices, and appears effective when used with IFN therapy for type C hepatitis with thrombocytopenia and HCC therapy (23,24). PSE has been demonstrated to be effective for the treatment of thrombocytopenia caused by hypersplenism and for improving liver function (25,26). It is also reportedly effective when combined with IFN therapy for hepatitis C with thrombocytopenia (27); however, the invasive nature of the procedure means that its indications are limited to those in which it is expected to deliver an adequate response.

In Japan, PEG-IFN (plus RBV) therapy is mainly used in patients with Child-Pugh class A cirrhosis subsequent to splenectomy or PSE. The two approaches yield increased platelet counts following treatment in the majority of patients, and treatment outcomes indicate a high SVR rate in those with

genotype 2 (28). Therefore, it is considered that a high SVR should be a prerequisite for undertaking invasive procedures such as splenectomy or PSE.

Even patients with hepatitis C genotype 1 and a high viral load who are refractory to dual therapy with PEG-IFN/RBV have exhibited a high SVR when receiving triple therapy with PEG-IFN/RBV/TVR, giving rise to expectations of expanded indications for PSE. In the present study, triple therapy consisting of PEG-IFN/RBV/TVR was used following PSE in 10 patients, including a patient with chronic hepatitis C genotype 1, a high viral load and thrombocytopenia, with the aim of achieving a high SVR. By opting to perform PSE in patients with chronic hepatitis C and thrombocytopenia, it was possible to initiate triple therapy and achieve a high SVR. Since this treatment modality has been found to reduce AFP values, it may help to inhibit carcinogenesis in patients with elevated AFP values who are at high risk of cancer due to liver fibrosis. Furthermore, the administration of PEG-IFN/RBV/TVR following PSE increased albumin levels and improved hepatic functional reserve through the antiviral effects. These benefits demonstrated by the combination therapy suggest that it may contribute to an improved prognosis for patients with chronic hepatitis C and thrombocytopenia.

It is recommended that a high SVR is a requirement when attempting invasive procedures such as PSE. Nevertheless, 1 patient with the IL-28B minor allele and a null response to pretreatment suffered an early relapse. This finding indicates that patients undergoing triple therapy in combination with PSE should either have the IL-28B major allele or a previous treatment history of relapse. With the exception of refractory patients, we consider that many patients should be eligible for this form of treatment, provided that sufficient care is taken to prevent PSE-associated complications.

Based on these data, it is possible to make more effective decisions concerning antiviral treatment options for patients and whether PSE should be performed. It is also important to monitor patients undergoing antiviral treatment for the development of HCC.

We consider that increased platelet counts following PSE will facilitate the safe use of PEG-IFN/RBV/TVR triple therapy in patients with chronic hepatitis C and thrombocytopenia. A further study with a larger number of patients is required to confirm the findings of the present study.

In conclusion, triple therapy combined after PSE is indicated to be an acceptable treatment that is expected to inhibit carcinogenesis in patients with chronic hepatitis C and thrombocytopenia perceived to be at high risk of cancer due to fibrosis of the liver.

## References

- Shiffman ML, Ghany MG, Morgan TR, Wright EC, Everson GT, Lindsay KL, Lok AS, Bonkovsky HL, Di Bisceglie AM, Lee WM, *et al*: Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. *Gastroenterology* 132: 103-112, 2007.
- Shimizu H, Takatsuka K, Nakano H, Tenjin T, Fujikawa T, Yoshida A, Yoshimatsu E, Matsui K and Iwabuchi S: Long-term evaluation of partial splenic embolization followed by interferon therapy in patients with hepatitis C virus (HCV) cirrhosis and thrombocytopenia. *Intern Med* 53: 925-931, 2014.
- Hanafiah M, Shahizon AM, Low SF and Shahrina MH: Severe thrombocytopenia due to hypersplenism treated with partial splenic embolisation. *BMJ Case Rep* 2013; pii: bcr201301016363, 2011.
- McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, McNair L, Alam J and Muir AJ; PROVE1 Study Team: Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 360: 1827-1838, 2009.
- Hézode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki JP, Bourlière M, Gharakhanian S, Bengtsson L, *et al*: Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 360: 1839-1850, 2009.
- McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, Heathcote EJ, Zeuzem S, Reesink HW, Garg J, *et al*: Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 362: 1292-1303, 2010.
- Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, *et al*: Telaprevir for retreatment of HCV infection. *N Engl J Med* 364: 2417-2428, 2011.
- Ikeda N, Imanishi H, Aizawa N, Tanaka H, Iwata Y, Enomoto H, Saito M, Iijima H, Iimuro Y, Fujimoto J, *et al*: Nationwide survey in Japan regarding splenectomy/partial splenic embolization for interferon treatment targeting hepatitis C virus-related chronic liver disease in patients with low platelet count. *Hepatol Res* 44: 829-836, 2014.
- Shimizu H, Takatsuka K, Yoshida A, Yoshimatsu E, Matsui K and Iwabuchi S: Partial splenic embolization reverses insulin resistance in patients with liver cirrhosis. *Intern Med* 48: 747-751, 2009.
- Ogawa E, Furusyo N, Nakamura M, Kajiwara E, Nomura H, Dohmen K, Takahashi K, Satoh T, Azuma K, Kawano A, *et al*; Kyushu University Liver Disease Study (KULDS) Group: Clinical milestones for the prediction of severe anemia by chronic hepatitis C patients receiving telaprevir-based triple therapy. *J Hepatol* 59: 667-674, 2013.
- Aster RH: Pooling of platelets in the spleen: Role in the pathogenesis of 'hypersplenic' thrombocytopenia. *J Clin Invest* 45: 645-57, 1966.
- Aoki Y, Hirai K and Tanikawa K: Mechanism of thrombocytopenia in liver cirrhosis: Kinetics of indium-111 tropolone labeled platelets. *Eur J Nucl Med* 20: 123-129, 1993.
- Nagamine T, Ohtuka T, Takehara K, Arai T, Takagi H and Mori M: Thrombocytopenia associated with hepatitis C viral infection. *J Hepatol* 24: 135-140, 1996.
- Ishikawa T, Ichida T, Matsuda Y, Sugitani S, Sugiyama M, Kato T, Miyazaki H and Asakura H: Reduced expression of thrombopoietin is involved in thrombocytopenia in human and rat liver cirrhosis. *J Gastroenterol Hepatol* 13: 907-913, 1998.
- Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, Weksler B and Esteban R: Thrombocytopenia associated with chronic liver disease. *J Hepatol* 48: 1000-1007, 2008.
- Linton RR, Jones CM and Volwiler W: Portal hypertension: the treatment by splenectomy and splenorenal anastomosis with preservation of the kidney. *Surg Clin North Am* 27: 1162-1170, 1947.
- Goldstone J: Splenectomy for massive splenomegaly. *Am J Surg* 135: 385-388, 1978.
- Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV and Facklam RR: Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA* 270: 1826-1831, 1993.
- Waghorn DJ and Mayon-White RT: A study of 42 episodes of overwhelming post-splenectomy infection: Is current guidance for asplenic individuals being followed? *J Infect* 35: 289-294, 1997.
- Okabayashi T and Hanazaki K: Overwhelming postsplenectomy infection syndrome in adults - A clinically preventable disease. *World J Gastroenterol* 14: 176-179, 2008.
- Maddison FE: Embolic therapy of hypersplenism. *Invest Radiol* 8: 280-281, 1973.
- Spigos DG, Jonasson O, Mozes M and Capek V: Partial splenic embolization in the treatment of hypersplenism. *Am J Roentgenol* 132: 777-782, 1979.
- Yoshida H, Mamada Y, Taniai N and Tajiri T: Partial splenic embolization. *Hepatol Res* 38: 225-233, 2008.
- Ishikawa T, Kubota T, Horigome R, Kimura N, Honda H, Iwanaga A, Seki K, Honma T and Yoshida T: Concurrent partial splenic embolization with transcatheter arterial chemoembolization for hepatocellular carcinoma can maintain hepatic functional reserve. *Hepatol Res* 44: 1056-1061, 2014.

25. Amin MA, el-Gendy MM, Dawoud IE, Shoma A, Negm AM and Amer TA: Partial splenic embolization versus splenectomy for the management of hypersplenism in cirrhotic patients. *World J Surg* 33: 1702-1710, 2009.
26. Hayashi H, Beppu T, Masuda T, Mizumoto T, Takahashi M, Ishiko T, Takamori H, Kanemitsu K, Hirota M and Baba H: Predictive factors for platelet increase after partial splenic embolization in liver cirrhosis patients. *J Gastroenterol Hepatol* 22: 1638-1642, 2007.
27. Miyake Y, Ando M, Kaji E, Toyokawa T, Nakatsu M and Hirohata M: Partial splenic embolization prior to combination therapy of interferon and ribavirin in chronic hepatitis C patients with thrombocytopenia. *Hepatol Res* 38: 980-986, 2008.
28. Tahara H, Takagi H, Sato K, Shimada Y, Tojima H, Hirokawa T, Ohyama T, Horiochi K, Naganuma A, Arai H, *et al*: A retrospective cohort study of partial splenic embolization for antiviral therapy in chronic hepatitis C with thrombocytopenia. *J Gastroenterol* 46: 1010-1019, 2011.