Romiplostim for severe thrombocytopenia in the treatment of chronic hepatitis C virus infection: a new option for clinicians?

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SUMMARY

We describe a case of a 64-year-old man with a history of ITP which had required several treatments including splenectomy, and with chronic hepatitis C virus (HCV) infection untreated due to severe thrombocytopenia. In March 2011, platelet count was 14,000/mmc and a thrombopoietic therapy with romiplostim was initiated at the dose of 2 mcg/kg/week that was increased to 8 mcg/kg/week. At week 32, platelet count was 65,000/mmc and an anti-HCV therapy with peginterferon and ribavirin was then started. At baseline laboratory tests indicated AST 99IU/l, ALT 125UI/l, HCV RNA 3,220 UI/ml and HCV genotype 2a/2c. An early virological response (EVR) with normalization of transaminases in the course of antiviral therapy, such as a sustained virological response (SVR) after its interruption were recorded. Therefore a satisfactory platelet count (range 54,000-179,000/mmc) at the dose of 4 mcg/week during antiviral therapy, such as at the dose of 2 mcg/kg/week after antiviral interruption (range 65,000-292,000/mmc) was recorded.

Romiplostim proved effective and safe in the course of antiviral treatment. Therefore it permitted the start of anti-HCV therapy despite severe thrombocytopenia and also avoided any peg-interferon dosage modification or discontinuation. Further prospective studies in larger patient cohort should be encouraged to validate this strategy.

KEY WORDS: Romiplostim, Thrombocytopenia, HCV treatment.
roids, intravenous immunoglobulin or anti-RhDIg, have been studied to treat HCV-related thrombocytopenia. Invasive procedures including splenectomy or partial splenic embolization are also considered an effective, but not always successful, therapeutic approach for thrombocytopenia (Sakuraya et al., 2002; Myake et al., 2008).

Currently, new thrombopoietic agents such as eltrombopag and romiplostim, which stimulate platelet production by a mechanism similar to that of endogenous thrombopoietin, have been approved for the treatment of chronic immune thrombocytopenic purpura (ITP) refractory to standard therapy (Kuter, 2007). Safety and efficacy of long-term treatment with these drugs in chronic ITP has been demonstrated in clinical trials (Bussel et al., 2009; Shipperus et al., 2011). Therefore eltrombopag has been shown to achieve and successfully maintain satisfactory platelet counts in patients with concomitant chronic hepatitis C liver disease, in many cases allowing the start of antiviral therapy which was successfully completed (Danish et al., 2010).

A preoperative use of romiplostim for elective surgical operations in thrombocytopenic patients with chronic hepatitis C and liver cirrhosis also seems a possible strategy to increase platelet counts without postoperative bleeding or thrombotic complications (Moussa et al., 2013). No data regarding the usefulness of romiplostim in the course of anti-HCV therapy are currently available, except for anecdotal reports. In two cases, romiplostim was used to control a severe interferon-induced thrombocytopenia; in both cases the anti-HCV protocol with PEG-interferon and ribavirin was completed without dose reduction or discontinuation (Voican et al., 2012).

In a HCV/HIV coinfected patient with persistent thrombocytopenia, the increased platelet count by administration of romiplostim was followed by initiation and maintenance of anti-HCV treatment without interference with the concomitant antiretroviral therapy (Taylor et al., 2012).

Here, we describe the case of a 64-year-old man diagnosed with chronic ITP in 1971 and HCV infection in 1994, who presented to our observation for the management of chronic ITP in March 2011. He had previously undergone splenectomy and blood transfusions for severe thrombocytopenia in 1981. In addition, he had been hospitalized for serious bleeding due to thrombocytopenia (15,000/platelets per cubic
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At the visit, the blood count showed mild leukocytosis (12,500/mmc), normal hemoglobin level (14.5 g/dl) and severe thrombocytopenia (14,000/mmc) and so a thrombopoietic therapy with romiplostim at the dose of 2 mcg/kg/week was started, with weekly platelet count monitoring; after 12 weeks, the romiplostim dose was changed into 8 mcg/kg/week. The evolution of platelet count during romiplostim therapy is shown in Figure 1.

During routine examinations, he presented hypertransaminasemia (>1.5 of normal) HCV RNA 3,220 UI/ml (PCR TaqMan real time method, cut off <16 UI/ml) and HCV genotype 2a/2c. He reported that he had never been treated for HCV because of his history of thrombocytopenia ranging from 12,000 to 25,000/mmc.

In October 2011, virological status and liver function parameters were re-assessed. Laboratory tests indicated elevation of aspartate aminotransferase (AST 99IU/l), alanine aminotransferase (ALT 125UI/l), gamma-glutamyl transpeptidase (gamma-GT 81UI/l), mild hypoalbuminemia (3.6 g/dl), hypergammaglobulinemia (31.8%), and normal levels of total bilirubin (0.63 mg/dl) and alkaline phosphatase (62UI/l). Other causes of liver disease were excluded. Abdominal ultrasound examination did not show suspect hepatic nodules or ascitis.

After 32 weeks on romiplostim treatment platelet count was 65,000/mmc and an anti-HCV therapy based on the combination of peginterferon at reduced dose (Pegasys 135 mcg/week) and ribavirin (Copegus 800 mg/die) was then started. At baseline, AST 89UI/l, ALT 101UI/l, gammaGT 88UI/l, leukocyte count 11,500/mmc, hemoglobin level 13.6 g/dl were recorded. After 4 weeks of anti-HCV therapy, the viral load became undetectable defining an early virological response (EVR) and serum levels of transaminases decreased (AST 63UI/l, ALT 59UI/l). Normalization of transaminases and gammaGT were recorded at week 8; on HCV treatment leukocyte count ranged between 7200 and 9100/mmc and hemoglobin levels between 9.1-13.1 g/dl. An irritating oral lichen occurred which was treated with VEA oris with partial relief. HCV-viremia remained below the limit of detection at week 24 (end of therapy); a sustained virological response (SVR, 48 weeks after antiviral therapy discontinuation) was obtained. During antiviral therapy, platelet counts ranged between 54,000/mmc and 179,000/mmc (median 101,000/mmc) with romiplostim at the dose of 4 mcg/kg/week reduced at week 12. After anti-HCV therapy interruption we administered romiplostim at the dose of 2 mcg/kg/week, maintaining the same dose until now and recording a satisfactory platelet count which ranged between 65,000/mmc and 292,000/mmc (median 141,000/mmc). No symptoms or signs of myelofibrosis post treatment were observed.

Therefore, the administration of romiplostim was effective and safe in our patient in the course of antiviral treatment, not only allowing the initiation of antiviral therapy despite severe thrombocytopenia but also avoiding any peg-interferon dosage modification or discontinuation and thus increasing the probability of SVR. Patients with chronic HCV infection with thrombocytopenia (<75,000/mmc) have been routinely excluded from clinical trials of interferon and ribavirin. Although a reduced platelet count is not an absolute contraindication to treatment with peginterferon and ribavirin, product labels advise that caution be used in patients with significant thrombocytopenia. Typically, thrombocytopenia occurs within the first 8 weeks of therapy, and the manufacturers of peginterferon alfa-2a and alfa-2b recommend dose reduction for platelet counts less than 50,000/mmc and discontinuation for platelet counts less than 25,000/mmc. (Roche. Prescribed information. Available at www.pegasys.com; Shering. Prescribed information. Available at HYPERLINK "http://www.pegintron.com" www.pegintron.com). Peginterferon dose reduction, however, is still associated with a decrease of SVR, indicating the importance of maintaining a full-dose antiviral therapy (Shiffman et al., 2007).

In our patient with a long history of ITP, the acquired HCV infection exacerbated the thrombocytopenia with a serious hemorrhagic event leading to hospitalization. Therefore, anti-HCV treatment was started not only to avoid liver disease progression but also to improve chronic ITP. In fact, the feedback between platelet count and thrombopoietin release is altered...
in HCV-related chronic liver disease (Peck-Radosavljevic et al., 1998; Giannini et al., 2003; Iga et al., 2005), thrombopoietin agonists seem to be a useful option for thrombocytopenia and facilitate interferon therapy use (McHutchison et al., 2007). However, these drugs are not currently approved for the treatment of thrombocytopenia in patients with HCV infection but only in patients with chronic ITP who are refractory to at least one standard treatment. Our patient’s case suggests that romiplostim might maintain a reasonable platelet count on antiviral therapy, without leading to the emergence of significant drug interferences with peg-interferon and ribavirin. Consequently, the platelet count in our patient was also indirectly improved by the normalization of liver function after the successful completion of the 24-week antiviral therapy.

In conclusion, romiplostim should be considered an alternative approach to peginterferon reduction or discontinuation for the management of thrombocytopenia in the course of anti-HCV therapy. Further prospective studies in larger patient cohorts should be encouraged to validate this strategy.

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