Idiopathic thrombocytopenic purpura resistant to eltrombopag, but cured with romiplostim

Andrea Piccin[1], Giovanni Amaddii[1], Fabrizio Natolino[2], Atto Billio[1], Sergio Cortelazzo[1]

[1]Haematology Department, San Maurizio Regional Hospital, Bolzano; [2]Pharmacology Department, University of Padua, Padua, Italy

Dear Sir,

The recent development of thrombopoietin-mimetic drugs offers the possibility of a new approach for second- or even third-line treatment of resistant idiopathic thrombocytopenic purpura (ITP). Here we report on the case of a patient with ITP who relapsed after standard first-line treatment with steroids and immunoglobulins and whose disease was resistant to splenectomy. Subsequent second-line treatment included an anti-CD20 monoclonal antibody (rituximab) and a first unsuccessful attempt with eltrombopag. The patient was subsequently cured with romiplostim. The therapeutic implications are discussed.

The patient was a 34-year old male, first diagnosed in January 1999 with ITP. The patient had a past medical history of neonatal epilepsy and for this reason was receiving treatment with phenobarbital, clonazepam and carbamazepine. A breath test was negative for Helicobacter pylori and serological tests for hepatitis A, B, C and human immunodeficiency viruses were also negative. The patient was initially treated with a course of prednisone (1mg/kg per os). However, because of a relapse, he was first treated with intravenous immunoglobulins (IVIG; 1 g/kg) and later, in September 1999, he underwent elective splenectomy. Hepatic scintigraphy ruled out splenunculi. The patient was subsequently treated on occasions with IVIG due to a falling platelet count. He received a total of ten courses of IVIG. However, in July 2007, due to a second relapse with a platelet count <20 10^9/L, he was treated unsuccessfully with IVIG followed by the anti-CD20 monoclonal antibody rituximab (375 mg/m^2) once a week for 4 weeks. The patient received four courses in total and obtained a sustained clinical response. However, in November 2011, the patient's platelet count dropped again to <20 10^9/L. At this time thrombopoietin-mimetics drugs were available and the patient was, therefore, treated with eltrombopag (50 mg once daily, per os) obtaining a good response and a platelet count >50 10^9 L. Unfortunately, 2 months later the drug was no longer available because of a supply shortage and the treatment had to be discontinued. One month later (January 2011) the patient's platelet count had dropped to 2 10^9/L and he developed severe epistaxis and rectorrhagia. A new trial of treatment with eltrombopag was commenced (50 mg once daily per os, for 1 month), but was unsuccessful. This was immediately followed by three courses of weekly rituximab, with oral prednisone (0.5 mg/kg). Despite this treatment, the platelet count did not reach the safety level of 20 10^9/L although no further episodes of bleeding occurred. For this reason, a new thrombopoeitin-mimetic was considered and the patient was started on subcutaneous romiplostim treatment (80 μg every 2 weeks) which produced a prompt platelet response (platelet count >50 10^9/L). He is currently being treated with romiplostim, his platelet count remains >100 10^9/L, and to date he has not shown any new signs of bleeding or haemorrhage.

It is important to remember that the two currently available thrombopoietin agonists, here mentioned, have different mechanisms of action. Eltrombopag is a non-peptide thrombopoietin agonist that interacts with the thrombopoietin receptor c-MPL at a different site from thrombopoietin, while romiplostim is a "peptibody", a combination of a peptide and an antibody, with two linked carrier-Fc domains, which potentiate its effectiveness.

An extensive Pubmed search of the literature revealed a similar case reported by Aoki T and colleagues, suggesting the absence of cross-resistance between the two drugs and different mechanisms of actions[1]. In addition, a study using a Bayesian meta-regression method compared the effectiveness of the two thrombopoietin-mimetics within several trials showing a statistical significant superiority for romiplostim compared to eltrombopag[2]. As our patient was splenectomised, it is relevant to add that so far, on the basis of currently available research, both thrombopoietin drugs have shown similar efficacy in splenectomised patients. Finally, it is not irrelevant that our patient was also taking anti-epileptic medications (phenobarbital, clonazepam and carbamazepine) throughout treatment and that previous studies have suggested that carbamazepine induces ITP[3]. A recent study also showed that clonazepam may induce pancytopenia[4] and overall antiepileptic drugs have been associated with bone marrow damage and hepatic

*Blood Transfus 2014; **12** Suppl 1: s149-50 DOI 10.2450/2013.0289-12*
© SIMTI Servizi Srl

toxicity[5]. We cannot, therefore, exclude the possibility that these drugs may have had either a direct role on the bone marrow by inducing ITP or by impairing the action of eltrombopag, or that they may have enhanced liver catabolic pathways reducing the bioavailability of eltrombopag. However, none of these theories have been proven.

In conclusion, the findings in this case suggest that the thrombopoietin agonists eltrombopag and rimoplostim have different mechanisms of action and that in the absence of a clinical response to one of these two drugs it is worth considering a trial treatment with the other. The possibility that other medications (e.g. anti-epileptic drugs) may interact with eltrombopag should be considered and if possible clarified.

Acknowledgements

We thank Ms. Delia Orsi for facilitating data collection.

Authors' contributions

Andrea Piccin reviewed the literature and wrote the manuscript; Giovanni Amaddii and Atto Billio were involved in the patient's management. Sergio Cortelazzo designed the study and reviewed the manuscript. Natolino Fabrizio was involved in the literature search on pharmacological interactions.

The Authors declare no conflicts of interest.

References

1) Aoki T, Harada Y, Matsubara E, et al. Thrombopoietin receptor agonists in refractory immune thrombocytopenia: differential responses to eltrombopag and romiplostim: a case report and possible explanations. J Clin Pharm Ther 2012; **37**: 729-32.
2) Cooper KL, Fitzgerald P, Dillingham K, et al. Romiplostim and eltrombopag for immune thrombocytopenia: methods for indirect comparison. Int J Technol Assess Health Care 2012; **28**: 249-58.
3) Ishikita T, Ishiguro A, Fujisawa K, et al. Carbamazepine-induced thrombocytopenia defined by a challenge test. Am J Hematol 1999; **62**: 52-5.
4) Bautista-Quach MA, Liao YM, Hsueh CT. Pancytopenia associated with clonazepam. J Hematol Oncol 2010; **3**: 24.
5) Wyllie E, Wyllie R. Routine laboratory monitoring for serious adverse effects of antiepileptic medications: the controversy. Epilepsia 1991; **32** (Suppl 5): S74-9.

Arrived: 8 December 2012 - Revision accepted: 7 February 2013
Correspondence: Andrea Piccin
Haematology Deptartment and Bone Marrow Transplant Unit
San Maurizio Regional Hospital
Via L. Bˆ hler 5
39100 Bozen, Italy
e-mail: apiccin@gmail.com