A patient with Fechtner syndrome successfully treated with romiplostim

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Dear Sirs,

Fechtner syndrome (1) is a rare autosomal-dominant disorder characterised by thrombocytopenia, giant platelets and features of Alport syndrome, i.e. nephritis, cataract and sensorineural hearing loss. It is one entity of a group of giant platelet disorders caused by mutations of the MYH9 gene, encoding the heavy chain of non-muscle myosin IIA (NMMHC-A) (2, 3). NMMHC-A is supposed to play a key role in the cytoskeleton function and contractile system of platelets and leukocytes (3). Most patients are asymptomatic or have a mild bleeding tendency. However, during major interventions or in case of ongoing bleeding symptoms, it might be desirable to increase the platelet count temporarily.

In 2010, Pecci et al. reported an observational study on the effect of eltrombopag, a thrombopoietin receptor agonist, in 12 patients with MYH9 related platelet disorders (4). In most of these patients bleeding tendency decreased or vanished. We present the case of a patient with Fechtner syndrome suffering from recurrent bleeding episodes during haemodialysis who was initially successfully treated with the thrombopoietin receptor agonist romiplostim, but in whom the effect on the platelet count decreased over time.

A 30-year-old Caucasian male patient presented with a history of thrombocytopenia diagnosed at the age of two. At the age of 12, he received the first platelet transfusion. None of his relatives had a history of thrombocytopenia. In December 2005, he developed progressive renal failure with severe hypertension, and an unselective urinary protein loss of 3.2 g/day. He remained severely thrombocytopenic. Wiskott-Aldrich syndrome was excluded, but invasive investigations of the renal disease were deferred due to low platelet count. Bone marrow examination showed a normal amount of megakaryocytes leading to the diagnosis of chronic immune-mediated thrombocytopenia (ITP) despite the absence of anti-platelet antibodies and no evidence for splenic platelet sequestration by scintigraphy. Treatments with dexamethasone, high-dose immunoglobulines and mycophenolate mofetil 1g/day twice daily failed to increase the platelet count.

Haemodialysis was started in March 2007. Because of repetitive bleeding incidents from venous access during haemodialysis under regular co-medication with heparin, the patient was treated with weekly platelet transfusions by his nephrologist, reducing his chances of successful kidney transplantation through alloantibody formation. In February 2008, the diagnosis of MYH9-related macrothrombocytopenia was made based on the presence of large platelets in the peripheral blood and Döhle-like inclusion bodies in the granulocytes (5). Mutation analysis revealed a mutation in exon 1: S96L of the MYH9 gene. Because the patient presented with moderate sensorineural hearing difficulties, presenile cataract, and renal failure, the diagnosis of Fechtner syndrome was made (1). The patient displayed a de novo mutation as none of his first degree relatives were affected. There were no antecedents of thrombotic events.

On the basis of the initial diagnosis of ITP, the patient was included in an AMG 531 clinical trial funded by Amgen (Thousand Oaks, CA, USA). Weekly subcutaneous treatment with romiplostim was started at a dose of 1 μg/kg body weight in October 2007 at a platelet count of 7,000/μl and was increased weekly to a maximum of 10 μg/kg body weight. This resulted in an increase of the platelet count to 66,000 platelets/μl in April 2008 (Fig. 1). No bleeding events or serious side effects such as thromboembolic events occurred. Follow-up bone marrow biopsies did not show evidence of any reticulin or collagen increase. However, despite continuous application of the maximum dose of 10 μg/kg body weight, platelet counts decreased again.

Received: July 13, 2011
Accepted after major revision: December 1, 2011
Prepublished online: January 25, 2012
doi:10.1160/TH11-07-0474
Thromb Haemost 2012; 107: 590–591

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Figure 1: Platelet counts during continuous treatment with romiplostim, arrows demonstrate start and stop of romiplostim.
after about 20 months, reaching pretreatment levels at 21 months after the beginning of treatment.

While in most patients with MYH9-related platelet disorders bleeding symptoms are mild, a minority of patients suffer from more severe bleeding. This patient received regular platelet transfusions for repetitive bleeding episodes at venous access for haemodialysis, putting his chances at odds for successful kidney transplantation due to allo-antibody formation. He did not experience any relevant side effects to romiplostim therapy. The reason for the fading of the treatment effect is unclear. Significant myelofibrosis is unlikely, as white blood cell and haemoglobin levels were still in the normal ranges after 21 months of therapy, and the peripheral blood smear did not show evidence of tear drops or other abnormalities. Furthermore, follow-up bone marrow biopsies at six and 12 months after treatment initiation did not show any evidence of bone marrow reticulin formation. However, subsequent bone marrow sampling was not performed due to the patient’s refusal. Anti-romiplostim-antibodies were not detected. Possible other reasons for treatment failure include stem cell depletion during romiplostim therapy. At months six and 12, the number of megakaryocytes in the bone marrow was not reduced, but a possible exhaustion at later stages cannot be entirely ruled out. Finally, desensitisation of the megakaryocytes to romiplostim might play a role, but the molecular basis for that remains to be elucidated. In a previous report by Pecci et al. (4) using eltrombopag, the patients were treated for a maximum of only six weeks, making it impossible to evaluate the long-term efficacy of this drug in MYH9-associated thrombocytopenia. Still, both drugs might be an appealing option for patients undergoing surgery or having repetitive episodes of major bleeding. Interestingly, the absolute platelet counts in our patient did not increase to levels reaching 100,000/μl. This mirrors the observations of the Italian study with eltrombopag (4). It remains unresolved whether this is due to ineffective platelet production or a reduced response of the megakaryocytes to thrombopoietin receptor agonists. Given the volume of MYH9-macrothrombocytopenia-derived platelets, a normalisation of the platelet count is not necessary to prevent bleeding and should be avoided to prevent thrombotic events. Other possible side effects are bone marrow fibrosis (6), and increases of bone marrow and peripheral blast counts in patients with myelodysplastic syndromes (7). Therefore, when using these compounds in MYH9-associated thrombocytopenia, the risk-benefit ratio should carefully be weighed.

To conclude, this report provides additional evidence that MYH9 thrombocytopenia-related bleeding symptoms can be treated by the administration of a thrombopoetin receptor analogon.

Conflict of interest:
A. Giagounidis is on the scientific advisory board of AMGEN.

References