First Successful Use of Eltrombopag Before Surgery in a Child With MYH9-Related Thrombocytopenia

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**Key Words**
MYH9-RD, thrombocytopenia, eltrombopag, prophylaxis

**Abbreviations**
MYH9—nonmuscle myosin IIa
MYH9-RD—MYH9-related disease
TPO—thrombopoietin

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**Abstract**

MYH9-related disease (MYH9-RD) is one of the most frequent autosomal-dominant forms of inherited macrothrombocytopenias and is caused by mutations in MYH9 (nonmuscle myosin IIa), the gene coding for the heavy chain of the nonmuscle myosin IIa. Affected individuals can present with isolated thrombocytopenia, and whereas only some will have bleeding events requiring intervention, nearly all will require the use of prophylactic platelet transfusions before surgery. Here we report the first prophylactic use of eltrombopag before surgery in a child with MYH9-RD. Our patient was a 13-year-old girl with an MYH9 S96L missense mutation who required a tympanoplasty due to chronic otitis media. Pretreatment microscopic platelet count was $10 \times 10^9/L$. The child was treated with eltrombopag starting 4 weeks before her planned surgery. On the day of surgery her platelet count was $70 \times 10^9/L$. She required no platelet transfusions and no abnormal bleeding was reported either during surgery or postoperatively. Given these results, the first reported in a child, we suggest that the use of this thrombopoietic agent should be further evaluated as a useful presurgical prophylactic option in this hereditary thrombocytopenia, thus avoiding the use of platelet transfusions and their associated risks, which include alloimmunization and the transmission of infectious agents. *Pediatrics* 2013;132:e793–e795
MYH9-related disease (MYH9-RD) is one of the most frequent autosomal-dominant forms of inherited macrothrombocytopenias and is caused by mutations in MYH9 (nonmuscle myosin IIa), the gene coding for the heavy chain of the nonmuscle myosin IIa. Affected individuals can present with isolated thrombocytopenia, and whereas only some will have bleeding events requiring intervention, nearly all will require the use of prophylactic platelet transfusions before surgery. Patients may also display extra-hematologic syndromic manifestations, including sensorineural hearing loss, present in nearly 70% of all MYH9-RD families, cataracts, and renal disease. Recently, Pecci et al reported that the orally bioavailable thrombopoietin (TPO) receptor agonist, eltrombopag, increases platelet counts in adults with MYH9-RD. Here we report the prophylactic use of eltrombopag before surgery in a child with MYH9-RD. Our patient was a 13-year-old girl with an MYH9 S96L missense mutation. Clinically, she had MYH9-RD nephritis and severe bilateral mixed hearing impairment. She did not have any reduction in kidney function and her serum creatinine and plasma protein levels were within normal ranges; however, she did have evidence of proteinuria. Baseline TPO levels before the administration of eltrombopag as measured by enzyme-linked immunosorbent assay were elevated (200 pg/mL; reference values: 0–30 pg/mL). Pretreatment microscopic platelet count was $10 \times 10^9$/L (Fig 1). Medical history was also notable for diffuse ecchymoses and menorrhagia and no previous surgeries or platelet transfusions.

A tympanoplasty was planned owing to a right chronic otitis media with perforated retraction pocket. Surgery was performed through an endaural approach, using an operating microscope. An incision was made into the ear canal and the remaining eardrum was elevated away from the bony ear canal. The portion of the eardrum retracted in the middle ear was removed and the tympanic perforation was closed by using a cartilaginous graft taken from the tragal cartilage. During middle ear surgery under an operating microscope, hemostasis cannot be achieved using direct pressure, electrocoagulation, or suture ligation. Only topical hemostatic agents may be used; however, these techniques require additional time in the operating room. Bleeding during the procedure can result in a number of complications, including difficulty in achieving a complete removal of the epidermic layer retracted in the middle ear, increased operating time, delayed wound healing, and infection.

After informed consent, eltrombopag (25 mg/day ×1 week, 50 mg/day ×3 weeks) was started 4 weeks before surgery. Platelet count (phase-contrast microscopy), liver enzymes, and renal function were measured weekly. Platelet count rose during the second week of treatment, and by day 33, the day of surgery, was $70 \times 10^9$/L (Fig 1). In vitro platelet aggregation as measured by Born’s method was within normal limits. The patient reported the remission of spontaneous bleeding after 17 days of treatment. No abnormal bleeding events were reported either during surgery or postoperatively, and the child recovered from her surgery without complication.

In general, and beyond the example provided in this case report, the risk/benefit ratio of short-term, presurgical TPO agonists in children with MYH9-RD thrombocytopenia has yet to be determined. This report provides the first example of such use in children, whereas 2 reports demonstrate the safety of eltrombopag administration in adult patients with MYH9-RD. Of importance, eltrombopag has been successfully used in 2 clinical trials including children with acquired immune thrombocytopenia. Despite these positive reports, it is important to note that adverse events associated with the use of eltrombopag have been identified. These include both minor events, consisting of headache, nausea, dry mouth, diarrhea, arthralgia, nonpetechial rash, and blurred vision, and major events, consisting of hepatobiliary laboratory abnormalities, thrombosis, and platelet counts decreased to levels lower than baseline. Additional potential risks also include bone marrow reticulin formation, bone marrow blasts in patients with myelodysplastic syndromes, cataracts, and phototoxicity. Nonetheless, no adverse effects were identified during and/or after the short-term eltrombopag
administration in our patient. No evidence of cataracts was detected by ophthalmologic examination 2 months after conclusion of treatment.

Given these results, the first reported in a child, we suggest that the use of this thrombopoietic agent should be further evaluated as a useful presurgical prophylactic option in this hereditary thrombocytopenia, avoiding the use of platelet transfusions and their associated risks. It is important that eltrombopag dosing requirements be individualized according to both the risk/benefit ratio of short-term administration and to the patient basal platelet count. The objective of treatment in this case was to obtain platelet counts above a level of $50 \times 10^9/L$. Future studies will be needed to better understand the safety of this strategy in the pediatric population with MYH9-related thrombocytopenia and for possible longer term therapies.

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