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Clinical Improvement without Increased Platelet Count with Eltrombopag in X-Linked Thrombocytopenia

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TITLE: Clinical Improvement without Increased Platelet Count with Eltrombopag in X-Linked Thrombocytopenia

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Abbreviation	*Definition*
WAS	Wiskott-Aldrich Syndrome
XLT	X-linked thrombocytopenia
XLN	X-linked neutropenia
ITP	Idiopathic Thrombocytopenia\
WASp	Wiskott-Aldrich syndrome protein
TPO	Thrombopoietin
TPO-RA	Thrombopoietin-receptor agonist
HSCT	Hematopoietic stem cell transplant
IVIG:	Intravenous Immunoglobulin
JAK/STAT	Janus kinase/signal transducers and activators of transcription.

To the Editor

Introduction:

Wiskott-Aldrich Syndrome (WAS) protein (WASp), encoded by WAS gene, is a multi-domain, adaptor protein that regulates actin-polymerization in the cytoplasm and RNA polymerase-II dependent transcription in hematoplymphoid cells[1]. WAS gene mutations have a broad range of phenotypic expressions usually grouped into three categories: Classical WAS, which manifest in immunodeficiency, autoimmunity, genomic instability, and cancer predisposition, X-linked neutropenia which present with neutropenia (XLN), and X-linked thrombocytopenia (XLT)[2–4].

Clinical presentation of WAS can be atypical and may require a full panel of diagnostic immunologic and hematologic tests before making the correct diagnosis to provide optimal treatment [3,5]. XLT, often misdiagnosed as Idiopathic thrombocytopenia (ITP), is a milder form of the disease associated with thrombocytopenia and small platelets. Microcytic thrombocytopenia is the hallmark of XLT leading to spontaneous and/or traumatic bleeding of varying severity[6]. In XLT patients, the incidence of malignancies is increased compared to general population but much lower than in classic WAS [3].

In the treatment of WAS and XLT a range of methods are employed based on the various phenotypic expressions from supportive care to more invasive options like splenectomy, hematopoietic stem cell transplant (HSCT), and gene therapy. Splenectomy can normalize platelet levels and sometimes correct mean platelet volume in XLT patients[7]. The use of thrombopoietin receptor agonists (TPO-RA) such as eltrombopag and romiplostim is approved for the treatment of ITP but has limited documented use in inherited thrombocytopenias[8–11].

Eltrombopag is an oral non-peptide TPO-RA with excellent bioavailability capable of stimulating platelet production by stimulating platelet precursor differentiation through signaling JAK/STAT pathway[9]. Eltrombopag used in the management of ITP in pediatric patients shows an increase in platelet count and reduced bleeding[12]. Eltrombopag can also be administered indefinitely to WAS/XLT patients who respond, increasing platelet count and reducing bleeding while awaiting the development of a low-risk curative treatment[13,14].

Clinical Presentation:

We report a rare case of a 9-year-old male of Asian descent recent immigrant to the USA, a product of a non-consanguineous marriage*, born full-term with no perinatal complications. He was diagnosed with XLT at 3 months of age in China with baseline platelet count ranging between 20 to 30,000/mm^3. He was found to have hemizygous WAS c.256C>T (p.Arg86Cys) mutation which was confirmed by us. The patient has previously been treated for frequent epistaxis with IV infusions of etamsylate and platelet transfusions. Of note, the patient also has a past surgical history significant for open-heart surgery at 6 months of age for a cardiac septal defect.*

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The patient was first seen in our emergency department at the age of 7 years with petechiae, ecchymoses, and intermittent, atraumatic high-volume epistaxis from both nares that is worsened with nasal manipulation, His initial platelet count was 26,000/mm^3. He had microcytic hypochromic anemia, presumably due to iron deficiency caused by recurrent epistaxis. The bleeding was controlled in the ED with local measures and aminocaproic acid.

During outpatient visit, the family was counseled and 25 mg of eltrombopag daily was started. Two weeks later the dose was increased to 50 mg daily due to persistent symptoms following which the family reported significant symptomatic improvement. In light of lack of platelet count response, we stopped eltrombopag and asked family to keep a bleeding journal. Within 4 days of stopping eltrombopag, the patient experienced a large nosebleed which was managed with local measures and aminocaproic acid. The patient experienced recurrent epistaxis in the ensuing weeks. Family insisted on restarting eltrombopag based on their observation of clinical response and eltrombopag was resumed at 50 mg daily. Within 2 weeks, family again reported reduced epistaxis and resolving bruises. The patient is currently stable on 50 mg Eltrombopag daily remaining asymptomatic/minimally symptomatic. (See Figure 1, epistaxis scoring was calculated using ISTH/SCC bleeding assessment tool. Epistaxis scoring was calculated using ISTH/SCC bleeding assessment tool [15]). Mean platelet volume (MPV) has been inconsistent ranging between 6.3 fL and 16 fL without correlation with symptoms or treatment.

Conclusions and Discussion:

The most commonly occurring clinical presentation of XLT is spontaneous and trauma-induced bleeding episodes. Managing bleeding episodes in is the goal of therapeutic options employed such as TPO- RAs until there is a definitive treatment becomes available. HSCT is considered largely curative in classical WAS as it provides a cure for all aspects of the disease contingent on whether hematologic and immune reconstitution is achieved [5]. However, the use of HSCT for XLT is still controversial, given the excellent long-term survival observed with medical management.

Eltrombopag use to increase platelet count in the pediatric population has been employed successfully in chronic ITP, severe aplastic anemia, and chronic hepatitis C infection[9]. Case reports of eltrombopag induced increase in platelet counts have been published in WAS[10,16] and in XLT[10,17]. One case of clinical response without numerical response was included in one report[10].

The known mechanism of action of Eltrombopag is to bind to a transmembrane portion of the TPO receptor, stimulating Megakaryocyte (MK) precursor cells and MK differentiation leading to an increase in platelet counts[18]. A systematic review of TPO-RA activity has also shown Eltrombopag appears to alter platelet activation, concerning levels of platelet-monocyte aggregates, soluble P-selectin, as well as possibly GPVI expression, and adhesion under flow[19,20]. However, Gerritts *et al* found no evidence of changes in agonist induced platelet activation by etrombopag[10].

Our report provides additional data for utilization of TPO-RAs in bleeding. The clinical improvement of this patient despite reduced platelet count over the 2-year course of treatment with eltrombopag suggests possible involvement of mechanisms other than an increase in platelet counts although an increased utilization of platelets at site of injury is also possible.

We conclude that TPO-RA may be effective even in the absence of a platelet number response and should considered in symptomatic management of XLT patients, and possibly other inherited thrombocytopenia cases.

FIGURE LEGEND: A: thrombopoietin receptor agonists (TPO-RA) dose. B: Platelet count (PLT) and epistaxis scores over time. ACA: Aminocaproic acid. Asterisk indicates prophylactic platelet transfusion prior to dental procedure.

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