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Update on the Use of Thrombopoietin-Receptor Agonists in Pediatrics

Jennifer Gebetsberger[1] Werner Streif[1] Christof Dame[2]

[1] Department of Pediatrics I, Medical University of Innsbruck, Innsbruck, Austria
[2] Department of Neonatology, Charité – Universitätsmedizin Berlin, Berlin, Germany

Address for correspondence Christof Dame, MD, Department of Neonatology, Charité - Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany (e-mail: christof.dame@charite.de).

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Abstract

This review summarizes the rationale and current data on the use of thrombopoietin receptor agonists (TPO-RAs) for treating severe thrombocytopenia in infants, children, and adolescents. It focuses on substances that have been approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for pediatric patients. Romiplostim and eltrombopag are already established as second-line treatment for persistent or chronic immune thrombocytopenia (ITP). As in adults, TPO-RAs are currently also evaluated in severe aplastic anemia (SAA), chemotherapy-induced thrombocytopenia (CIT), myelodysplastic syndromes (MDS), and poor engraftment after hematopoietic stem cell transplantation in pediatric and adolescent patients. Moreover, studies on the implication of TPO-RA in treating rare inherited thrombocytopenias, such as Wiskott-Aldrich syndrome (WAS), congenital amegakaryocytic thrombocytopenia (CAMT), or *MYH9*-associated thrombocytopenia, deserve future attention. Current developments include testing of avatrombopag and lusutrombopag that are approved for the treatment of thrombocytopenia associated with chronic liver disease (CLD) in adult patients. In pediatric and adolescent medicine, we expect in the near future a broader use of TPO-RAs as first-line treatment in primary ITP, thereby considering immunomodulatory effects that increase the rate of sustained remission off-treatment, and a selective use in rare inherited thrombocytopenias based on current clinical trials.

Keywords

- avatrombopag
- eltrombopag
- lusutrombopag
- romiplostim
- thrombopoietin
- thrombopoietin receptor
- thrombopoietin receptor agonist
- thrombocytopenia
- platelet count

Zusammenfassung

Diese Übersicht fasst die Rationale und aktuellen Daten zur Anwendung von Thrombopoietin-Rezeptor-Agonisten (TPO-RAs) bei der Behandlung schwerer Thrombozytopenien bei Kindern und Jugendlichen zusammen. Der Fokus liegt auf Substanzen, die von der U.S. Food and Drug Administration (FDA) und der European Medicines Agency (EMA) für pädiatrische Patienten zugelassen wurden. Romiplostim und Eltrombopag sind bereits als Zweitlinientherapie für die chronische immunvermittelte Thrombozytopenie (ITP) etabliert. Wie bei Erwachsenen wird die Anwendung von TPO-RAs auch bei schwerer aplastischer Anämie (SAA), Chemotherapie-induzierter Thrombozytopenie (CIT), myelodysplastischem Syndromen (MDS) und unzureichender Megakaryopoiese nach hämatopoietischer Stammzelltransplantation bei pädiatrischen Patienten untersucht. Darüber hinaus verdienen Studien zur Bedeutung von TPO-RA bei der

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Schlüsselwörter
- Avatrombopag
- Eltrombopag
- Lusutrombopag
- Romiplostim
- Thrombopoietin
- Thrombopoietin Rezeptor
- Thrombozyten
- Thrombozytopenie

Behandlung seltener erblicher Thrombozytopenien, wie dem Wiskott-Aldrich-Syndrom (WAS), der kongenitalen amegakaryozytären Thrombozytopenie (CAMT) oder der *MYH9*-assoziierten Thrombozytopenie Aufmerksamkeit. Aktuelle Entwicklungen umfassen randomisierte kontrollierte Studien zur Anwendung von Avatrombopag und Lusutrombopag, die bei erwachsenen Patienten bereits zur Behandlung von mit chronischer Lebererkrankung (CLD) assoziierter Thrombozytopenie zugelassen sind. Basierend auf den aktuellen klinischen Erfahrungen und Studienergebnissen erwarten wir auch bei Kindern und Jugendlichen zukünftig eine Anwendung von TPO-RAs als „first-line" Medikation bei primärer ITP, wobei die immunmodulatorischen Effekte und die Rate einer anhaltenden Remission nach Therapiebeendigung von besonderem Interesse sind, sowie eine selektive Anwendung von TPO-RAs bei Kindern und Jugendlichen mit seltenen angeborenen Thrombozytopenien.

Introduction

Prevention of major bleeding in pediatric and adolescent patients with severe inherited or acquired thrombocytopenia is still very challenging.[1] The frequency and severity of bleeding is not strictly associated with the number of platelets,[2] but may be accompanied by platelet dysfunction, particularly in inherited thrombocytopenias.[3] Inherited thrombocytopenias are rare, but result from a wide variety of genetic defects and must often be understood as symptom of a multisystemic disorder.[4] Since prophylactic transfusion of (adult) donor platelets associates with potential harm through selective inflammatory or immune processes,[5,6] pharmacologic treatment options gain a more predominant position in strategies for preventing bleeding complications. Over the last decade, the spectrum of options to manage inherited thrombocytopenias or bleeding disorders has been significantly expanded. Nowadays, the administration of thrombopoietin receptor agonists (TPO-RAs) in children and adolescents is also included, as it is most intensively studied for second-line treatment in persistent and chronic primary immune thrombocytopenia (ITP).

TPO-RAs are a class of drugs that mimic the action of thrombopoietin (TPO), the primary humoral regulator of megakaryopoiesis.[7] Through binding to the TPO receptor (TPO-R), they activate downstream JAK2/STAT5 signaling pathways, thereby enhancing the proliferation and differentiation of megakaryocytes (MK) in the bone marrow.[8,9] TPO-RAs effectively increase circulating platelet counts. They replaced first-generation megakaryopoietic growth factors, such as recombinant human TPO (rhTPO), pegylated megakaryocyte growth and development factor (PEG-rHuMGDF), and TPO–cytokine fusion proteins (e.g., promegapoietin), following reports that rhTPOs were associated with the risk of developing anti-TPO antibodies.[10] The group of TPO-RAs consists mainly of TPO peptide mimetics (e.g., romiplostim) and TPO non-peptide mimetics (e.g., eltrombopag).[11] These substances are used mainly to selectively treat pediatric and adult patients with persistent or chronic primary ITP, severe aplastic anemia (SAA), and adult patients with thrombocytopenia associated with chronic liver disease (CLD).[11–13] The use of TPO-RAs has significantly reduced the long-term immunologic or infectious complications associated with repetitive platelet transfusions, potent immunosuppressants, and splenectomy.[14]

This review summarizes current data on the use of TPO-RAs for treating severe thrombocytopenia in infants, children, and adolescents. It focuses on substances approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in these age groups. Specific emphasis is given to the rationale and the limited data on the use of TPO-RAs in rare inherited thrombocytopenias. Despite often moderately (or eventually highly) elevated endogenous TPO plasma concentrations in these thrombocytopenias, the individual use of TPO-RA follows the concept of inducing TPO-R downstream signaling through alternate TPO-R binding or increasing platelet mass to enhance platelet activation, immune response, or immune modulation. Future developments in the use of various TPO-RAs in pediatric patients are outlined based on ongoing registered randomized controlled trials (RCTs).

Methods

For this narrative review, a literature search strategy was performed by consulting the PubMed platform of the National Center for Biotechnology Information (NCBI). The literature search included peer-reviewed papers, published in English and German language, updated from January 2018 to May 2023. We used the MeSH term "platelet disorders" *or* "thrombocytopenia" *and* "child" *or* "pediatrics" *or* "adolescent" *and* the search terms "romiplostim" *or* "eltrombopag" *or* "avatrombopag" *or* "lusutrombopag" *or* "hetrombopag," respectively. We also searched in the resource provided by the U.S. National Library of Medicine for clinical trials (https://clinicaltrials.gov/) on the use of TPO-RA in pediatric and adolescent patients. Additionally, results from personal communication within the THROMKIDplus working group of the *Gesellschaft für Thrombose und Hämostaseforschung* (GTH) during the pediatric GTH (pedGTH) meeting held in September 2022 in Igls (Austria) were considered.

Thrombopoietin Receptor Agonists: Similar, but Different

Two different TPO-RAs, romiplostim (TPO peptide mimetic) and eltrombopag (TPO non-peptide mimetic/small molecule), were both licensed in 2008, and subsequently approved for use in pediatric and adolescent patients. They are currently widely used for the treatment of persistent (disease duration of 4–12 months) or chronic (>12 months of disease) ITP in children older than 1 year and adults who are refractory to standard treatment.[15] Eltrombopag has been also approved for children aged over 2 years with SAA in combination with standard immunosuppressive treatment.[11,12] The use of both drugs was initially very carefully monitored, especially concerning their putative risk of causing bone marrow fibrosis that usually reverses after discontinuation of treatment[16–18] and proapoptotic effects of TPO in experimental models of brain injury.[19–21]

Notably, there are marked differences between romiplostim and eltrombopag (►Table 1), which may explain different responsiveness and compliance of patients, in particular children. More recently, two additional nonpeptide TPO-RAs, avatrombopag and lusutrombopag, are available and already used in adults for the treatment of ITP (avatrombopag) and thrombocytopenia associated with CLD (both substances).[11,12] In addition, hetrombopag has been developed in China as fourth non-peptide TPO-RA and successfully applied in adults with persistent or chronic ITP and SAA.[22–24] Due to the variety of these substances (►Table 1), it is important to understand pharmacological characteristics when evaluating treatment options for children and adolescents with ITP or severe inherited thrombocytopenias at risk for hemorrhage and bleeding disorders.

Romiplostim is a 14-amino acid peptide with no sequence homology to TPO. This chimeric molecule (60 kDa) is composed of human IgG1 antibody Fc fragments, which binds directly and competitively to the extracellular domain of the TPO-R and mostly stimulates mature megakaryocyte precursors.[8] Romiplostim is subcutaneously (sc) applied and, in pediatric RCTs, mostly given in titrated doses (starting with 1 µg/kg per week up to 10 µg/kg per week) upon the individual response in platelet counts. In children and adolescents (≥1 year to <18 years) with primary ITP (≥6 months of disease), a multicenter phase 3 RCT ($n = 62$ patients; 2:1 allocation; 1 µg/kg/week single dose sc; increasing doses with 1 µg/kg/week, up to 10 µg/kg/weeks; NCT01444417) showed in 52% of patients the efficacy of romiplostim over a treatment period of 24 weeks (primary endpoint: platelet counts ≥50 to ≤200/nL).[25] Systematic reviews indicated a beneficial effect as second-line treatment in children older than 1 year with persistent/chronic ITP.[26–28] These reviews, however, did not include most recent data of the subsequent international phase 3b RCT on the long-term use of romiplostim in children with ITP, following the same protocol over a 36-month period (NCT02279173). This RCT showed a median remission rate of 50.0% (interquartile range (IQR) 16.7–83.3%) during the first 6 months, increasing to 78.2% (IQR 26.7–90.4%) during the overall 36-month treatment period.[29] Eleven patients (5.4%) achieved sustained responses (consecutive platelet counts ≥50/nL without other ITP medications for ≥24 weeks). Treatment-related adverse events (AEs) occurred in 56 out of 203 patients (27.6%, including epistaxis, headache, and vomiting), with 8 (3.9%) experiencing serious treatment-related AEs. Together with 43 cases (21.2%) with lack of efficacy, this finding contributed to the discontinuation of treatment in 95 out of 203 patients (46.8%). There were eight cases (3.9%) of neutralizing antibodies (romiplostim, $n = 7$ [transient: $n = 4$]; endogenous TPO, $n = 1$ [transient]). Bleeding occurred in 141 patients (69.5%), decreasing over time; grade ≥3 bleeding events occurred in 20 (9.9%). At year 2 of treatment, 8 of 63

Table 1 Clinically relevant characteristics of thrombopoietin-receptor agonists (TPO-RA)

	Romiplostim	Eltrombopag	Avatrombopag	Lusutrombopag	Hetrombopag
Structure	Peptide TPO-RA	Small molecule/ non-peptide TPO-RA	Small molecule/ non-peptide TPO-RA	Small molecule/ non-peptide TPO-RA	Small molecule/ non-peptide TPO-RA
Binding site	Binds competitively to the extracytoplasmic domain of the TPO-R in same ways as TPO	Binds to the transmembrane and juxtamembrane domains of the TPO-R	Binds to the transmembrane domain of the TPO-R	Binds to the transmembrane domain of the TPO-R	Binds to the transmembrane domain of the TPO-R
Effect on endogenous thrombopoietin	Can displace TPO from its receptor	No displacement of TPO, may be additive	No displacement of TPO, may be additive	No displacement of TPO, may be additive	No displacement of TPO, may be additive
Confirmed signaling pathways	JAK2/STAT5 P13K/Akt ERK STAT3	JAK2/STAT5 P13K/Akt ERK	JAK2/STAT5 STAT3 ERK	JAK2/STAT5 STAT3	JAK2/STAT5 P13K/Akt ERK STAT3
Route of administration	Subcutaneous	Oral	Oral	Oral	Oral
Dosing frequency	Weekly	Daily	Daily	Daily	Daily
Approved indications by FDA and EMA	• Immune thrombocytopenia (adults and children)	• Immune thrombocytopenia (adults and children) • Hepatitis C–associated thrombocytopenia (adults) • Severe aplastic anemia (adults and children)	• Periprocedural thrombocytopenia in chronic liver disease patients (adults) • Immune thrombocytopenia (adults)	• Periprocedural thrombocytopenia in chronic liver disease patients (adults)	• None so far

evaluable patients (12.7%) showed grade 2 reticulin staining in bone marrow specimens. Although the authors concluded that long-term romiplostim resulted in sustained on-treatment platelet responses with an overall safety profile consistent with previous studies,[29] an updated meta-analysis is pending.

Concerning rare inherited disorders, the use of romiplostim has been reported in one patient with macrothrombocytopenia in Fechtner syndrome (OMIM #155100),[30] and in one patient with another missense mutation (c.5507A >G) in the *MYH9* gene locus, encoding the non-muscle myosin heavy chain II-A (OMIM #160775).[31] Pecci et al described a family with congenital amegakaryocytic thrombocytopenia (CAMT) caused by a homozygous mutation (p.R119C) of the *THPO* gene (CAMT2; OMIM #620481) and low circulating TPO concentrations, who was successfully treated with romiplostim.[32] A retrospective analysis on the safety and efficacy of romiplostim treatment (9 µg/kg weekly for at least 4 weeks) showed benefits in reducing thrombocytopenia and bleeding tendency in 67 children (median age: 1–3 years) with genetically confirmed Wiskott-Aldrich syndrome (WAS, an inherited X-linked disorder caused by mutations in the *WAS* gene, encoding WAS protein that exhibits three distinct functional domains important for actin cytoskeleton control; NCT04350164), in which thrombocytopenia is characterized by small platelet size and increased splenic destruction involving both immune and non-immune mechanisms. The individual follow-up was performed for 8 months (range: 1–12 months).[33] Complete or partial responses (platelet counts >100/nL or >50/nL after 1 week) were observed in 22 (33%) and 18 (27%) patients, respectively. In the non-responder group, the risk of hemorrhagic events decreased significantly to 21% after the first month of treatment.[33] An ongoing monocentric randomized open-label, two-arm phase 2 trial recruiting 30 children with WAS (age < 18 years) compares the effect of romiplostim (1×9 µg/kg/week sc for 4 weeks) versus eltrombopag (2–3 mg/kg/d orally [po] in the age of 0–5 years; 75 mg/d po in the age of ≥ 6 years for 4 weeks) with a primary endpoint of platelet counts > 100/nL and with a switch in the study arm of non-responders (NCT04371939, Shcherbina A et al, Moscow, Russia).

Another monocentric open-label phase 1 / phase 2 trial currently analyses the short-term safety and efficacy of romiplostim in patients at the age of 0 to 21 years with inherited and acquired hematopoietic failure. This study recruits 25 patients into two study arms. *Arm A*: romiplostim treatment (1×5 µg/kg/weeks sc, increasing with additional 2.5 µg/kg/week to a maximum of 20 µg/kg/week for 24–52 weeks) in (1) aplastic anemia, (2) refractory cytopenia of childhood without an evidence of cytogenetic abnormality with predisposition to leukemia, (3) myelo-suppression contributing to severe pancytopenia, and (4) inherited bone marrow failure without chromosomal fragility disorder. *Arm B*: romiplostim treatment (1×2 µg/kg/weeks sc, increasing with additional 1 µg/kg/week to a maximum of 10 µg/kg/week for 24–52 weeks) in (1) myelo-suppression with thrombocytopenia in children with solid tumors secondary to chemotherapy or radiation therapy, and (2) patients undergoing stem cell transplantation and experiencing persistent thrombocytopenia. Primary outcome is a platelet number >100/nL (NCT04478227; Sharathkumar A et al, Iowa, United States). Concerning the use of romiplostim in CIT, a retrospective multicenter study in children and young adults (3–33 years age) with Ewing sarcoma (of different stages, including bone metastases) showed safety of romiplostim and its efficacy associated with higher doses (starting dose: 3 µg/kg [range: 1–5 µg/kg], with dose escalation weekly or every other week by 1 to 2 µg/kg [maximum dose: 4–10 µg/kg]).[34] This information is important, since (1) CIT is the primary issue in maintaining high treatment intensity in Ewing sarcoma, and (2) the implication of TPO/TPO-R in regulating bone hemostasis.[35,36]

Eltrombopag is an allosteric small molecule which binds to the transmembrane and juxtamembrane domains of the TPO-R on the surface of platelet-producing cells, stimulating MK precursor cells and MK differentiation by activation of the STAT3, P13K/Akt, and ERK signaling pathways down of the TPO-R domain.[37,38] However, eltrombopag also has off-target effects. As such, it chelates both extra- and intracellular calcium and iron, and can shuttle iron out of cells.[39] The iron-chelating action has an antiproliferative effect on leukemic cell lines,[40] and a TPO-independent function on stimulating stem cells and MK precursors in vivo.[41,42]

Eltrombopag is an oral medication that is taken once daily. It is approved for the treatment of children older than 1 year and adolescents with persistent/chronic ITP or SAA, and in adults with hepatitis C-associated thrombocytopenia. Established doses are 0.7 mg/kg/d (maximum: 2 mg/kg/d) in children at the age between 1 and 5 years, and 25 mg/d (maximum: 75 mg/d) at the age between 6 and 17 years. It is recommended to monitor liver function, and dose adjustments can be necessary in certain populations (e.g., Asian patients and patients with impaired liver function).

Most experience in using eltrombopag in children and adolescents results from the PETIT (Eltrombopag in PEdiatric patients with Thrombocytopenia from ITp) trials.[43,44] The efficacy of 7 or 13 weeks' therapy with eltrombopag (up to 2 mg/kg/d in children at an age between 1 and 5 years; up to 75 mg/d at higher age) as second-line treatment was compared with that of placebo in patients aged 1 to 17 years with previously treated ITP (≥6 months) in these multicenter phase 2 and 3 RCTs (PETIT, NCT00908037, and PETIT-2, NCT01520909). The platelet response rate (primary endpoint of PETIT) and the sustained platelet response rate (primary endpoint of PETIT-2) were significantly higher with eltrombopag than with placebo. In PETIT-2, 63 patients were assigned to receive eltrombopag, and 29 patients assigned to receive placebo. In 3 out of 63 patients, eltrombopag treatment was discontinued because of increased liver aminotransferases, while one withdrew occurred in the placebo group because of abdominal hemorrhage. Twenty-five (40%) patients who received eltrombopag, compared with one (3%) patient who received placebo, achieved the primary outcome of platelet counts of at least 50/nL for 6 of the last 8 weeks of the double-blind period (odds ratio: 18; $p < 0.001$).

Responses were independent of the children's age. Proportionately, fewer patients who received eltrombopag (23 of 63 patients, 37%) had WHO grades 1 to 4 bleeding at the end of the double-blind study period than those who received placebo (16 of 29 patients, 55%); grades 2 to 4 bleeding events were similar (three [5%] patients who received eltrombopag vs. two [7%] patients who received placebo).[44] A recent meta-analysis of both PETIT trials, however, indicated that in children there was no overall difference between eltrombopag (total $n = 108$) and placebo (total $n = 51$) for a platelet response $\geq$50/nL (RR: 3.93; 95% CI: 0.56–27.79) and the number of AEs (RR: 0.59; 95% CI: 0.25–1.41) as secondary outcome measures. However, a lower incidence of bleeding was observed (RR: 0.47; 95% CI: 0.27–0.83). Notably, the certainty of evidence concerning these measures was low to moderate.[45] The results of the meta-analysis contrast to reports of nonrandomized (mostly retrospective observational) cohorts successfully treated with eltrombopag as second-line treatment of persistent/chronic ITP in childhood and adolescence.[46–51] This raises the question, how previous first-line treatment with other medication or their combination with eltrombopag affects treatment response. In adults, a meta-analysis on multiple drugs for the treatment of ITP showed that the efficacy of eltrombopag plus rituximab was significantly superior than placebo or dexamethasone alone.[52] A systematic review of prospective studies in pediatric ITP showed that rituximab and TPO-RAs had similar rates of overall platelet response ($\geq$50/nL), but rituximab was associated with higher rates of rescue therapy.[53] This indicates that (1) comparative studies with eltrombopag and other drugs for second-line treatment of pediatric ITP and (2) RCTs on the use of eltrombopag for first-line treatment (either alone and combined with standard treatment) are warranted. Indeed, the results of a multicenter, open-label, phase 3 RCT (NCT03939637) that compares eltrombopag to standard first-line management (steroids vs. immunoglobulins vs. Rho(D) immunoglobulin) in children ($n = 162$) with newly diagnosed ITP ($\leq$3 months from diagnosis) are expected in 2024.[54]

The fact that eltrombopag binds to the transmembrane and juxtamembrane but not to the classical extracellular binding domains of the TPO-R makes this substance appealing for use in rare inherited thrombocytopenia, especially in CAMT. This group of congenital thrombocytopenias is characterized by ineffective megakaryopoiesis without typical features of syndromic conditions. In most cases, CAMT is caused by deleterious (homozygous or compound heterozygous) mutations in the *MPL* gene CAMT-MPL/CAMT1 (OMIM 604498).[55] Seventy percent of all mutations are located in the five coding exons of the extracellular cytokine receptor homology domain, providing the rationale to use a TPO-RA-such as eltrombopag, which finds alternate receptor binding and activates downstream signaling.[56] Yet, Pecci et al reported on 12 patients with *MYH9*-associated thrombocytopenia (<50/nL) treated with eltrombopag for 3 weeks (NCT01133860).[57] A total of eight patients achieved platelet counts of $\geq$100/nL or a threefold increase in baseline platelet count. In three patients, a doubling of the baseline value was still achieved, and in only one patient there was no platelet increase. Only mild headache was reported as adverse effect. Zaninetti et al reported in a multicenter, open-label, dose-escalation phase 2 trial 20 patients with *MYH9*-associated thrombocytopenia (NCT02422394) who experienced a decrease in bleeding tendency during eltrombopag treatment.[58,59] Case reports of successful treatment with eltrombopag are available in five other patients with *MHY9*-associated thrombocytopenia.[60–63]

Besides one case report,[64] Gerrits et al described eight patients with WAS (grades 2–4) who were treated with eltrombopag for a time period ranging from 22 to 209 weeks (NCT00909363).[65] In five patients an increase in platelet count to >50/nL or a doubling of the baseline value was achieved during treatment with eltrombopag. Six patients showed reduced bleeding symptoms. Two patients were classified as non-responders responders. One of these patients was subsequently successfully treated with romiplostim. No serious side effects were observed in any of these patients. Moreover, one patient has been reported who was successfully treated with eltrombopag for the hereditary A*NKRD26*-related thrombocytopenia (OMIM 188000),[66] with normal platelet size, modestly increased TPO plasma concentrations, high number and size of megakaryocyte precursors, but delayed differentiation.[67] In addition, nine patients with WAS were treated with eltrombopag in the aforementioned study by Zaninetti et al.[58] In five patients, mild bleeding symptoms disappeared, while one patient was considered as non-responder.[58] Currently, a prospective, open-label, two-arm RCT is conducted to evaluate the safety and efficacy of eltrombopag in comparison to romiplostim for the treatment of thrombocytopenia in pediatric patients with WAS, and the results are expected to be published in 2024 (NCT04371939, Shcherbina A et al, Moscow, Russia).

Of note, the use of eltrombopag may be extended to other systemic diseases or conditions associated with thrombocytopenia in children and adolescents. As in adults, eltrombopag has been tested in patients aged 1 to 18 years with SAA in combination with cyclosporine A (CsA) versus CsA alone. Recruitment of this phase 1/phase 2 open label trial (ELTROPLASTIC, NCT03243656) has been completed, but publication of the results is pending (Ahmed MA et al, Asyut, Egypt). There are two other trials in SAA ongoing: A multicenter phase 2 RCT testing eltrombopag combined with cyclosporine and human anti-thymocyte globulin (hATG) versus hATG and CsA as first-line treatment (NCT03413306; Novichkova G and Maschan A, Moscow, Russia), and a multicenter, open label, intrapatient dose escalation phase 2 study to characterize the pharmacokinetics of eltrombopag in combination with immunosuppressive therapy in pediatric patients with previously untreated or relapsed/refractory SAA or recurrent aplastic anemia (NCT03025698, United States).

In pediatric oncology, an open label, single-arm prospective pilot trial (phase 1) currently aims to test eltrombopag in patients aged 1 to 18 years undergoing intensive chemotherapy for malignant solid tumors (NCT04485416, Pawar A et al,

Sacramento, California, United States). REGALIA, a prospective phase 2 RCT, currently recruits pediatric patients to demonstrate whether eltrombopag improves poor graft function after allogenic hematopoietic cell transplantation (NCT03948529, Yakoub-Agha I et al, Lille, France).

These ongoing studies suggest that the use of eltrombopag may be extended in pediatric thrombocytopenia of different origin.

Avatrombopag, a more recently developed TPO-RA, is also an oral non-peptide small molecule that apparently binds to the TPO-R similar to eltrombopag, but does not have any dietary limitations.[68,69] Therefore, avatrombopag may potentially be more suitable in pediatrics. Avatrombopag has been approved by FDA in adult patients for the treatment of thrombocytopenia-associated CLD,[70] and subsequently for second-line treatment of ITP.[71,72] A recent systematic review comparing various TPO-RAs in adults with persistent or chronic ITP showed that avatrombopag may yield the highest efficacy, because it has the most favorable balance of benefits and acceptability.[73] Thus, recent studies focus on the therapeutic values of switching TPO-RA treatment from romiplostim or eltrombopag to avatrombopag. An observational multicenter trial in adults ($n = 44$) with chronic ITP showed a significant benefit of avatrombopag in 14 non-responders to previous treatment with romiplostim or eltrombopag. On avatrombopag, 41/44 patients (93%) achieved a platelet response (≥50/nL) and 38/44 patients (86%) achieved a complete response (≥100/nL). The median platelet count was 28/nL on romiplostim/eltrombopag versus 88/nL on avatrombopag ($p = 0.025$). Fifty-seven percent of patients receiving concomitant ITP medications before switching discontinued them after switching, including 63% of patients permanently receiving corticosteroids.[74] This indicates that in heavily pretreated chronic ITP patients, avatrombopag can be a very attractive choice of TPO-RAs. The efficacy and safety of avatrombopag as first choice TPO-RA is also currently tested in an international multicenter phase 3 RCT with open-label extension phase in pediatric and adolescent patients (age of 1–17 years) with persistent/chronic ITP ($n = 72$; 3:1 allocation). Herein, avatrombopag (20 mg/d po) is tested as second-line treatment in study arm A for 12 weeks and in study arm B for up to 2 years (NCT04516967, Sobi Inc., United States). Concerning rare inherited thrombocytopenias, one adult patient with a *MYH9*-related disorder was recently successfully treated with avatrombopag, following failed treatment with eltrombopag.[75]

Lusutrombopag, another more recently developed TPO-RA, is also an oral non-peptide small molecule, which can activate the TPO-R signal transduction pathway as endogenous TPO.[76] It was first approved in Japan by Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of thrombocytopenia associated with CLD in adult patients.[77] In 2018, the substance was also approved for this indication by FDA and EMA. In single patients, portal vein thrombosis has been reported as serious AE associated with lusutrombopag. Apparently, no indication for ITP or IT is yet being pursued. Data on the use of lusutrombopag in children and adolescents are not accessible yet.

Hetrombopag is another similar oral TPO-RA that has been recently developed in China and tested for various conditions of thrombocytopenia in adults, including chronic ITP.[22,78–80] It is not yet approved for clinical use by the FDA and EMA. There are currently no data on the use of hetrombopag in pediatrics accessible. However, the results of a monocentric two-part, double-blind, randomized, placebo-controlled, and open-label phase 3 study to investigate the efficacy and safety of hetrombopag in pediatric patients ($n = 117$, age 6–17 years) with previously treated ITP (≥6 months) are expected to be completed soon (NCT04737850, Wang et al,[48] Beijing, China).

Switching between TPO-RAs

TPO-RAs differ in their molecular structure, binding sites, pharmacokinetic profile, and the manner in which they stimulate the TPO-R. In pediatric ITP, the efficacy and safety of two TPO-RA, romiplostim and eltrombopag, have been compared not only to placebo but also directly in a total of 261 patients aged 1 to 17 years,[81] included in the aforementioned RCTs.[25,43,44] These studies confirmed that TPO-RAs were superior to placebo, but found no significant difference in the efficacy and safety between romiplostim and eltrombopag.[81] Similarly, a previous retrospective multicenter trial (ICON2), which compared TPO-RA treatment in 79 children (28 eltrombopag, 43 romiplostim, 8 trialed on both) at different stages of ITP (18% with new diagnosed, 22% with persistent, and 61% with chronic ITP), showed similar response rates (platelets >50/nL) with romiplostim (86%) and eltrombopag (81%). However, only 40% of patients demonstrated a stable response with consistent dosing over time.[82] This raises the question of whether switching between TPO-RAs can provide beneficial longer-term effects. Unlike romiplostim, eltrombopag and avatrombopag do not compete with endogenous TPO for the classical TPO-R binding site (►Table 1). Binding to the classic TPO-R domain may induce greater Akt pathway activation compared with JAK2/STAT5 effects following transmembrane TPO-R activation.[83] These subtle mechanistic differences seem to have clinically relevant effects, as patients experiencing toxicities or lack of efficacy with one TPO-RA may benefit from switching to an alternative TPO-RA. Consequently, the most common reasons for switching include loss or lack of efficacy of the initial TPO-RA followed by patient preferences (oral, less frequent drug taking without food restrictions) or side effects.[84,85] The potential impact of switching from eltrombopag to avatrombopag was retrospectively studied in 11 children with chronic ITP, who changed medication due to ineffectiveness ($n = 7$), adverse effects, or inconvenience. Overall response was achieved in 9 out of 11 patients (including 2 who had responded to eltrombopag). The median platelet count increased from 7/nL (range: 2–33/nL) up to 74/nL (15–387/nL; $p < 0.05$), with 6 out of 11 achieving complete remission (>100/nL). Notably, treatment was terminated in

7 out of 11 patients within 3 to 6 months after switching to avatrombopag.[86]

Importantly, recent studies generally indicate that pharmacologic differences among TPO-RA therapies may have real-life effects on the efficacy of agents in the individual patient.[12,74,83,84] In addition, the pharmacokinetics of different TPO-RAs vary considerably, particularly in terms of maximum concentration (C_{max}), area under the curve (AUC_{0-inf}), and time to maximum concentration (T_{max}). This variation is particularly notable for eltrombopag, where food composition can interfere with absorption or causes chelation of polyvalent cations, in contrast to avatrombopag and lusutrombopag.[11] In comparison to orally administered TPO-RA, administration of romiplostim in adult ITP patients has been reported to result in exaggerated pharmacologic effects, leading to wide variations in platelet counts.[11] An unexpected but important outcome of TPO-RA treatment in adult ITP patients is that up to 30% achieve sustained remission off-treatment (SROT). While romiplostim and eltrombopag demonstrate similar SROT rates, recent data suggest that first and early use of romiplostim, especially within the first year of diagnosis, may be associated with higher SROT rates.[87] This directs current research toward exploring the immunomodulatory effects of TPO-RA, both as standalone treatment and in combination with other first- or second-line drugs used in pediatric and adult ITP.

Immunomodulation by TPO-RA

Although the primary mechanism of action of all TPO-RAs is to increase platelet production, they also exhibit immunomodulatory effects. These include stimulation of regulatory T and B cell activities and promoting a macrophage switch from a pro-inflammatory to an anti-inflammatory phenotype.[88–92] Growing evidence suggests that TPO-RAs support or even induce SROT in adult ITP.[88,93] For adults with primary ITP ($\leq$6 months of disease) showing an insufficient response to first-line treatments like corticosteroids and immunoglobulins, a multicenter phase 2 RCT demonstrated treatment-free remission (platelets >50/nL) in 32% of patients for at least 6 months posttreatment.[94] This led to the FDA approval for extending romiplostim use as first-line treatment in newly diagnosed adult ITP.

In young adults with primary ITP treated with first-line romiplostim (iROM study), SROT was linked with a more rapid increase in platelet mass, but suppression of $CD4^+CD25^-$ cells,[88] higher FOXP3 and GATA3 mRNA expression in regulatory T cells and Th2 cells, respectively,[93] as well as higher circulating levels of TGF-β than in relapsed patients.[88,93] In adult ITP, eltrombopag normalized elevated monocyte counts, the IFN-γ/IL-4 ratio, and restored Th1/Th2 imbalance,[95] while in pediatric ITP, eltrombopag was found to mediate macrophage polarization from the M1 to M2 phenotype.[92] These immunomodulatory effects strongly argue for using TPO-RA as first-line treatment in ITP to efficiently achieve a rapid increase in platelet counts. Such increase in platelet mass not only stabilizes per se hemostasis and reduces the portion of activated platelets but also may modulate the immune response and induce immune tolerance in pediatric ITP.[93,96]

Future Directions

There are some future directions in treating inherited thrombocytopenias with TPO-RAs:

- TPO-RAs have shown promise in the treatment of some subtypes of inherited thrombocytopenias such as WAS, *ANKRD26*-related thrombocytopenia, and *MYH9*-related disease. However, it is important to identify the specific conditions (e.g., type of genetic variant) in which pediatric patients may benefit from a selective TPO-RA therapy.
- Further studies are needed to determine the optimal dosing and duration of TPO-RA therapy in pediatric patients with severe inherited thrombocytopenias. This must include careful monitoring of bleeding risks.
- TPO-RAs may be used in combination with other treatments, such as antibodies or immunomodulants, to achieve better outcomes in pediatric patients with ITP.
- While TPO-RAs have been shown to be safe and effective in the short term, there is a need for long-term safety studies to determine any potential adverse effects associated with longer-term TPO-RA therapy in children and adolescents.
- The impact of TPO-RA for SROT in newly diagnosed or persistent ITP deserves further research and clinical trials.

Conclusion

TPO-RAs have shown promise in the treatment of persistent/chronic, acquired or rare inherited thrombocytopenias in children and adolescents. The long-term follow-up of patients included in the pivotal clinical studies and "real-life" data generally provide reassuring results. Several of the initial theoretical concerns, such as uncontrolled stem cell proliferation and myelofibrosis, have not materialized. However, the long-term safety and efficacy of TPO-RAs in children and adolescents still need to be evaluated. Therefore, it is important to discuss the potential benefits and risks of TPO-RAs during the counseling of families. Future research will focus on optimizing dosing and duration of therapy, investigating combined therapies, and ensuring long-term safety of the various TPO-RAs.

Conflict of Interest

WS: Grants or contracts from any entity: SOBI, Octapharma, Biotest, Pfizer, Takeda, Roche, CSL-Behring, Bayer, ÖHG; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Takeda, Biotest, SOBI, Roche; Participation on a Data Safety Monitoring Board or Advisory Board: Takeda, Sobi, Biotest, NovoNordisk; Receipt of equipment, materials, drugs, medical writing, gifts or other services: Takeda. CD and JG have no conflicts of interest.

References

1 Stephanos K, Dubbs SB. Pediatric hematologic and oncologic emergencies. Emerg Med Clin North Am 2021;39(03):555–571
2 Fustolo-Gunnink SF, Huisman EJ, van der Bom JG, et al. Are thrombocytopenia and platelet transfusions associated with major bleeding in preterm neonates? A systematic review. Blood Rev 2019;36(10):1–9
3 Aquino CC, Borg Debono V, Germini F, et al. Outcomes for studies assessing the efficacy of hemostatic therapies in persons with congenital bleeding disorders. Haemophilia 2021;27(02): 211–220
4 Johnson B, Fletcher SJ, Morgan NV. Inherited thrombocytopenia: novel insights into megakaryocyte maturation, proplatelet formation and platelet lifespan. Platelets 2016;27(06):519–525
5 McFadyen JD, Kaplan ZS. Platelets are not just for clots. Transfus Med Rev 2015;29(02):110–119
6 Fustolo-Gunnink SF, Roehr CC, Lieberman L, et al. Platelet and red cell transfusions for neonates: lifesavers or Trojan horses? Expert Rev Hematol 2019;12(10):797–800
7 Hitchcock IS, Hafer M, Sangkhae V, Tucker JA. The thrombopoietin receptor: revisiting the master regulator of platelet production. Platelets 2021;32(06):770–778
8 Erickson-Miller CL, Delorme E, Tian SS, et al. Preclinical activity of eltrombopag (SB-497115), an oral, nonpeptide thrombopoietin receptor agonist. Stem Cells 2009;27(02):424–430
9 Broudy VC, Lin NL. AMG531 stimulates megakaryopoiesis in vitro by binding to Mpl. Cytokine 2004;25(02):52–60
10 Li J, Yang C, Xia Y, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood 2001;98 (12):3241–3248
11 Gilreath J, Lo M, Bubalo J. Thrombopoietin receptor agonists (TPO-RAs): drug class considerations for pharmacists. Drugs 2021;81 (11):1285–1305
12 Kuter DJ. The structure, function, and clinical use of the thrombopoietin receptor agonist avatrombopag. Blood Rev 2022; 53:100909
13 Kuter DJ, Tarantino MD, Lawrence T. Clinical overview and practical considerations for optimizing romiplostim therapy in patients with immune thrombocytopenia. Blood Rev 2021;49 (09):100811
14 Chen F, McDonald V, Newland A. Experts' review: the emerging roles of romiplostim in immune thrombocytopenia (ITP). Expert Opin Biol Ther 2021;21(11):1383–1393
15 Capecchi M, Serpenti F, Giannotta J, et al. Off-label use of thrombopoietin receptor agonists: case series and review of the literature. Front Oncol 2021;11(09):680411
16 Brynes RK, Orazi A, Theodore D, et al. Evaluation of bone marrow reticulin in patients with chronic immune thrombocytopenia treated with eltrombopag: data from the EXTEND study. Am J Hematol 2015;90(07):598–601
17 Kuter DJ, Mufti GJ, Bain BJ, Hasserjian RP, Davis W, Rutstein M. Evaluation of bone marrow reticulin formation in chronic immune thrombocytopenia patients treated with romiplostim. Blood 2009;114(18):3748–3756
18 Ghanima W, Cooper N, Rodeghiero F, Godeau B, Bussel JB. Thrombopoietin receptor agonists: ten years later. Haematologica 2019;104(06):1112–1123
19 Ehrenreich H, Hasselblatt M, Knerlich F, et al. A hematopoietic growth factor, thrombopoietin, has a proapoptotic role in the brain. Proc Natl Acad Sci U S A 2005;102(03):862–867
20 Hoffmann O, Rung O, Im AR, et al. Thrombopoietin contributes to neuronal damage in experimental bacterial meningitis. Infect Immun 2011;79(02):928–936
21 Bastian TW, Duck KA, Michalopoulos GC, et al. Eltrombopag, a thrombopoietin mimetic, crosses the blood-brain barrier and impairs iron-dependent hippocampal neuron dendrite development. J Thromb Haemost 2017;15(03):565–574
22 Xie C, Zhao H, Bao X, Fu H, Lou L. Pharmacological characterization of hetrombopag, a novel orally active human thrombopoietin receptor agonist. J Cell Mol Med 2018;22(11):5367–5377
23 Mei H, Liu X, Li Y, et al. A multicenter, randomized phase III trial of hetrombopag: a novel thrombopoietin receptor agonist for the treatment of immune thrombocytopenia. J Hematol Oncol 2021; 14(01):37
24 Peng G, He G, Chang H, et al. A multicenter phase II study on the efficacy and safety of hetrombopag in patients with severe aplastic anemia refractory to immunosuppressive therapy. Ther Adv Hematol 2022;13(03):20406207221085197
25 Tarantino MD, Bussel JB, Blanchette VS, et al. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. Lancet 2016;388 (10039):45–54
26 He X, Ran N, Wang T, Shao Z. Efficacy and quality of life of romiplostim in adults and children with immune thrombocytopenia: a review. Medicine (Baltimore) 2022;101(50):e32345
27 de Oliveira FL, Sequeira FS, Garanito MP. Safety and efficacy of romiplostim in children and adolescents with immune thrombocytopenia: a systematic review. Hematol Transfus Cell Ther 2023; 45(01):83–89
28 Grainger JD, Kühne T, Hippenmeyer J, Cooper N. Romiplostim in children with newly diagnosed or persistent primary immune thrombocytopenia. Ann Hematol 2021;100(09):2143–2154
29 Grainger J, Bussel J, Tarantino M, et al. A single-arm, long-term efficacy and safety study of subcutaneous romiplostim in children with immune thrombocytopenia. Blood Adv 2023;7(03):396–405
30 Gröpper S, Althaus K, Najm J, et al. A patient with Fechtner syndrome successfully treated with romiplostim. Thromb Haemost 2012;107(03):590–591
31 Yamanouchi J, Hato T, Kunishima S, Niiya T, Nakamura H, Yasukawa M. A novel MYH9 mutation in a patient with MYH9 disorders and platelet size-specific effect of romiplostim on macrothrombocytopenia. Ann Hematol 2015;94(09):1599–1600
32 Pecci A, Ragab I, Bozzi V, et al. Thrombopoietin mutation in congenital amegakaryocytic thrombocytopenia treatable with romiplostim. EMBO Mol Med 2018;10(01):63–75
33 Khoreva A, Abramova I, Deripapa E, et al. Efficacy of romiplostim in treatment of thrombocytopenia in children with Wiskott-Aldrich syndrome. Br J Haematol 2021;192(02):366–374
34 Merjaneh N, Young J, Mangoli A, et al. Chemotherapy-induced thrombocytopenia in Ewing sarcoma: implications and potential for romiplostim supportive care. Pediatr Blood Cancer 2022;69 (07):e29548
35 Meijome TE, Ekwealor JTB, Hooker RA, et al. C-Mpl is expressed on osteoblasts and osteoclasts and is important in regulating skeletal homeostasis. J Cell Biochem 2016;117(04):959–969
36 Bethel M, Barnes CL, Taylor AF, et al. A novel role for thrombopoietin in regulating osteoclast development in humans and mice. J Cell Physiol 2015;230(09):2142–2151
37 Will B, Kawahara M, Luciano JP, et al. Effect of the nonpeptide thrombopoietin receptor agonist Eltrombopag on bone marrow cells from patients with acute myeloid leukemia and myelodysplastic syndrome. Blood 2009;114(18):3899–3908
38 Sun H, Tsai Y, Nowak I, Liesveld J, Chen Y. Eltrombopag, a thrombopoietin receptor agonist, enhances human umbilical cord blood hematopoietic stem/primitive progenitor cell expansion and promotes multi-lineage hematopoiesis. Stem Cell Res (Amst) 2012;9(02):77–86
39 Vlachodimitropoulou E, Chen YL, Garbowski M, et al. Eltrombopag: a powerful chelator of cellular or extracellular iron(III) alone or combined with a second chelator. Blood 2017;130(17): 1923–1933
40 Roth M, Will B, Simkin G, et al. Eltrombopag inhibits the proliferation of leukemia cells via reduction of intracellular iron and induction of differentiation. Blood 2012;120(02):386–394

41 Kao YR, Chen J, Narayanagari SR, et al. Thrombopoietin receptor-independent stimulation of hematopoietic stem cells by eltrombopag. Sci Transl Med 2018;10(458):eaas9563
42 Di Paola A, Palumbo G, Tortora C, et al. Eltrombopag in paediatric immune thrombocytopenia: iron metabolism modulation in mesenchymal stromal cells. Br J Haematol 2022;197(01): 110–119
43 Bussel JB, de Miguel PG, Despotovic JM, et al. Eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia (PETIT): a randomised, multicentre, placebo-controlled study. Lancet Haematol 2015;2(08):e315–e325
44 Grainger JD, Locatelli F, Chotsampancharoen T, et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. Lancet 2015; 386(10004):1649–1658
45 de Barros Torelli DFH, Oliveira CBS, Nai GA, Trindade EM, Prestes-Carneiro LE. Eltrombopag for adults and children with immune-refractory thrombocytopenic purpura: a systematic review. J Clin Med 2023;12(12):3872
46 Giordano P, Lassandro G, Barone A, et al. Use of eltrombopag in children with chronic immune thrombocytopenia (ITP): a real life retrospective multicenter experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP). Front Med (Lausanne) 2020;7(02):66
47 Palumbo G, Farruggia P, Ramenghi U, et al. Pediatric immune thrombocytopenia: a focus on eltrombopag as second-line therapy. Hematology 2023;28(01):2210906
48 Wang Z, Wang L, Liu Y, et al. Sustained response off treatment in eltrombopag for children with persistent/chronic primary immune thrombocytopenia: a multicentre observational retrospective study in China. Br J Haematol 2023;202(02):422–428
49 Noun P, Inati A, Raffoul R, Younes JA, Mardini J, Khalife H. Eltrombopag in pediatric chronic and refractory ITP: data from a retrospective multicenter study from Lebanon. Ann Hematol 2022;101(05):991–997
50 Cheng X, Fu L, Ma J, et al. Spotlight on eltrombopag in pediatric ITP in China: a long-term observational study in real-world practice. Blood Adv 2021;5(19):3799–3806
51 Koca Yozgat A, Leblebisatan G, Akbayram S, et al. Outcomes of eltrombopag treatment and development of iron deficiency in children with immune thrombocytopenia in Turkey. Turk J Haematol 2020;37(03):139–144
52 Zhou H, Fan J, He J, Hu S. Comparative efficacy of 19 drug therapies for patients with idiopathic thrombocytopenic purpura: a multiple-treatments network meta-analysis. Ann Hematol 2022;101 (05):953–961
53 Ayad N, Grace RF, Al-Samkari H. Thrombopoietin receptor agonists and rituximab for treatment of pediatric immune thrombocytopenia: a systematic review and meta-analysis of prospective clinical trials. Pediatr Blood Cancer 2022;69(03): e29447
54 Shimano KA, Grace RF, Despotovic JM, et al. Phase 3 randomised trial of eltrombopag versus standard first-line pharmacological management for newly diagnosed immune thrombocytopaenia (ITP) in children: study protocol. BMJ Open 2021;11(08):e044885
55 Germeshausen M, Ballmaier M. Congenital amegakaryocytic thrombocytopenia - not a single disease. Best Pract Res Clin Haematol 2021;34(02):101286
56 Fox NE, Lim J, Chen R, Geddis AE. F104S c-Mpl responds to a transmembrane domain-binding thrombopoietin receptor agonist: proof of concept that selected receptor mutations in congenital amegakaryocytic thrombocytopenia can be stimulated with alternative thrombopoietic agents. Exp Hematol 2010;38 (05):384–391
57 Pecci A, Gresele P, Klersy C, et al. Eltrombopag for the treatment of the inherited thrombocytopenia deriving from MYH9 mutations. Blood 2010;116(26):5832–5837
58 Zaninetti C, Gresele P, Bertomoro A, et al. Eltrombopag for the treatment of inherited thrombocytopenias: a phase II clinical trial. Haematologica 2020;105(03):820–828
59 Zaninetti C, Barozzi S, Bozzi V, Gresele P, Balduini CL, Pecci A. Eltrombopag in preparation for surgery in patients with severe MYH9-related thrombocytopenia. Am J Hematol 2019;94(08): E199–E201
60 Pecci A, Barozzi S, d'Amico S, Balduini CL. Short-term eltrombopag for surgical preparation of a patient with inherited thrombocytopenia deriving from MYH9 mutation. Thromb Haemost 2012;107 (06):1188–1189
61 Favier R, Feriel J, Favier M, Denoyelle F, Martignetti JA. First successful use of eltrombopag before surgery in a child with MYH9-related thrombocytopenia. Pediatrics 2013;132(03): e793–e795
62 Conte G, López M, Alarcón P. [Hereditary thrombocytopenia associated with a mutation in the MYH-9 gene. Report of one case]. Rev Med Chil 2018;146(09):1074–1078
63 Lassandro G, Carriero F, Noviello D, et al. Successful eltrombopag therapy in a child with MYH9-related inherited thrombocytopenia. Children (Basel) 2022;9(12):1839
64 Gabelli M, Marzollo A, Notarangelo LD, Basso G, Putti MC. Eltrombopag use in a patient with Wiskott-Aldrich syndrome. Pediatr Blood Cancer 2017;64(12):. Doi: 10.1002/pbc.26692
65 Gerrits AJ, Leven EA, Frelinger AL III, et al. Effects of eltrombopag on platelet count and platelet activation in Wiskott-Aldrich syndrome/X-linked thrombocytopenia. Blood 2015;126(11): 1367–1378
66 Fiore M, Saut N, Alessi MC, Viallard JF. Successful use of eltrombopag for surgical preparation in a patient with ANKRD26-related thrombocytopenia. Platelets 2016;27(08):828–829
67 Drachman JG, Jarvik GP, Mehaffey MG. Autosomal dominant thrombocytopenia: incomplete megakaryocyte differentiation and linkage to human chromosome 10. Blood 2000;96(01): 118–125
68 Bussel JB, Kuter DJ, Aledort LM, et al. A randomized trial of avatrombopag, an investigational thrombopoietin-receptor agonist, in persistent and chronic immune thrombocytopenia. Blood 2014;123(25):3887–3894
69 Markham A. Avatrombopag: a review in thrombocytopenia. Drugs 2021;81(16):1905–1913
70 Tran TB, Downing L, Elmes JB, Arnall JR, Moore DC. Avatrombopag for the treatment of immune thrombocytopenia and periprocedural thrombocytopenia associated with chronic liver disease. J Pharm Pract 2024;37(01):184–189
71 Song AB, Al-Samkari H. An updated evaluation of avatrombopag for the treatment of chronic immune thrombocytopenia. Expert Rev Clin Immunol 2022;18(08):783–791
72 Tsykunova G, Ghanima W. Avatrombopag for the treatment of adult patients with chronic immune thrombocytopenia (cITP): focus on patient selection and perspectives. Ther Clin Risk Manag 2022;18(03):273–286
73 Deng J, Hu H, Huang F, et al. Comparative efficacy and safety of thrombopoietin receptor agonists in adults with thrombocytopenia: a systematic review and network meta-analysis of randomized controlled trial. Front Pharmacol 2021;12(07):704093
74 Al-Samkari H, Jiang D, Gernsheimer T, et al. Adults with immune thrombocytopenia who switched to avatrombopag following prior treatment with eltrombopag or romiplostim: a multicentre US study. Br J Haematol 2022;197(03):359–366
75 Arif AR, Zhao M, Chen W, Xue M, Luo S, Wang Y. Avatrombopag improves thrombocytopenia in MYH9-related disorder following eltrombopag treatment failure. Platelets 2022;33(08):1307–1311
76 Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MAAmerican Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117(16):4190–4207

77 Rodeghiero F. Recent progress in ITP treatment. Int J Hematol 2023;117(03):316–330
78 Zheng L, Liang MZ, Zeng XL, et al. Safety, pharmacokinetics and pharmacodynamics of hetrombopag olamine, a novel TPO-R agonist, in healthy individuals. Basic Clin Pharmacol Toxicol 2017;121(05):414–422
79 Wang Z, Chen L, Zhang F, et al. First-in-patient study of hetrombopag in patients with chronic idiopathic thrombocytopenic purpura. J Thromb Haemost 2020;18(11):3053–3060
80 Shen N, Qiao J, Jiang Y, et al. Safety of non–peptide thrombopoietin receptor agonists in patients with immune thrombocytopenia: a systematic review and meta–analysis of short–term double–blind randomized clinical trials. Exp Ther Med 2023;26 (02):393
81 Tumaini Massaro J, Chen Y, Ke Z. Efficacy and safety of thrombopoietin receptor agonists in children with chronic immune thrombocytopenic purpura: meta-analysis. Platelets 2019;30 (07):828–835
82 Neunert C, Despotovic J, Haley K, et al; Pediatric ITP Consortium of North America (ICON) Thrombopoietin receptor agonist use in children: data from the pediatric ITP Consortium of North America ICON2 Study. Pediatr Blood Cancer 2016;63(08):1407–1413
83 González-Porras JR, Godeau B, Carpenedo M. Switching thrombopoietin receptor agonist treatments in patients with primary immune thrombocytopenia. Ther Adv Hematol 2019;10(05): 2040620719837906
84 Depré F, Aboud N, Mayer B, Salama A. Bidirectional inefficacy or intolerability of thrombopoietin receptor agonists: new data and a concise review. Blood Transfus 2018;16(03):307–312
85 Jansen AJG, McDonald V, Newland A, et al. Patient preferences and experiences regarding thrombopoietin-receptor agonists for immune thrombocytopenia in the Netherlands (TRAPeze Netherlands study). Hematology 2023;28(01):2267942
86 Cheng X, Wang Z, Dong S, et al. Outcomes of switching to avatrombopag following treatment failure with eltrombopag in paediatric immune thrombocytopenia: a real-world study in China. Br J Haematol 2023;202(03):636–644
87 Lozano ML, Mingot-Castellano ME, Perera MM, et al. Deciphering predictive factors for choice of thrombopoietin receptor agonist, treatment free responses, and thrombotic events in immune thrombocytopenia. Sci Rep 2019;9(01):16680
88 Bao W, Bussel JB, Heck S, et al. Improved regulatory T-cell activity in patients with chronic immune thrombocytopenia treated with thrombopoietic agents. Blood 2010;116(22):4639–4645
89 Wan YY, Flavell RA. 'Yin-Yang' functions of transforming growth factor-beta and T regulatory cells in immune regulation. Immunol Rev 2007;220(12):199–213
90 Schifferli A, Kühne T. Thrombopoietin receptor agonists: a new immune modulatory strategy in immune thrombocytopenia? Semin Hematol 2016;53(Suppl 1):S31–S34
91 Zufferey A, Kapur R, Semple JW. Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). J Clin Med 2017;6(02):16
92 Di Paola A, Palumbo G, Merli P, et al. Effects of eltrombopag on in vitro macrophage polarization in pediatric immune thrombocytopenia. Int J Mol Sci 2020;22(01):97
93 Schifferli A, Rüfer A, Rovo A, et al. Immunomodulation with romiplostim as a second-line strategy in primary immune thrombocytopenia: the iROM study. Br J Haematol 2023;203(01):119–130
94 Newland A, Godeau B, Priego V, et al. Remission and platelet responses with romiplostim in primary immune thrombocytopenia: final results from a phase 2 study. Br J Haematol 2016;172 (02):262–273
95 Yang F, Zong H, Li F, et al. Eltrombopag modulates the phenotypic evolution and potential immunomodulatory roles of monocytes/macrophages in immune thrombocytopenia. Platelets 2023;34(01):2135694
96 Ignatova AA, Suntsova EV, Pshonkin AV, et al. Platelet function and bleeding at different phases of childhood immune thrombocytopenia. Sci Rep 2021;11(01):9401