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# Update on the Use of Thrombopoietin-Receptor Agonists in Pediatrics

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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<br>P13K/Akt<br>ERK<br>STAT3 | JAK2/STAT5<br>P13K/Akt<br>ERK | JAK2/STAT5<br>STAT3<br>ERK | JAK2/STAT5<br>STAT3 | JAK2/STAT5<br>P13K/Akt<br>ERK<br>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)<br>• Hepatitis C–associated thrombocytopenia (adults)<br>• Severe aplastic anemia (adults and children) | • Periprocedural thrombocytopenia in chronic liver disease patients (adults)<br>• 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 ($1 \times 9$ 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 ($1 \times 5$ 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 ($1 \times 2$ 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.

 

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