Novel Perspectives on Thrombopoietin Receptor Agonists Applications

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Abstract

Second-generation thrombopoietin receptor agonists (TPO-RAs), romiplostim, eltrombopag, and avatrombopag, have been proved to be significant stimulators of megakaryopoiesis and, in the last decade, they have been incorporated in the treatment options against refractory immune thrombocytopenia in children and adults that do not respond to conventional therapy. Additionally, given their beneficial impact on hematopoiesis, they have successfully been applied in cases of non-immune thrombocytopenia, such as aplastic anemia, HCV-related thrombocytopenia, chronic liver disease, and most recently acute radiation syndrome. During the past years, a wide variety of clinical studies have been performed, in regard to the use of TPO-RAs in various thrombocytopenic settings, such as malignant hematology and hematopoietic stem cell transplantation, hereditary thrombocytopenias, and chemotherapy-treated patients with solid organ tumors. Although data indicate that TPO-RAs may be an effective and safe option for managing disease- or treatment-related thrombocytopenia in these patients, further research is needed to determine their efficacy and safety in these settings. Furthermore, recent studies have highlighted novel properties of TPO-RAs that render them as potential treatment candidates for reducing tumor burden or fighting infections. Herein, we discuss the potential novel applications of TPO-RAs and focus on data regarding their efficacy and safety in these contexts.

Keywords

- eltrombopag
- romiplostim
- avatrombopag

Zusammenfassung

Zweitgeneration Thrombopoetin-Rezeptor-Agonisten (TRA), Romiplostim, Eltrombopag und Avatrombopag, wurden als bedeutende Stimulatoren der Megakaryopoese nachgewiesen und sind im letzten Jahrzehnt in den Behandlungsoptionen bei refraktärer Immunthrombozytopenie bei Kindern und Erwachsenen, die nicht auf konventionelle Therapie ansprechen, integriert worden. Zusätzlich zu ihrem positiven Einfluss auf die Hämatopoese wurden sie erfolgreich in Fällen von nicht-immunthrombozytopenen Erkrankungen eingesetzt, wie zum Beispiel aplastische Anämie, HCV-bedingte Thrombozytopenie, chronische Lebererkrankungen und zuletzt dem akuten Strahlensyndrom. In den letzten Jahren wurde eine Vielzahl von klinischen Studien durchgeführt, die den Einsatz von TRA in verschiedenen thrombozytopenischen Situationen betrachten, wie in der malignen Hämatologie und der hämatopoetischen Stammzelltransplantation, bei erblichen Thrombozytopenien und bei Patienten mit soliden

Schlüsselwörter

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Organtumoren, die einer Chemotherapie unterzogen wurden. Obwohl Daten darauf hindeuten, dass TRA eine wirksame und sichere Option zur Behandlung von krankheits- oder therapiebedingter Thrombozytopenie bei diesen Patienten sein könnten, sind weitere Forschungen erforderlich, um ihre Wirksamkeit und Sicherheit in diesen Kontexten zu bestimmen. Darüber hinaus haben aktuelle Studien neuartige Eigenschaften von TRA hervorgehoben, die sie als potenzielle Behandlungskandidaten zur Reduzierung der Tumorlast oder Bekämpfung von Infektionen darstellen. Hierin diskutieren wir potenzielle neue Anwendungen von TRA, wobei wir uns auch auf Daten zu ihrer Wirksamkeit und Sicherheit in diesen Kontexten konzentrieren.

Introduction

Thrombocytopenia poses a common problem and may accompany various conditions, such as hematologic malignancies (HMs), aplastic anemia (AA), chronic liver disease (CLD), and patients with solid organ tumors (SOT) receiving chemotherapy. Moreover, immune-mediated platelet destruction may be established abruptly, as is in the case of immune thrombocytopenia (ITP).

Thrombopoietin (TPO) constitutes the master regulator of platelet production.[1,2] TPO is primarily produced in the liver and acts through binding to the extracellular domain of partially predimerized cell surface TPO receptor (TPO-R), thus leading to conformational changes, which initiate a cascade of signaling events, involving the JAK/STAT, RAS/MAPK, and PI3K/AKT pathways.[1,2] In particular, TPO-R has no intrinsic kinase activity and mostly utilizes janus kinase 2 (JAK2), which is phosphorylated upon TPO signaling, to transduce signals within the target cell.[1,2] TPO exerts its effects in various stages of platelet differentiation, thereby augmenting megakaryocytes proliferation and maturation, whereas more recent data highlight its impact on hematopoietic stem cells (HSCs), where TPO plays a double role. On the one hand, it promotes proliferation and survival of CD34+ and other early progenitor cells, without affecting polarization toward a specific hematopoietic linage, on the other hand it stimulates cell cycle arrest in more primitive HSCs in the osteoblastic niches, preserving them in quiescence and thus protecting of their exhaustion, in cases of great needs.[1,2] In addition, it seems that TPO may play a role in DNA repair in HSCs.[1,2]

In the past years, given the favorable properties of endogenous TPO, remarkable progress has been made in the development of TPO receptor agonists (TPO-RAs). Recombinant human thrombopoietin (rhTPO) and pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) were the first agents to be developed but were soon abandoned due to the appearance of anti-TPO autoantibodies, thereby leading to second-generation TPO-RAs development, which are biochemically unrelated to endogenous TPO and eliminate the possibility of autoantibody occurrence. Romiplostim (ROMI) is a peptibody that antagonizes endogenous TPO for binding to extracellular domain of TPO-R but with a 25-fold lower affinity. Thus, in cases where endogenous TPO levels are elevated, such as in acute myeloid leukemia (AML), use of ROMI may be limited.[2–5] In vitro and in vivo studies showed that ROMI stimulates the growth of colony-forming unit-megakaryocyte (CFU-MK); increases the number, size, and ploidy of megakaryocytes; and improves platelet production.[2–5]

Eltrombopag (EP) is an oral synthetic nonpeptide, which, unlike endogenous TPO, binds to the transmembrane domain of TPO-R, thus having an additive rather than competitive effect and rendering it an attractive option even in cases where TPO levels are elevated. EP effectively augments proliferation and survival of megakaryocytes, through activation of various downstream pathways, such as JAK/STAT, MAPK, AKT, ERK, but at a different extent in comparison to ROMI.[6] For instance, previous in vitro studies showed that EP is capable of eliciting a balanced activation of both AKT and ERK 1/2 pathways, both in hematopoietic progenitors and mature megakaryocytes; besides proliferation of megakaryocytes, it probably further prospers proplatelet formation, whereas ROMI triggers for megakaryocyte growth through activation of AKT almost exclusively, and barely affects proplatelet formation.[6] These different activation patterns of downstream pathways may further influence employment of these agents in different settings. Moreover, different properties of EP and ROMI may be responsible for different adverse events. For example, neutralizing antibodies against ROMI have been detected in ROMI-treated patients and have been correlated with loss of response, while treatment with EP, which is a small molecule, seems to confer no such risk.[4] Furthermore, EP contains a metal chelate group in the center that makes it a powerful iron chelator and also displays a spectrum of off-target effects.[2–5,7] These iron chelating properties of EP seem to be responsible for a TPO-independent effect on stimulating stem cells and megakaryocyte precursors in vivo.[4] Recent studies in ITP and AA have also demonstrated immunomodulatory and anti-inflammatory capacities of these agents, mainly attributable to their interference with transforming growth factor-β (TGF-β).[2–5,7] Increased TGF-β secretion is considered to be primarily accountable for augmented reticulin bone marrow (BM) fibrosis, which is observed mostly in EP-treated ITP patients, and although it is reversible, it tends to worsen in a time-dependent fashion.[7] Notably, myeloproliferative neoplasm (MPN)-like changes, with a tendency of megakaryocytes to form clusters, have also been observed in

the BM of EP-treated patients.[7] Nonetheless, these newly discovered properties of EP remain a subject of intensive study and pave the way for further exploitation of this drug. Recently, three more oral TPO-RAs, which also bind on the transmembrane TPO-R domain, were developed in China: avatrombopag, lusutrombopag, and hetrombopag.[4,8]

Advent of TPO-RAs led to novel therapeutic approaches in thrombocytopenic patients, primarily in chronic ITP.[2] EP, ROMI, and avatrombopag are currently approved for the treatment of persistent or chronic ITP, unresponsive to previous first-line agents or splenectomy.[9] Several studies have reported overall response rates of 60 to 90% in ITP patients receiving TPO-RAs.[9] Results of increased efficacy in ITP patients along with understanding TPO's effects on HSCs gave rise to employment of TPO-RAs in a variety of thrombocytopenic settings.[2] EP has been shown effective in the management of thrombocytopenia related to hepatitis C virus (HCV) infection, thus allowing initiation and maintenance of interferon-based therapy.[1–4] EP has also been approved for the management of severe AA, either as first-line treatment, combined with standard immunosuppressive therapy, or as second-line treatment in refractory patients.[4,7] Recently, avatrombopag and lusutrombopag have also been approved for use in patients with CLD that undergo surgery or invasive procedures.[4,10] Efficacy of both of these agents has been validated in large, randomized, phase 3 trials and results are in accordance with real-world data that report no requirement for preoperative platelet transfusions in 65 to 93% of CLD patients receiving a TPO-RA prior to an invasive procedure. Importantly, these agents have also been met with a favorable safety profile and have low potential for drug-to-drug interactions.[10]

Collectively, these results have laid the basis for further exploration of TPO-RAs in other thrombocytopenic settings. In this review, we discuss a broad spectrum of thrombocytopenic conditions where TPO-RAs could be incorporated as a treatment option, highlighting potent novel uses of these drugs, while we also discuss, in the context of drug repurposing, about novel findings of use of TPO-RAs in the case of infections.

Thrombopoietin Receptor Agonists in Hematologic Malignancies

Thrombopoietin Receptor Agonists in Myelodysplastic Neoplasms

Myelodysplastic neoplasms (MDS) comprise a heterogenous group of HMs that are defined by one or more cytopenias and uni- or multi-linage dysplasia, with a tendency to evolve to AML.[11] Clinical presentation reflects the existing inadequate hematopoiesis, with profound anemia being the most prevalent feature, while neutropenia is responsible for recurrent infections.[11] Thrombocytopenia, which is observed in up to 25%, is associated with increased bleeding risk and is predictive of early death.[12]

Management of MDS patients is individualized and depends mostly on clinical status, MDS subtype and prognosis, and the presence of specific mutations that pose as targets for novel treatments. Common therapeutic options include administration of growth factors (e.g., erythropoietin [EPO] or luspatercept), hypomethylating (HMA) or immunomodulatory agents, as well as targeted treatments, while allogeneic hematopoietic stem cell transplantation (allo-HSCT) stands as the ideal option for fit patients. Regarding thrombocytopenia, therapeutic choices are confined.[11] Although platelet transfusions play a primary role in patients with lifelong thrombocytopenia, they have several drawbacks; since they are associated with short-term efficacy, they have limited availability, and they also bear the risk of acute reactions and alloimmunization with subsequent refractoriness to latter transfusions.[11,12]

Considering that TPO-RAs effectively incite for expansion of HSCs and stimulate for bi- or tri-lineage hematopoiesis, their utility was also investigated in MDS. ROMI was first evaluated in a prospective phase I/II trial of patients with low-risk MDS and thrombocytopenia on supportive care only and the results showed a raise in platelet counts in most of the patients, while a durable response was observed in 46%, who remained transfusion free for 8 weeks.[13] At the same time, another phase II study examined ROMI's efficacy in low- or intermediate-risk MDS patients who receive azacytidine and demonstrated a potential clinical benefit.[14] Subsequent studies investigated coadministration of ROMI with decitabine[15] and lenalidomide[16] in low- or intermediate-risk MDS and showed a decrease of clinically significant thrombocytopenic events, which is grade 3 or 4 thrombocytopenia on day 15 of treatment cycle or need for platelet transfusions during treatment. An additional phase II study demonstrated that ROMI was efficacious in the same setting, achieving high platelet counts and fewer bleeding episodes and transfusions, but terminated early due to concerns of potential risk for progression to AML, which was associated with a ROMI-mediated transient increase in peripheral blast cell counts; however, despite initial concerns, follow-up study of the patients has demonstrated similar survival and AML rates between ROMI and placebo group.[17]

Although well tolerated, results from a study showed that ROMI was responsible for an increase in peripheral blasts in 9% of patients, that diminished after drug interruption, thus prompting to concerns of potent clonal evolution.[13] In vitro studies demonstrated that various TPO concentrations trigger for TPO-R-mediated expansion of specific blast cells of myeloid lineage.[3,13] However, recent data indicate that this expansion may be limited to patients with preexisting leukemogenic mutations (e.g., AML1-ETO fusion) that act in synergy.[3,13] Moreover, just as ROMI, granulocyte colony-stimulating factor (G-CSF), which is used in these patients for a longer period, leads to an increase in peripheral blasts.[13] In addition, it was shown later that patients of the aforementioned terminated study were observed for 5 years and had the same risk for evolution to AML, regardless of ROMI administration.[17,18] Ensuing studies and meta-analyses demonstrated same results.[19,20] Nevertheless, more studies need to be conducted so as to assess safety of ROMI in this group.

In the wake of these encouraging results, EP's efficacy was also explored in MDS patients. A phase I study showed that administration of 200 mg EP along with azacytidine in MDS

patients was safe and tolerable, while similar results were reported from subsequent studies.[21] EQoL-MDS study demonstrated that EP was efficacious and tolerable in patients with low- and intermediate-risk MDS and thrombocytopenia, raising platelet counts and decreasing bleeding episodes, whereas a second phase of the study, concerning duration of platelet response and long-term safety and tolerability, is still in progress.[22] Another recent study also reported that EP, as monotherapy in patients with low or intermediate-1 risk patients, achieved hematologic responses in 44% of them, with hypocellular BM, high TPO levels, and the presence of paroxysmal nocturnal hemoglobinuria clones being predictive of response.[23] Similar outcomes were also reported during combination of EP with lenalidomide.[24] While EP's efficacy was demonstrated in low- and intermediate-risk MDS, data regarding high-risk MDS are conflicting. ASPIRE study evaluated EP's efficacy in high-risk MDS and AML patients and described a reduction of grade 3 or 4 bleeding events and need for platelet transfusion in EP recipients.[25] On the contrary SUPPORT study of high-risk MDS patients, which investigated efficacy of EP's coadministration with azacytidine versus azacytidine monotherapy, showed a deterioration in platelet responses, more adverse events, and a tendency to AML progression in the combination arm, thus leading to early termination of the study.[26] Similar results regarding efficacy were also reported in the more recent ELASTIC study.[27] Modest platelet responses were also observed in post-HMA failure patients.[28,29]

Although tolerable, a major concern regarding the use of EP in HMs is that it could contribute to blast proliferation and clone expansion, considering also that TPO-R is variably expressed in leukemic cells of AML patients at ~50% and given the increased frequency of clonal cytogenetic abnormalities, chromosome 7 disorders included, observed in AA patients receiving EP.[30] Further research, however, highlighted that EP probably displays antitumor properties.[31–37] In particular, EP suppressed leukemic cell lines and declined their survival.[31–33,35,36] This action was independent of TPO-R expression on leukemic cells and was not diminished if TPO, EPO, or G-SCF was given or TPO-R was silenced and it was also observed in mice, which lack TPO-R species-specific binding site, thus indicating that EP acts in a TPO-R-independent way.[31–36]

Further investigation of the underlying mechanisms demonstrated that these effects are mostly attributed to EP's induced iron chelation. A study previously denoted that EP disrupts cell growth in human and murine leukemia cells, through an arrest in G(1) phase of cell cycle, and leads to their increased differentiation and also indicated that these EP's effects were associated in a dose-dependent way with a reduction of intracellular iron.[35] Similar results were also described for other non-myeloid cellular lines, as is hepatocellular carcinoma (HCC).[37] In general, leukemic and cancer cells have high metabolic needs; hence, iron deprivation could crucially impact their growth.[35] Exceptionally, EP is also capable of binding other polyvalent cations such as copper and zinc, which are also vital for these cells.[35] A study showed that EP rapidly decreases intracellular reactive oxygen species (ROS), especially hydrogen peroxide (H_2O_2), thus generating rapid apoptosis of leukemic cells.[36] ROS are an elemental component of cells' homeostasis, regulating a variety of cellular processes and their levels fluctuate among various cells.[36] For instance, cancer cells have elevated ROS levels that establish a permanent pro-oxidative state. Whichever disorder in ROS levels leads to imbalance and apoptosis.[36] A recent study also showed that EP stimulates for self-renewal and proliferation of HSCs, through an iron-mediated molecular reprogramming caused by labile iron pool alterations, an effect independent of TPO-R, since it was not observed in TPO-R lacking mice treated with ROMI.[38] Antitumor properties, mediated by its iron chelating ability, were also observed in pediatric AML patients treated with cytarabine,[39] indicating a potential synergism, as well as in other cancers, such as HCC and Ewing's sarcoma.[36,40] Finally, EP was also found to be an allosteric inhibitor of the METTL3–14 methyltransferase complex, which is abundant in AML cells, thereby suppressing cell proliferation.[41]

Concisely, EP possibly exerts antiproliferative effects. Also, considering EP's low molecular weight and lipophilicity that allow cellular uptake and high chelator efficacy, it could represent a powerful weapon for patients with HMs, not only as a hematopoiesis stimulator but also as an antileukemic drug, incorporated into chemotherapy regimens. Of note, due to EP's iron chelating properties, iron-deficiency anemia may arise; so, patients should be closely monitored.

Thrombopoietin Receptor Agonists in Acute Myeloid Leukemia

Thrombocytopenia in AML is also a frequent complication leading to increased morbidity and is exacerbated due to underlying BM infiltration and chemotherapy-induced myelotoxicity.[42]

Even though EP is tolerable in AML patients, evidence concerning its efficacy remains ambiguous.[42–46] EP proved to have a favorable safety profile in AML patients to doses up to 300 mg.[43] Additionally, although EP inhibits breast cancer resistance protein (BCRP), which is a substrate for daunorubicin, thus implementing increased risk for cardiotoxicity, a study denoted no cardiotoxic effects in patients receiving both EP and daunorubicin; yet, EP's efficacy was not demonstrated.[42] A recent study in patients receiving induction chemotherapy reported that although EP addition led to significant decrease in platelet transfusions, it did not affect survival.[44] ASPIRE study also described a decline of clinically related thrombocytopenic events.[25] Moreover, Mukherjee et al reported that EP hastened platelet response rates and reduced transfusions during induction chemotherapy, which is in accordance with findings from a study of EP during consolidation chemotherapy.[45,46] Data regarding ROMI's use are scarce, since AML patients present with elevated TPO levels that may prevent ROMI's action.[2–4]

Besides EP's newly emerged antileukemic properties, TPO-RAs are promising candidates for treating thrombocytopenic AML patients. However, more prospective studies need to be conducted to first prove their efficacy and then define optimal dose and schedule of administration as well as durability of responses.

Thrombopoietin Receptor Agonists in Other Hematologic Malignancies

Several ongoing trials investigate the utility of TPO-RAs in the treatment of secondary ITP or chemotherapy-induced thrombocytopenia (CIT) associated with HMs, such as lymphomas. A recent study of lymphoma patients with CIT demonstrated reduced bleeding episodes and platelet transfusions and higher platelet counts in EP and rhTPO recipients, thus indicating a potential benefit.[47]

Another clinical trial evaluated EP's use in patients with chronic myeloid leukemia or myelofibrosis upon treatment with tyrosine kinase inhibitors or ruxolitinib, respectively, where thrombocytopenia frequently is an obstacle, resulting in treatment delay or dose reduction.[48] EP managed to achieve a complete response in 30% of patients for at least 3 months and permitted treatment continuation.[48]

Considerably, a study previously showed that EP can trigger megakaryopoiesis in BM progenitors of patients with relapsed multiple myeloma (rMM) through stimulation of AKT signaling pathways, without provoking myeloma cells' expansion or altering lenalidomide's and bortezomib's apoptotic effects, thus implementing a potential use in rMM.[49]

Thrombopoietin Receptor Agonists in Chemotherapy-Induced Thrombocytopenia in Patients with Solid Organ Tumors

CIT, which is frequently defined as platelet counts below 100,000/mL, constitutes the most common cause of thrombocytopenia in SOT patients and its incidence and severity are contingent on cancer subtype and chemotherapy regimen.[50,51] Besides increasing bleeding risk, CIT also acts as a limiting factor for anticoagulant initiation or submission to surgery or invasive procedure.[50,51] Additionally, CIT often induces treatment interruption or reduction of chemotherapy-relative dose intensity, thus affecting overall survival. Recombinant interleukin-11 (oprelvekin) was efficiently used, yet serious adverse events occurred, thus leaving only platelet transfusions as an option.[50,51]

Efficacy of rhTPO has been previously evaluated in SOT patients with CIT and currently rhTPO is approved for use in this setting only in China.[52] During past years, management of CIT with second-generation TPO-RAs has also been studied. Findings from most important studies are summarized in ►Table 1.[52–66] Retrospective studies of ROMI's use in CIT highlighted a raise in platelet counts in the vast majority and importantly no treatment delay or discontinuation or dose reduction was observed.[53–55,58,59,61] In agreement, some prospective studies also indicated ROMI's efficacy and safety in this setting, with one of them reporting sustained platelet responses.[56,57,60] It was demonstrated that BM infiltration, prior pelvic irradiation, and prior exposure to temozolomide were predictive of non-response to ROMI, while lower TPO levels were correlated with better responses.[58,59] While ROMI was mostly utilized for CIT treatment, EP was mostly tested for CIT prevention, with available data suggesting a potential benefit.[62–64] Most recent studies explored avatrombopag's use for CIT management, also pointing at a potential therapeutic use.[52,65,66]

Use of TPO-RAs in cancer patients raises concerns regarding their theoretical risk for thrombosis or tumor proliferation; yet, TPO-R is barely expressed in cancer cells, which makes the latter rather impossible.[51] Additionally, previous findings indicate that TPO-RAs do not increase platelet reactivity in vitro.[51] Moreover, aforementioned studies proved TPO-RAs' safety and tolerability, whereas thromboembolic event rates were analogous to those historically observed in cancer patients.[52–66] As seen in ►Table 1, available data from trials have reported different thromboembolic event (TEE) rates, with avatrombopag yielding the lowest TEE rates.[52–66] It is not certain whether these differences can be solely attributed to the type of TPO-RA that has been used; however, similar results, indicating low rates of thrombosis with avatrombopag, have also been reported in patients with CLD.[10] Hence, based on these results, avatrombopag may seem more preferable in SOT patients. Of note, recent guidelines by the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee on Hemostasis and Malignancy suggest the use of ROMI over other TPO-RAs, whenever TPO-RAs are used for CIT, outside of the context of a clinical trial.[67] Nonetheless, further investigation is required for strong conclusions to be drawn.

Briefly, existing literature supports that TPO-RAs are potential candidates for either prevention or management of CIT in SOT patients. Several trials are ongoing and further investigation is certainly warranted to shed light on optimum TPO-RA dose, when TPO-RAs ideally should be given during chemotherapy cycle and who are the patients that could benefit the most.

Thrombopoietin Receptor Agonists in Allogeneic Hematopoietic Stem Cell Transplantation

Persisting thrombocytopenia post–allo-HSCT is a common complication with severe morbidity and mortality and its etiology is multifactorial.[68] Available literature reports two types of thrombocytopenia after engraftment. Primary failure of platelet recovery refers to remaining platelet counts below 20,000/μL in the absence of graft failure, meaning a recovery of neutrophil counts, while secondary failure of platelet recovery (SFPR) refers to platelet counts below 20,000/μL for 7 consecutive days or reappearance of need for transfusions, while previous platelet counts were above 50,000/μL for 7 consecutive days without transfusions.[68] SFPR can be found in up to 20% of allo-HSCT patients.[68] Also, some authors report prolonged isolated thrombocytopenia (PIT) as dependence on platelet transfusions $>$ 90 days after allo-HSCT.[69] Recently, American Society for Transplantation and Cellular Therapy defined platelet recovery post-allo-HSCT as the raise of platelets above 20,000/μL for the first 3 consecutive days in the absence of platelet transfusion for 7 consecutive days.[70] Also, poor graft function (PGF), a controversial entity that occurs in up to 20% of patients, is defined as persistent cytopenias with transfusion

Table 1 Studies of second-generation thrombopoietin receptor agonists in chemotherapy-induced thrombocytopenia

	Type of study	Patient population	TPO-RA used and dose administrated	Baseline PLT counts prior to TPO-RA initiation	Major efficacy results	TEE rate
Romiplostim						
Parameswaran et al[53]	Retrospective	$N = 20$ patients with various SOTs receiving a range of treatments	ROMI 1–2 µg/kg weekly, dose-titrated	<100,000/µL (mean PLTs 58,000/mL)	1. Correction of PLT counts ≥100,000/µL: 95% 2. Chemotherapy resumption without dose reduction: 75%	DVT in 15%
Miao et al[54]	Retrospective	$N = 42$ patients with various SOTs receiving a range of treatments	ROMI 2 µg/kg	<100,000/µL (median PLTs 71,000/µL)	1. Correction of PLT counts ≥100,000/µL: 94% 2. Chemotherapy resumption: 91.8%	14.3%
Al-Samkari et al[55]	Retrospective	$N = 22$ patients with various SOTs receiving a range of treatments	ROMI 3 µg/kg weekly, dose-titrated	74,000/µL (21,000–145,000/µL)	1. Correction of PLT counts ≥100,000/µL: 94% 2. Chemotherapy resumption for at least 2 cycles: 100%, 82% without dose reduction	No TEEs observed
Soff et al[56]	Randomized phase II trial	$N = 60$ patients with various SOTs receiving a range of treatments: $N = 15$ randomly assigned on ROMI $N = 8$ randomly assigned on observation $N = 37$ single-arm ROMI phase	ROMI 2.0 µg/kg weekly, dose-titrated vs. observation	< 100,000/µL (mean PLT count 62,000/µL)	1. Correction of PLTs ≥100,000/µL within 3 wk: - 93% in ROMI arm vs. 12.5% in observation arm ($p < 0.01$) - 81% in single-arm ROMI phase - 85% in all ROMI patients 2. Chemotherapy resumption for 8 wk or at least 2 cycles, without recurrent CIT: 85%, all responders to ROMI continued with maintenance ROMI without chemotherapy interruption	10.2%
Le Rhun et al[57]	Phase II multicenter single-arm trial	$N = 20$ patients with newly diagnosed glioblastoma that were to be treated with standard first-line concomitant TMZ/RT and maintenance TMZ for 6 cycles and were to develop CTCAE grade 3/4 thrombocytopenia	ROMI 750 µg starting dose, weekly for a maximum of 6 cycles of maintenance TMZ	53,500/µL (6,000–59,000/µL)	Percentage of thrombocytopenic patients treated with ROMI that are able to complete 6 cycles of maintenance TMZ exceeds 10% (secondary prophylaxis of TMZ-induced thrombocytopenia): 60% success rate (95% CI: 36–81%)	5%
Al-Samkari et al[58]	Retrospective	$N = 153$ patients with various SOTs receiving a range of treatments	ROMI median initiating dose 3 µg/kg, weekly or intracycle dosing	<100,000/µL (median PLTs: 54,000/µL)	1. Correction of PLT counts ≥ 75×10^9/L and at least 30×10^9/L than pretreatment baseline: 71% 2. Achievement of PLT counts ≥100,000/µL: 85% 3. Chemotherapy resumption: 98%, 79% without dose reduction or delay 4. Need for PLT transfusions: 89% without need for PLT transfusions	5.2%

Table 1 (*Continued*)

	Type of study	Patient population	TPO-RA used and dose administrated	Baseline PLT counts prior to TPO-RA initiation	Major efficacy results	TEE rate
Song et al[59]	Retrospective	$N = 63$ patients with various SOTs receiving a range of treatments	ROMI 2–3 µg/kg dose-titrated, weekly	42,000/µL (17,000–64,000/µL)	1. Correction of PLT counts $\geq 75 \times 10^9$/L and at least 30×10^9/L than pretreatment baseline: 85.7% overall response, 42.9% moderate response, 42.9% superior response 2. Need for PLT transfusions: 27%	NR
Wilkins et al[60]	Extended phase of the Soff et al study[56]	$N = 21$ patients who were treated with ROMI for ≥ 1 y	ROMI 3–5 µg/kg weekly		Prevention of chemotherapy dose reduction/delays due to CIT (PLTs $< 100{,}000$/µL): 70%	9.5%
Cheloff et al[61]	Retrospective	$N = 5$ patients with various SOTs receiving niraparib	ROMI 2 µg–5 µg/kg weekly	41,000/µL (14–97,000)	1. Correction of PLT counts $\geq$ 100,000/µL: 80% 2. Chemotherapy resumption: 100%	No TEEs observed
Eltrombopag						
Kellum et al[62]	Randomized, multicenter double-blind, placebo-controlled	$N = 183$ patients with various SOTs who were to receive first-line carboplatin/paclitaxel $N = 46$ randomly assigned on placebo $N = 44$ randomly assigned on 50 mg EP	Placebo or EP 50 mg, 75 mg, or 100 mg (1:1:1:1) on day 2 through 11 of each 21-d chemotherapy cycle	Mean Gi/L Placebo: 321.8 50 mg EP: 290.6 75 mg EP: 317.7 100 mg EP: 324	1. Change in PLT counts from day 1 in cycle 1 to PLT nadir in cycle 2: EP did not significantly decrease the change in PLT counts during cycle 2, compared with placebo, although all patients in the EP arms had higher PLT counts on day 1 of cycles 2 and 3 2. Chemotherapy dose intensity: mean dose of carboplatin and paclitaxel was similar across all patient groups	TEEs Placebo: 7% 50 mg EP: 5% 75 mg EP: 5% 100 mg EP: 13%
Winer et al[63]	Randomized, multicenter phase I	$N = 26$ patients with various SOTs who were to receive gemcitabine/cisplatin (group A) or gemcitabine monotherapy (group B) Group A: EP $N = 9$, placebo: $N = 3$ Group B: EP $N = 10$, placebo: $N = 4$	Four dose cohorts of EP: 100 mg, 150 mg, 225 mg, 300 mg given on days -5 to -1 and days 2 to 6 of each cycle, beginning on cycle 2	Mean PLT counts Group A: EP: 108.6×10^9/L Placebo: 140×10^9/L Group B: EP: 269.2×10^9/L Placebo: 263.7×10^9/L	1. Mean platelet nadirs across cycles 2–6: Group A EP: 115×10^9/L Placebo: 53×10^9/L Group B EP 143×10^9/L Placebo: 103×10^9/L 2. Chemotherapy dose reduction/delays across cycles 2–6: Group A EP: 22% Placebo: 33% Group B EP: 40% Placebo: 75%	DVT Group A: EP: 22% Placebo: 0% Group B: EP: 10% Placebo: 0%

(*Continued*)

Table 1 (*Continued*)

	Type of study	Patient population	TPO-RA used and dose administrated	Baseline PLT counts prior to TPO-RA initiation	Major efficacy results	TEE rate
Winer et al[64]	Randomized, multicenter placebo-controlled phase 2	$N = 75$ patients with various SOTs who were to receive ≥ 2 cycles of gemcitabine monotherapy or combination chemotherapy with either carboplatin or cisplatin Combination chemotherapy: $n = 22$ EP, $n = 11$ placebo Gemcitabine monotherapy: $n = 30$ EP, $n = 12$ placebo	EP 100 mg once daily or placebo on days -5 to -1 and days 2 to 6 of each chemotherapy cycle, initiated at first cycle	Mean pre-chemotherapy PLT counts $>100{,}000/\mu L$ in all groups	1. Pre-chemotherapy (day 1) PLT counts across ≤ 6 cycles and PLT nadirs: higher pre-chemotherapy PLT counts and higher PLT nadirs in EP-treated patients vs. placebo in both arms 2. Frequencies of grades 3/4 thrombocytopenia: Combination therapy arm: EP 77 vs. 100% placebo Monotherapy arm: EP 36% vs. 42% placebo 3. Chemotherapy dose delays/reductions: Combination therapy arm: EP 77% vs. 91% placebo Monotherapy arm: EP 62% vs. 83% placebo	Gemcitabine monotherapy: 13% in EP arm vs. 8% in placebo arm Combination chemotherapy: 5% in EP arm vs. 9% arm
Avatrombopag						
Cui et al[52]	Multicenter, open-label, single-arm	$N = 74$ patients with various SOTs receiving a range of treatments	Avatrombopag 60 mg once daily for 5–10 d	$< 75{,}000/\mu L$	1. Correction of PLT counts $\geq 100 \times 10^9/L$ or $\geq 75 \times 10^9/L$ or increase $\geq 100\%$ from baseline in the cycle after TPO-R initiation: 56.8, 59.5, 36.5%, respectively 2. Need for PLT transfusions: 18.9%	No TEEs observed
Gao et al[65]	Single-arm, single-center	$N = 13$ patients with various SOTs receiving a range of treatments	Avatrombopag 60 mg once daily for 8 wk	NR	1. Correction of PLT counts $\geq 50 \times 10^9/L$: 61.3% 2. Transfusion independence: 76.9%	NR
Al-Samkari et al[66]	Randomized, double-blind, placebo-controlled, phase 3	$N = 122$ patients with various SOTs receiving a range of treatments $N = 82$ randomly assigned to avatrombopag 60 mg daily $N = 40$ randomly assigned to placebo	Avatrombopag 60 mg once daily vs. placebo for 5 d before and after chemotherapy administration	31,000/μL (16,000–42,000/μL)	Proportion of responders not requiring PLT transfusions or either a $\geq 15\%$ chemotherapy dose reduction or a $\geq$ 4-d chemotherapy delay: 70%, 95% CI: 58–79 in avatrombopag group vs. 73%, 95% CI: 56–85	2% in avatrombopag group, 3% in placebo

Abbreviations: CIT, chemotherapy-induced thrombocytopenia; CTCAE, common terminology criteria for adverse events; EP, eltrombopag; PLT, platelet; ROMI, romiplostim; RT, radiotherapy; SOTs, solid organ tumors; TEEs, thromboembolic events; TMZ, temozolomide; TPO-RA, thrombopoietin receptor agonists.

dependency or regular growth factor administration in the absence of other possible causes, as are drugs or infections.[70] Notwithstanding the various definitions, thrombocytopenia in these patients is a major problem and failure to achieve platelet counts more than 50,000/μL until 60th day independently correlates with higher treatment-related mortality and poorer overall survival.[71] Platelet transfusions remain the backbone of therapy, while boost doses of $CD34^+$ cells have been used in PGF.[68]

Some retrospective studies, as seen in ►Table 2, examined TPO-RA's role in this context, with reported response rates varying from 39.3 to 83.3%,[72–83] whereas results from few prospective studies are mostly conflicting.[84,85] Both ROMI and EP, and recently avatrombopag, proved to be as safe and effective and possibly cost-effective in comparison to transfusions in thrombocytopenia after allo-HSCT and PGF.[69,72–84] Notably, EP can elicit multilineage responses and along with its immunomodulatory and anti-inflammatory effects can induce enhancement of impaired hematopoiesis in allo-HSCT patients with PGF.[69,74,75,78–81] EP-induced iron chelation is also beneficial in these patients, which are characterized by high ferritin levels and iron overload, since iron decrease could result in BM microenvironment reconstitution.[78] Moreover, newly discovered antiviral properties of EP could contribute to impediment of cytomegalovirus (CMV) reactivation, which is a major cause of PGF.[86] Given the retrospective nature of most of the studies, prospective trials, which are currently conducted, will hopefully shed light on TPO-RA's efficacy in this scenario.

Thrombopoietin Receptor Agonists in Inherited Thrombocytopenias

Inherited thrombocytopenias (ITs) embrace a heterogenous group of rare disorders, which are defined by reduction of platelet numbers with a bleeding tendency at various extents, depending on the severity of thrombocytopenia.[87] ITs may derive either from ineffective platelet production, mostly due to defects in commitment-differentiation of HSC to megakaryocytes, transcription factors necessary for megakaryocyte maturation or proplatelet formation, or from increased platelet clearance.[87] Although breakthrough advances on the recognition of IT genetics have been made, with multiple genes being incriminated, management of these conditions remains troublesome.[87] Besides suggesting patients for taking precautions, antifibrinolytics and platelet transfusions are the only available treatment options for most cases, in the event of a major bleeding or an invasive procedure, whereas allo-HSCT remains as the only curative solution.[87]

Use of TPO-RAs in the management of ITs is a highly promising approach. The rationale for their use in ITs lies upon the fact that TPO-RAs could stimulate for megakaryopoiesis in ITs, provided that megakaryocyte maturation in response to TPO is not disrupted, as is, for instance, in the case of myosin heavy chain 9 (MYH9) related disorders (MYH9-RDs).[87] So far, experience in this setting is restricted. As seen in ►Table 3, reports from the available studies showed that TPO-RAs were well-tolerated and achieved an increase in platelet numbers in the vast majority, thus indicating a potential benefit.[88–91] Importantly, a retrospective study evaluated the use of ROMI in pediatric patients with Wiskott-Aldrich syndrome (WAS) as bridging treatment until HSCT displayed good responses, thus making it a probable safe transit until HSCT.[91] Moreover, increasing case series and reports, mostly in IT patients with an imminent invasive procedure or an elective surgery, demonstrate a successful transient raise in platelet counts with the use of TPO-RAs, thus potentially replacing pre- or perioperative platelet transfusions.[87]

In the wake of these results, TPO-RAs could potentially be considered in the management of ITs, either as a short-term treatment for preparation for an invasive procedure or as an intermediate step before HSCT, as prolonged treatment in patients with serious bleeding events, so as to achieve a durable reduction of bleeding severity and frequency. Additional research is needed to establish the efficacy and safety of TPO-RAs in thrombocytopenia of genetic origin as well as to define the proper dose and timing of administration.

Thrombopoietin Receptor Agonists in Infections

EP has been efficiently utilized in the management of thrombocytopenic patients due to HCV infection and laid the foundation for subsequent investigation of EP's use in the case of infections. During the past years, EP has been examined not only as a means for raising platelet counts in some infections but also as an antimicrobial, antiviral, and antifungal agent, in the context of drug repurposing.

Eltrombopag in Dengue Virus–Related Thrombocytopenia

Dengue virus (DENV), a mosquito-transmitted flaviviridae RNA virus, strikes as an increasing problem in tropical and subtropical regions, where it is endemic and is accountable for high morbidity and mortality rates.[92] It usually presents with a mild or moderate febrile syndrome; yet in 1 to –5%, it presents with severe bleeding manifestations, that is, dengue hemorrhagic fever (DHF).[92] Thrombocytopenia is a common finding, even in the mildest cases and is associated with the clinical outcome. It usually occurs between the third and the seventh day of fever, with platelet counts reaching below 30,000/μL.[92] Thrombocytopenia is multifactorial and is attributed to reduced platelet production, mostly due to DENV-associated myelosuppression, as well as increased peripheral platelet destruction.[92] Therapeutic choices are restricted with variable efficacies and include platelet transfusions, anti-D immune globulin, and papaya Carica leaves.[92]

A randomized controlled phase II clinical trial evaluated the efficacy and safety of EP to improve thrombocytopenia in moderate to severe dengue patients at doses of 25 and 50 mg, given for 3 consecutive days when platelets first fell below 100,000/μL.[93] It was shown that EP led to significant increase in platelet counts, above 150,000/μL, on day 7 of enrollment, in 91% of patients, contrary to 55% of control-group

Table 2 Retrospective studies of thrombopoietin receptor agonists' use in post-allogeneic stem cell transplant

	Patients (*n*)	Posttransplant thrombocytopenia	TPO-RA	Response definition	Response rates	Time from start of TPO-RA to PLT response	Predictive factors of response
Hartranft et al[72]	$n = 13$	PFPR ($n = 4$) and SFPR ($n = 9$)	ROMI 1–10 μg/kg	PLT $\geq 50 \times 10^9$/L for 7 consecutive days without PLT transfusion	R: 53.8%	35 (14–56) d to response	Inclusion of an antilymphocyte agent (ATG or alemtuzumab) was more common among the nonresponders
Bosch-Vilaseca et al[73]	$n = 20$	PFPR ($n = 2$) and SFPR ($n = 18$)	ROMI 1–7 μg/kg ($n = 18$) EP 50–150 mg ($n = 2$)	CR: $\geq 30 \times 10^9$/L for 7 consecutive days without PLT transfusion	60% ROMI: 66.6% EP: 0%	28 d to response	Age < 40 y, previous response to other hematopoietic growth factors, and presence of MK in BM were associated with higher responses
Fu et al[74]	$n = 38$	SFPR ($n = 15$), PGF ($n = 15$), DPE ($n = 8$)	EP 50–100 mg daily	CR: PLT recovery to $\geq 50 \times 10^9$/L for 7 consecutive days without PLT transfusion R: PLT recovery to independence from PLT transfusion but with a PLT count $< 50 \times 10^9$/L during or within 7 days after EP treatment OR: CR and R	OR: 63.2% CR: 52.6% R: 10.5%	17 (2–89) d to PLT response 32 (7–127) d to CR	Presence of MK before initiation
Yuan et al[75]	$n = 13$	PFPR ($n = 6$) and SFPR ($n = 7$)	EP 25–50 mg	PLT $\geq 50 \times 10^9$/L for 7 consecutive days without PLT transfusion	62%	33 (11–68) d to response	Both patients with adequate and decreased MK in BM responded
Marotta et al[76]	$n = 13$	PFPR ($n = 1$) PGF ($n = 12$)	EP 50–150 mg	CR: PLT $> 80 \times 10^9$/L, Hb > 11 g/dL, and ANC $> 1.5 \times 10^9$/L	46%	28–120 d to response	NR
Bento et al[77]	$n = 86$	PIT ($n = 16$) and SFPR ($n = 71$)	EP 25–150 mg ($n = 51$) ROMI 1–7 μg/kg ($n = 35$)	PLT $\geq 50 \times 10^9$/L for 7 consecutive days without PLT transfusion	72%	66 (2–247) d to response	Decreased numbers of MK in BM were associated with a slower response
Aydin et al[78]	$n = 12$	PEF ($n = 1$), PGF ($n = 11$)	EP 50–150 mg daily	CR: PLT $> 50 \times 10^9$/L, ANC $> 1.500 \times 10^6$/L, Hb > 10 g/dL without transfusions or G-CSF support	CR: 83.3%	66 (44–425) d for PLT counts 141 (6–291) d for Hb levels 200 (21–379) d for ANC	NR

Table 2 (*Continued*)

	Patients (*n*)	Posttransplant thrombocytopenia	TPO-RA	Response definition	Response rates	Time from start of TPO-RA to PLT response	Predictive factors of response
Gao et al[79]	$n = 32$	PGF ($n = 15$), SFPR ($n = 17$)	EP 50–100 mg daily	CR: PLT $\geq 100 \times 10^9$/L for 7 consecutive days without transfusion PR: PLT $\geq 50 \times 10^9$/L but $< 100 \times 10^9$/L for 7 consecutive days without PLT transfusion OR: CR and PR	CR: 43.8% PR: 22.8% OR: 65.6%	41 d to PR, 62 d to CR	PGF-independent risk factor of OR, decreased MK amounts, and splenomegaly independent risk factors of CR
Halahleh et al[80]	$n = 14$	PGF	EP 50–150 mg	PLT $> 50 \times 10^9$/L, Hb > 10 g/dL, and ANC $> 1.0 \times 10^9$/L	57%	30 (6–43) d to response	All patients with adequate MK in BM responded
Giammarco et al[81]	$n = 48$	PGF	EP 25–100 mg	CR: PLT $> 50 \times 10^9$/L, Hb > 10 g/dL, ANC $> 1.5 \times 10^9$/L PR: transfusion independence, Hb > 8 g/dL, PLT $> 20 \times 10^9$/L, ANC $> 0.5 \times 10^9$/L	CR: 50% PR: 25% OR: 75%	60 (14–300) d to response	HLA-matched donor, $CD34^+$ dose at transplant $> 4 \times 10^6$/kg, EP initiation at least 90 d after transplantations were positive predictors of response
Yan et al[82]	$n = 34$	PIT ($n = 7$) and SFPR ($n = 27$)	EP 25–100 mg	CR: PLT $> 50 \times 10^9$/L for 7 consecutive days without PLT transfusion PR: PLT $> 20 \times 10^9$/L for 7 consecutive days without PLT transfusion	CR: 60.7% PR: 72.1%	8 (1–51) d to PR, 23 (2–117) d to CR	Hypoplasia of BM and decreased MK numbers were found to be risk factors for CR and OR
Zhou et al[83]	$n = 61$	DPE ($n = 35$), SFPR ($n = 26$)	Avatrombopag 20–60 mg	CR: PLT $> 50 \times 10^9$/L for 7 consecutive days without PLT transfusion OR: PLT $> 20 \times 10^9$/L for at least 7 consecutive days with independence of PLT transfusion	CR: 39.3% OR: 68.9%	21 (6–33) d to response, 25 (9–40) d to CR	Adequate number of MK-independent protective factor for OR and CR

Abbreviations: ANC, absolute neutrophil count; ATG, antithymocyte globulin; BM, bone marrow; CR, complete response; DPE, delayed platelet engraftment; EP, eltrombopag; G-CSF, granulocyte-colony-stimulating factor; Hb, hemoglobin; HLA, human-leucocyte antigen; MK, megakaryocytes; NR, not reported; OR, overall response; PEF, primary engraftment failure; PFPR, primary failure of platelet recovery; PGF, poor graft function; PIT, persistent isolated thrombocytopenia; PLT, platelets; PR, partial response; R, response; ROMI, romiplostim; SFPR, secondary failure of platelet recovery.

Table 3 Results from studies of the use of thrombopoietin receptor agonists in inherited thrombocytopenias

	Disease	Type of study	Sample	TPO-RA	PLT counts	Response rate	Treatment duration
Pecci et al[88]	MYH9-RD	Prospective, Phase II	$n = 12$	EP 50–75 mg/d	31.2×10^9/L	R: 92% CR: 67% BR: 80%	3–6 wk
Gerrits et al[89]	WAS	Prospective, Phase II	$n = 8$	EP 9–75 mg/d	19×10^9/L	R: 62.5% CR: 50% BR: 75%	20–187 wk
Zaninetti et al[90]	MYH9-RD ANKRD26-RT WAS mBSS ITGB3-RT	Prospective, Phase II	$n = 24$	EP 25–75 mg/d	40×10^9/L	R: 91.3% CR: 47% BR: 83%	3–6 wk
Khoreva et al[91]	WAS	Retrospective	$n = 67$	ROMI 9 µg/kg/wk	2,109/L	R: 60% CR: 33% BR: 100%	1–12 mo

Abbreviations: ANKRD26-RT, ankyrin repeat domain containing 26 related thrombocytopenia; BR, reduction or absence of bleeding events independent of platelet count raise; CR, complete response; EP, eltrombopag; ITGB3-RT, integrin subunit β3-related thrombocytopenia; mBSS, monoallelic Bernard-Soulier syndrome; MYH9-RD, myosin heavy chain 9 related disorders; PLT, platelet; R, response, whichever response observed; ROMI, romiplostim; WAS, Wiskott-Aldrich syndrome.

patients.[93] Moreover, both doses were equally effective, whereas 25-mg dose was safer than the higher one.[93] Similarly, a cross-sectional observational study also investigated efficacy and safety of short-course EP, given at the aforementioned doses in DHF, and showed high platelet recovery rates in up to 94%.[94] Finally, a case report demonstrated efficacy of ROMI in a patient with multiple myeloma and DENV-associated thrombocytopenia.[95]

Considerably, these findings indicate a potential use of TPO-RAs in the management of DHF; yet, more studies need to be conducted to further determine their efficacy and optimize dose and timing of administration.

Thrombopoietin Receptor Agonists in Staphylococcal Infections

Staphylococcus epidermidis (*S. epidermidis*) is a common Gram (+) bacterium that is present both in the environment and human skin.[96] Due to its capacity to form biofilms, an assemblage of bacterial biomass, which is firmly adhered to a surface, represents a serious concern, as it can enter circulation and trigger systemic infection, particularly in immunocompromised patients.[96] Moreover, persister cells inside biofilms contribute to significant resistance to conventional antibiotics.[96] *Staphylococcus aureus* (*S. aureus*) is the most frequent cause of bacterial infections worldwide, with surfacing multiresistant pathogens, such as methicillin-resistant *S. aureus* (MRSA), hindering management of these infections.[97] Hence, the need for development of novel treatments has arisen.

In the context of drug repurposing, an in vitro study evaluated the antistaphylococcal effects of EP against 2 strains and 12 clinical isolates of *S. epidermidis* and showed that EP exerts bacteriostatic effects against them, with a minimal inhibition concentration (MIC) of 8 µg/mL.[96] Additionally, it has bactericidal potential, with minimal bactericidal concentrations being slightly higher than MICs and dose-dependent.[96] Importantly, EP was competent to impede in a strain-dependent way biofilm formation and eradicate preexisting ones.[96] Furthermore, persister cells, which are resistant to vancomycin even in high doses, were efficiently eliminated by EP, but in a dose- and strain-dependent way.[96] Of note, concurrent administration of low-dose EP with vancomycin demonstrated a synergistic efficacy, while higher EP doses were not toxic for mammalian cells.[96]

Similar findings were reported regarding efficacy against *S. aureus*.[97,98] EP had bacteriostatic against 55 *S. aureus* clinical isolates, including resistant ones, with MIC comparable to that of common antibiotics, and also inhibited *S. aureus* intestinal colonies growth in a cell line model, with minimum toxicity.[97] Furthermore, it exhibited antimicrobial activity in an in vivo mouse infection model.[97] Correspondingly, a recent study reported EP's potency against *S. aureus*, MRSA included, both alone and in combination with vancomycin.[98] It also showed that it can hamper dose dependently *S. aureus* biofilm formation, while in vivo activity against MRSA was also confirmed, using a wound and a thigh infection model, and a peritonitis model as well, without

toxicity being observed.[98] Although exact mechanism of EP's antistaphylococcal activity is unknown, previous studies suggested that endopeptidase lytE and endonuclease yokF may be involved, while it was also shown that EP disrupts and weakens proton motive force, which is vital for bacteria.[97,98]

Conclusively, EP displays antistaphylococcal activity and is an appealing agent that could possibly be employed in the treatment of these infections, especially MRSA.

Thrombopoietin Receptor Agonists in Viral Infections

CMV poses a great threat to HSCT recipients and is a significant cause of morbidity and transplantation failure.[86] Although various treatment options such as ganciclovir exist, they are usually correlated to critical adverse events, as is thrombocytopenia.[86] A single case report demonstrated an efficient response of platelet counts when EP was administrated in a patient with CMV-associated thrombocytopenia, previously unresponsive to conjugated immunosuppressive and antiviral treatment.[99]

Engrossingly, a subsequent study revealed that EP bears antiviral activity through its iron chelation properties.[86] Specifically, it was shown that EP hampers viral replication during the late stages of replication cycle of various CMV strains, resistant ones included, with concentrations being within therapeutic plasma concentration range.[86] Moreover, its combination with either ganciclovir or foscarnet exerted synergistic effects against CMV.[86] Trying to unveil its inhibitory mechanism of action, it was demonstrated that EP impedes viral replication, in a TPO-R-independent way, since same effects were observed in human and murine fibroblasts, which lack TPO-R.[86] Also, it was reported that these effects were attributed to iron depletion provoked by EP, given that addition of Fe^{3+} obstructed EP's action and coadministration with deferasirox displaying antagonistic effects.[86] Importantly, although iron chelators were previously shown to inhibit CMV replication, some of them also affected other dividing cells, and EP did not affect cell proliferation.[86]

Although results for CMV derive from a single study, similar findings regarding EP's antiviral potency were previously described. In particular, EP exhibited antiviral activity against severe fever with thrombocytopenia syndrome virus.[86] Conversely, EP was found to be a lead activator of HIV-1 proviral transcription, which could be useful for activating and then eliminating latently infected cells.[100] In conclusion, EP's utility in viral infections is of great interest and initial results are quite encouraging, thereby sowing the seeds for further research.

Thrombopoietin Receptor Agonists in Fungal Infections

Fungal infections are an increasing threat that are responsible for notable morbidity, mainly in immunocompromised patients, with Cryptococcosis, an invasive fungal infection provoked by *Cryptococcus neoformans* (*C. neoformans*)/*Cryptococcus gattii* (*C. gattii*) species complex, being among the most prevalent.[100] Cryptococcosis treatment is rather troublesome, since amphotericin B is nephrotoxic, 5-flucytosine is usually locally available, and fluconazole-resistant isolates keep emerging.[101]

An in vitro study investigated EP's antifungal activity against Cryptococcus isolates and other fungi as well.[101] It was demonstrated that EP was fungistatic but not fungicidal, particularly in higher temperatures, against *C. neoformans/C. gattii* species complex, *Candida glabrata*, and *Trichophyton rubrum*, whereas no activity was observed against other Candida species, *Aspergillus fumigatus*, or *Fusarium solani*.[101] Moreover, EP disrupted cryptococcal virulence factors, inducing a reduction of biofilm and capsule development and impairment of melanin production, thus confining cryptococcal spread.[101] It was also suggested that EP's mechanism of action may be mediated by calcineurin pathway and is different from that of azoles.[101]

In conclusion, although available data derive from a single in vitro study, EP exhibited excellent anticryptococcal activity and this should provide the basis for further research of EP's potency as an antifungal agent.

Thrombopoietin Receptor Agonists in Acute Radiation Syndrome

Acute radiation syndrome (ARS) is a rare but usually lethal event and involves whole body irradiation exposure for a short time.[102] High penetrating radiation doses are demanded for the manifestation of ARS.[102] Depending on radiation doses and tissues' radiosensitivity, ARS can be presented with various clinical syndromes of variable severity, which frequently involves the gastrointestinal, the hematopoietic, and central nervous system (CNS) and may lead either to multiorgan failure and a prompt death or a delayed passing, within weeks or months, usually because of recurrent infections or bleedings induced by underlying BM failure.[102]

Management of ARS is an emergency, particularly in the case of nuclear accidents, and it should not be detained. Medical countermeasures encompass standard supportive care such as fluids and antibiotics, transfusions, G-CSF, EPO, and interleukin-3 administration, until restoration of hematopoiesis is accomplished, whereas HSCT, which would be favorable, is not widely available and is accompanied by higher complication rates, exceptionally when it is urgently conducted.[102] Efforts have been made to optimize a treatment protocol for ARS and recently incorporation of ROMI to ARS therapy has been examined.

Hirouchi et al evaluated survival of mice exposed to lethal γ-radiation doses after adding ROMI to standard G-CSF, EPO, and nandrolone administration and demonstrated superior survival in the combination arm that reached 100% on day 30 versus 50% in the arm where ROMI was not administered.[103] Another study investigated ROMI's use as monotherapy in the same setting and reported that ROMI was competent to suppress lethal γ-irradiation effects, with survival rates reaching 85% on 200th day.[104] Remarkably, ROMI not only improved all hematologic parameters but also augmented reconstitution and recovery of intestinal mucosa.[104] In agreement with these findings, enhanced repair of liver damage was also described.[105] Similar findings

regarding the mitigative effects of ROMI were also reported by its coadministration with pegfilgrastim in non-human primates.[106]

Interestingly, ROMI's mechanism of action in ARS was also explored. Previous data support that BM stem cell deficiency can result in promoted hematopoiesis in the lungs, where hematopoietic progenitors are present, and can further migrate and repopulate BM.[105] Correspondingly, a study indicated that ROMI enhanced megakaryopoiesis in the lungs and spleen of irradiated mice, where increased megakaryocyte progenitors were observed.[105] Rapid hematopoiesis in the spleen along with an increase in mesenchymal cells was also reported.[105] It has been previously shown that TPO-RAs contribute to non-homologous end joining (NHEJ) DNA repair in HSCs.[3] The aforementioned studies reported that ROMI repressed DNA double-strand breakage in BM cells of irradiated mice and led to increased DNA repair and also inhibited cellular apoptosis.[104,105] Moreover, a study demonstrated ROMI-induced reduction in expression of three miRNAs, miR-296–5p, miR-328–3p, and miR-486–5P, which were elevated in irradiated mice and correlated with radiation-induced leukemogenesis.[105] MiRNAs are enclosed in exosomes, which derive from various cells such as MSCs and maintain parental properties as is tissue damage repair. Given the observed expansion of MSCs in the spleen of irradiated mice, ROMI could possibly regulate miRNAs expression and exert its actions via exosomes targeting HSCs.[105] Of note, some studies reported decreased levels of plasminogen activator inhibitor 1 (PAI-1) among irradiated mice on ROMI administration.[105] PAI-1 is a significant regulator of cellular senescence and its downregulation enacts antioxidative enzymes and suspends ROS production. Collectively, these findings support that ROMI, apart from improving hematopoiesis in various organs, produces significant multitarget effects that contribute to increased survival rates and recovery of damaged tissues.

In light of these results, ROMI got FDA approval, under the animal rule, as a medical countermeasure for ARS.[107] Further studies should be conducted to determine appropriate dose and duration of treatment and to elucidate the exact mechanisms of action.

Conclusions

Evidently, use of TPO-RAs is progressively being incorporated in the management of non–immune-mediated thrombocytopenia, both in benign and malignant diseases. TPO-RAs are easy to administer and have low potential for drug-to-drug interactions. Besides TPO agonism, increasing evidence highlights a broad spectrum of multitarget effects that TPO-RAs, and EP in particular, may possess and could render TPO-RAs as a highly promising approach, in terms of efficacy in heterogenous contexts, in the near future. TPO-RAs could possibly be employed as a supportive measure in the management of HSCT patients or those with HMs or SOTs, to whom disease- or treatment-related thrombocytopenia poses a major problem. Similar to patients with CLD, TPO-RAs could be of use in patients with ITs as a short-term treatment, whenever an invasive procedure is planned. Although data are restricted and mostly derive from small studies, thorough research and future trials will possibly pave the way for TPO-RAs' application not only in thrombocytopenic patients but also in infections as an antiviral, antibacterial, or antifungal agent. It is important to note that while these potential uses of TPO-RAs are intriguing, further research is needed to establish their safety and efficacy in these contexts. Although TEE rates and transient blast proliferation seem not to be correlated with a particular TPO-RA, and are probably a class effect or are attributed to the underlying disease, further study is needed to draw strong conclusions. Finally, increasing use of TPO-RAs in various settings may be accompanied by previously infrequent risks, such as increased incidence of neutralizing antibodies against ROMI, EP-induced MPN-like features, and reticulin fibrosis or EP-mediated iron-deficiency anemia; so, patients should receive these agents in the context of a clinical trial and be carefully monitored, whenever possible. In conclusion, the future of novel TPO-RA applications holds exciting possibilities and ongoing research will potentially expand TPO-RA's use beyond their current approved indications.

What is known about this topic?

- Thrombopoietin receptor agonists (TPO-RAs) are potent stimulators of megakaryopoiesis and can elicit tri-linage responses well.
- TPO-RAs are widely used in the management of immune thrombocytopenia, aplastic anemia, HCV-related thrombocytopenia, and recently in patients with chronic liver disease undergoing invasive procedures.

What does this paper add?

- A comprehensive review of potential novel TPO-RAs' uses, based on findings from recent studies in various thrombocytopenic settings, including hematologic malignancies, chemotherapy-induced thrombocytopenia, inherited thrombocytopenias, and thrombocytopenia post-hematopoietic stem cell transplantation, as well as acute radiation syndrome.
- An insight into employment of TPO-RAs in infections, as an antistaphylococcal, antiviral, and antifungal agent, in terms of drug repurposing.
- Shedding light on possible multitarget effects of TPO-RAs.

Conflict of Interest

The authors declare that they have no conflict of interest.

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