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Optimal use of thrombopoietin receptor agonists in immune thrombocytopenia

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Abstract: The thrombopoietin receptor agonists (TPO-RAs) are a class of platelet growth factors commonly used to treat immune thrombocytopenia (ITP). There are three agents that have been investigated for the treatment of chronic ITP: the peptide agent romiplostim and the small molecule agents eltrombopag and avatrombopag. These agents offer a higher clinical response rate than most other ITP therapies but may require indefinite use. This review is a critical appraisal of the TPO-RAs in adult ITP, defining the optimal patient groups to receive these agents and assisting the hematologist with agent choice, goals of treatment, dosing strategies, and toxicity management. Use of endogenous thrombopoietin levels to predict response to eltrombopag and romiplostim treatment is discussed and alternative dosing protocols suited for certain patient subgroups are described. Finally, indications for discontinuation and combination therapy with other agents are considered.

Keywords: avatrombopag, eltrombopag, immune thrombocytopenia, ITP, platelets, romiplostim, thrombopoietin, thrombopoietin receptor agonist

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Introduction

Over the past decade, the thrombopoietin receptor agonists (TPO-RAs) have been established as a mainstay in the treatment of immune thrombocytopenia (ITP).[1,2] TPO-RAs are a class of platelet growth factors that mimic the action of endogenous thrombopoietin (TPO) on megakaryocytes and megakaryocyte precursors, promoting their growth and differentiation and increasing platelet production.[3] In addition to their approval in ITP, these agents have been approved or are under investigation in numerous other thrombocytopenic disorders.[4–7] Their use in ITP is supported by pathophysiologic studies demonstrating that ITP is characterized by both increased platelet destruction as well as inappropriately low platelet production, with the latter thought secondary to the proapoptotic action of glycoprotein-specific platelet autoantibodies and cytotoxic lymphocytes on megakaryocytes.[8–10] Therefore, the efficacy of thrombopoietic agents in ITP is attributed to their ability to promote megakaryocyte survival and increase platelet production, thereby improving the platelet count through reversal of the underproduction defect.

There are three TPO-RAs that have been demonstrated to be effective in the management of ITP in multiple phase III studies.[1,2,11] Romiplostim (Nplate, Amgen, Thousand Oaks, CA, USA) is a peptide TPO-RA administered subcutaneously on a weekly schedule and eltrombopag (Promacta, Novartis, Basel, Switzerland) and avatrombopag (Doptelet, Dova, Durham, NC, USA) are small molecule TPO-RAs administered orally on a once-daily schedule.[12–14] Given the numerous available treatment options for patients with ITP, including on-label, off-label, and experimental agents, recognizing when to choose a TPO-RA over immunosuppressive or immunomodulatory agents or splenectomy is important. Similarly, understanding how to choose between the TPO-RAs, their dosing, switching between TPO-RAs, recognizing when discontinuation is appropriate (either because remission has been achieved or clinical response has been inadequate), considering combination therapy in treatment-refractory patients, and managing side effects are essential to the optimal use of these agents. Unfortunately, current guidelines[15,16] are outdated and give little guidance. This review

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will address these areas, providing an evidence-based framework for the practicing adult hematologist.

Who to treat with a thrombopoietin receptor agonist

Approval for TPO-RAs in ITP is currently limited to those patients with chronic ITP (disease duration of 1 year or more, in contrast with acute ITP and persistent ITP in which disease duration is <3 months and 3–12 months, respectively[17]) who have failed treatment with glucocorticoids, splenectomy, or intravenous immunoglobulin (IVIG). It is important to note that in many of the pivotal studies, ITP was considered chronic if present for over 6 months.[1,2,11] Despite this, use of these agents for patients with acute or persistent ITP is frequent in clinical practice and first-line use is under investigation.[18] Indeed, a recent meta analyses of all romiplostim studies demonstrated that the response rates and adverse event profiles were virtually identical for patients with ITP for <1 year (with acute or persistent disease) and patients with ITP for ⩾1 year.[19]

Table 1 summarizes the phase III studies examining TPO-RA use in ITP. The decision to initiate a TPO-RA over an immunosuppressive agent or splenectomy is complex and should account for numerous patient and disease-related factors. Overall, TPO-RAs have a higher clinical response rate (~80%) than most other agents (<60%) used in the second-line and beyond,[20] but may require prolonged use. Splenectomized patients who have not previously received a TPO-RA had a response rate of 39–62% in phase III trials that included large numbers of such patients.[2,21,22] There is little tachyphylaxis to TPO-RAs in patients with ITP, as responding patients are typically able to maintain a response for extended durations of time.[23] Studies have been published demonstrating durable remissions in a minority of patients treated with TPO-RAs (often treated for extended periods before remission is achieved), although this phenomenon is poorly understood, unpredictable, and may simply represent spontaneous remission that would have occurred in the absence of TPO-RA treatment.[24,25] Therefore, patients in whom compliance is a concern, who dislike taking medication on a chronic basis, who desire treatments with a higher likelihood of treatment-free remission, or those with limited access to TPO-RAs are best treated with other agents. In the second-line setting, the typical alternatives to TPO-RAs include rituximab and splenectomy. Given that a significant minority of adults with ITP will achieve remission with medical therapy during the first year following diagnosis, the authors prefer to use medical therapies for at least 1 year before considering splenectomy in most adult patients with ITP. In one study, one-third of nonsplenectomized patients with acute or persistent ITP achieved remission when treated with romiplostim for up to 1 year.[24]

As eltrombopag is potentially hepatotoxic and its use has been associated with venous thromboembolism (VTE) in patients with chronic liver disease,[5,29] avoidance of this agent in patients with ITP with chronic liver disease is advised. There are few published data regarding the safety of romiplostim in the chronic liver disease population. Avatrombopag has been extensively studied in chronic liver disease patients without ITP and has not demonstrated significant hepatotoxicity or increased VTE risk in this patient group.

Recent data have emerged demonstrating an inverse relation between the endogenous TPO level and response to treatment with eltrombopag and romiplostim in patients with ITP.[30–32] Lower endogenous TPO levels predicted improved probability and depth of response to these two agents. In those patients with a normal baseline TPO level (⩽100 pg/ml, as assessed by the only currently commercially available assay validated for clinical use, an enzyme-linked immunosorbent assay-based test from Quest Diagnostics, San Juan Capistrano, CA, USA), likelihood of robust response to either agent was high.[30] In contrast, patients with significant TPO elevations (>200 pg/ml) were unlikely to have a satisfactory response to either agent, suggesting that these patients may be better managed with other modalities. Figure 1 illustrates a predictive model of response fraction (fraction of measured platelet counts on TPO-RA treatment that are $\geqslant 50 \times 10^9$/l and $\geqslant 20 \times 10^9$/l higher than pretreatment baseline) based on the TPO level. Given these data, TPO level measurement can be considered for patients in whom TPO receptor agonist treatment is anticipated to help guide clinical decision making. Due to the turn-around time of this send-out assay it is best assessed in advance of the need to initiate therapy, and it can be readily measured at any point as TPO levels in patients with ITP do not appear to be significantly affected by platelet count, disease duration, or receipt of ITP-directed therapies.[31,33]

Table 1. Phase III trials of TPO-RAs in ITP. Each trial was a prospective, multicenter, randomized, placebo-controlled, double-blind study except Kuter and colleagues[1] which was open label.

Study	Patient number (*n*)	Location	Study population	Major results (compared with placebo)
Bussel[22]	Eltrombopag $n = 76$ Placebo $n = 38$	Worldwide (63 sites)	Adults with ITP for ⩾6 months and a pretreatment Plt $<30 \times 10^9$/l 39% splenectomized	Significantly higher rate of platelet response[a] Significantly less bleeding
Cheng[2]	Eltrombopag $n = 135$ Placebo $n = 62$	Worldwide (75 sites)	Adults with ITP for ⩾6 months and a pretreatment Plt $<30 \times 10^9$/l 36% splenectomized	Significantly higher rate of platelet response[a] Reduced use of concomitant ITP medications Reduced need for rescue therapy
Tomiyama[26]	Eltrombopag $n = 15$ Placebo $n = 8$	Japan	Adults ⩾20 years old with ITP for ⩾6 months and a pretreatment Plt $<30 \times 10^9$/l 70% splenectomized	Significantly higher rate of platelet response[a] Significantly less bleeding Lower doses of eltrombopag were effective in Japanese patients
Yang[27]	Eltrombopag $n = 104$ Placebo $n = 51$	China	Adults with ITP for ⩾12 months and a pretreatment Plt $<30 \times 10^9$/l 16% splenectomized	Significantly higher rate of platelet response[a]
Kuter[21]	Romiplostim $n = 83$ Placebo $n = 42$ (patients from two parallel studies)	United States and Europe	Adults with ITP for ⩾12 months and a screening mean Plt $<30 \times 10^9$/l 50% splenectomized	Significantly higher rate of platelet response[a] Reduced use of concomitant ITP medications
Kuter[1]	Romiplostim $n = 157$ Standard of care $n = 77$	North America, Europe, and Australia	Adults with ITP for ⩾12 months and a pretreatment Plt $<50 \times 10^9$/l 0% splenectomized	Significantly higher rate of platelet response[a] Reduced use of concomitant ITP medications Lower rate of treatment failure Lower rate of splenectomy Significantly less bleeding and transfusions Significantly improved quality of life
Shirasugi[28]	Romiplostim $n = 22$ Placebo $n = 12$	Japan	Adults ⩾20 years old with ITP for ⩾6 months and a screening Plt $\leqslant 30 \times 10^9$/l 44% splenectomized	Significantly higher rate of platelet response[a] Reduced need for rescue therapy
Jurczak[11]	Avatrombopag $n = 32$ Placebo $n = 17$	Europe, Asia, and Australia	Adults with ITP for ⩾12 months and a screening mean Plt $<30 \times 10^9$/l 33% splenectomized	Significantly higher rate of platelet response[a] Reduced use of concomitant ITP medications

[a]Platelet response defined as a platelet count ⩾50×10^9/l at a given assessment on treatment with TPO-RA or placebo.
ITP, immune thrombocytopenia; Plt, platelet; TPO-RA, thrombopoietin receptor agonist.

Which thrombopoietin receptor agonist to select

Currently, only romiplostim and eltrombopag are United States Food and Drug Administration (US FDA)-approved for the treatment of chronic ITP, although a supplemental new drug application has been accepted by the US FDA for the use of avatrombopag to treat chronic ITP. Therefore,

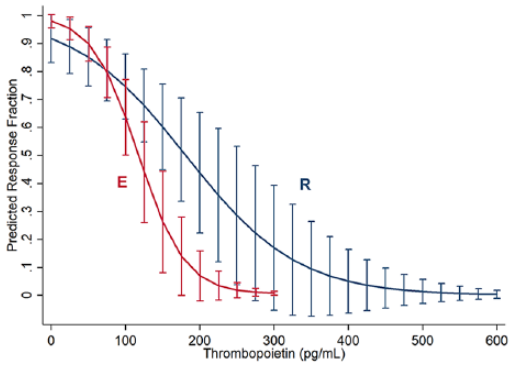

Figure 1. Impact of endogenous thrombopoietin level on clinical response to eltrombopag and romiplostim in patients with ITP. Predicted mean response fraction (fraction of measured platelet counts $\geq 50 \times 10^9$/l and $\geq 20 \times 10^9$/l higher than the pretreatment baseline) based on thrombopoietin level for treatment with eltrombopag (red, E) or romiplostim (blue, R). Error bars represent 95% confidence interval (shown at intervals of 25 pg/ml). Reproduced from Al-Samkari and Kuter.[30]
ITP, immune thrombocytopenia.

this agent may be approved for ITP in the future. The pharmacologic characteristics of these TPO-RAs are compared in Table 2.

Although each of these agents demonstrates comparable initial overall response rates, several considerations impact agent selection. Eltrombopag and avatrombopag offer the convenience of oral administration, compared with romiplostim which usually requires weekly clinic visits for subcutaneous administration. The patient's insurance coverage may dictate which agent is covered. Eltrombopag absorption is severely impacted by consumption of fat or divalent cations, essentially requiring a 4-hour fasted window around its administration (6 h if 50 mg calcium is consumed, an amount which is present in a single serving of numerous dairy, grain, and vegetable products) otherwise its effectiveness may be compromised.[34,35] In contrast, avatrombopag may be taken with or without food (and absorption is actually optimized when taken with food).[36,37] Patients with modest elevations in baseline endogenous TPO level (TPO 100–200 pg/ml) may respond better to romiplostim than eltrombopag (Figure 1).[30] While response to avatrombopag has been shown to be impacted by baseline TPO level in patients with thrombocytopenia of chronic liver disease,[38] studies have not yet assessed the role of TPO levels in predicting avatrombopag response in patients with ITP. The higher rates of clinical response to romiplostim over eltrombopag observed in patients with TPO level elevations may be related to agent potency. In healthy volunteers, maximal doses of romiplostim and avatrombopag produced peak platelet counts 8–10 times higher and 3–5 times higher, respectively, than maximal doses of eltrombopag.[36,39,40] Figure 2 demonstrates the relative potency of each of these three agents in an ITP patient who received all three drugs.[41]

Cost is an important consideration when deciding to use TPO-RA treatment, as these agents remain expensive. In consideration of which agent is more cost effective, US-based cost-effectiveness analyses comparing eltrombopag with romiplostim have reported conflicting results (one favoring eltrombopag and the other favoring romiplostim).[42,43] The average wholesale price in the US for each of the three agents is given in Table 2.

How to dose thrombopoietin receptor agonists

Romiplostim

The prescribing information recommends an initial dose of 1 μg/kg/week, with sequential increases of 1 μg/kg each week to achieve a platelet count $\geq 50 \times 10^9$/l.[13] In clinical practice, however, patients are frequently initiated at a higher dose to shorten the time required to titrate to a patient's optimized dose.[44] Evidence suggests this is well tolerated, since in a large study including 120 patients with ITP initiated at ≥2 μg/kg/week the rate of thrombocytosis was only 4%.[44] Additionally, in a phase III study of romiplostim, all patients were initiated at a dose of 3 μg/kg/week.[1] Initiation at even higher doses in patients with glucocorticoid and IVIG-refractory disease and acute bleeding symptoms may also be prudent. In a small study of hospitalized patients with refractory ITP who were initiated on romiplostim, initiating romiplostim at ≥2 μg/kg/week (median starting dose of 4.5 μg/kg/week) resulted in less bleeding, shorter hospital length of stay, and higher likelihood of achieving a platelet count $\geq 50 \times 10^9$/l with no thrombotic events, than initiating romiplostim at 1 μg/kg/week.[45] The authors routinely start most patients at 3 μg/kg/week, 5 μg/kg/week if severely thrombocytopenic, and occasionally at 10 μg/kg/week for an initial two doses in cases of clinical emergencies (such as bleeding with profound thrombocytopenia).

Table 2. Comparison of the TPO-RAs used in ITP treatment.

	Romiplostim	Eltrombopag	Avatrombopag
Molecular structure	Peptide	Small molecule	Small molecule
TPO receptor site of action	Extracellular domain	Transmembrane domain	Transmembrane domain
Route of administration	Subcutaneous	Oral	Oral
Dosing frequencya	Weekly	Daily	Daily
Relevant food interactions	N/A	Yes	No
Average USD wholesale price	$2165.34 per 250 µg vial $4330.68 per 500 µg vial	$182.46 per tablet (12.5 mg or 25 mg) $330.20 per tablet (50 mg) $495.30 per tablet (75 mg)	$1132.80 per 20 mg tablet
Current indications	Chronic ITP (adults and children)	Chronic ITP (adults and children) Hepatitis C-associated thrombocytopenia Severe aplastic anemia	Periprocedural thrombocytopenia in patients with CLD
Selected indications under investigation	Chemotherapy-induced thrombocytopenia Perioperative thrombocytopenia	Acute ITP (first-line setting) Inherited thrombocytopenia	Chronic ITP (adults) Chemotherapy-induced thrombocytopenia Perioperative thrombocytopenia

[a]Per drug label.
CLD, chronic liver disease; ITP, immune thrombocytopenia; N/A, not applicable; TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist.

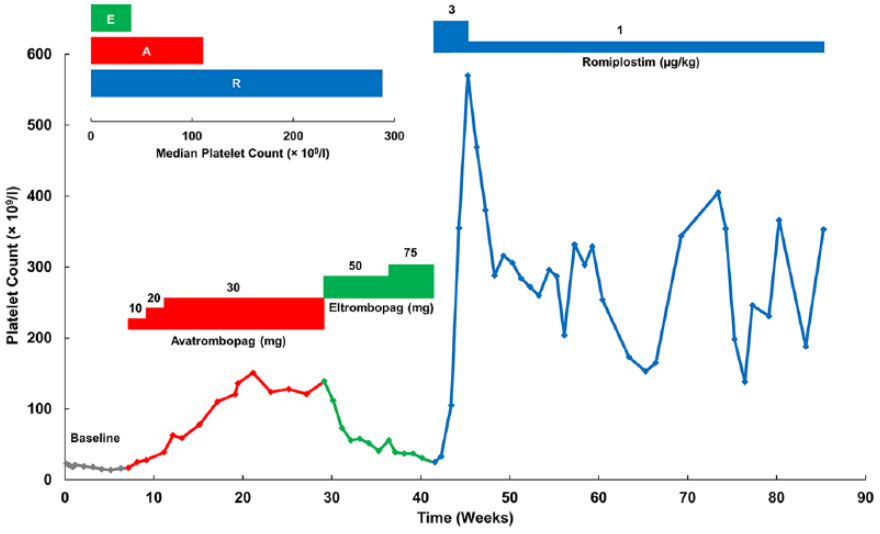

Figure 2. Relative potency of eltrombopag (E), avatrombopag (A), and romiplostim (R) in a patient with ITP. The magnitude of response of this ITP patient to each of these TPO-RAs is comparable to what is seen in healthy volunteers. Dosing for each agent is given above the platelet trend line, and median platelet counts for each agent in this patient are given in the inset bar graph. Reproduced from Al-Samkari and Kuter.[41]
ITP, immune thrombocytopenia.

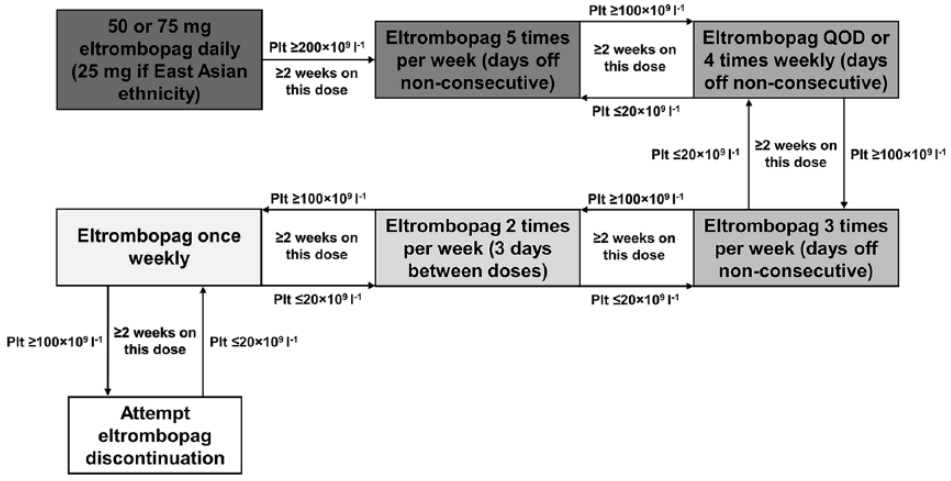

Figure 3. Alternative intermittent eltrombopag dosing protocol. Protocol for administration of eltrombopag less frequently than once daily in patients who poorly tolerate daily dietary restrictions. Can also be used to taper eltrombopag. Reproduced from Al-Samkari and Kuter.[46]
Plt, platelet; QOD, every other day.

Likewise, the authors typically increase the dose by more than 1 μg/kg at a time in nonresponding or poorly responding patients, a rate faster than advised in the prescribing information. The gradual rate of romiplostim dose escalation described in the prescribing information may result in longer durations of profound thrombocytopenia and an increased bleeding risk, whereas more rapid dose escalation presents a risk of thrombocytosis (and a theoretical risk of thromboembolism). The clinician should weigh these risks in determining a rate of dose escalation most appropriate for a given patient.

The prescribing information advises withholding a dose if platelet count is $>400 \times 10^9$/l.[33] However, up to 15% of patients so treated will have a rebound thrombocytopenia to below their prior baseline which may increase their risk of bleeding.[21] While no studies have been published comparing dose reduction and dose withholding in patients with thrombocytosis, our experience is that dose reduction (typically a dose reduction of one-third to two-thirds) is effective in eliminating thrombocytosis with considerably less platelet count fluctuation than with dose withholding.

Eltrombopag

The recommended initial dose of eltrombopag is 50 mg daily in all patients except those of east Asian descent, those with chronic liver disease and children 1–5 years of age, in whom the recommended initial dose is 25 mg daily.[14] Dose increase by one tablet strength (to a maximum of 75 mg) is advised for platelet count $<50 \times 10^9$/l and dose reduction by one tablet strength (to a minimum of 12.5 mg) is advised for platelet count $\geqslant 200 \times 10^9$/l to $<400 \times 10^9$/l. Although used at higher doses in aplastic anemia (150 mg daily), there are few data to support dose escalation to this level in patients with ITP.

Many patients may struggle with the dietary requirements to ensure adequate eltrombopag absorption and may not be fully compliant with the required 4–6 h window of food avoidance. Adhering to the food avoidance window is not trivial given that many patients may receive this agent for extended time periods. In compliant patients with robust platelet count responses to eltrombopag who struggle with dietary quality of life issues, alternative intermittent (AI) eltrombopag dosing may be considered.[46] AI dosing utilizes intermittent eltrombopag dosing 1–5 times weekly rather than daily dosing (Figure 3), usually using the 75 mg dose. Given the kinetics of thrombopoiesis and the 26–35 h half-life of eltrombopag in patients with ITP, dosing less frequently than once daily is rational. Beyond quality of life issues, AI dosing may also be appropriate in lieu of prescribing information dose-reduction instructions and may be an option for use of eltrombopag in resource-poor settings. It is also a suitable option for the slow tapering of this agent.

Similar to romiplostim, the eltrombopag prescribing information advises withholding drug for platelet counts $\geq 400 \times 10^9$/l.[14] Except in cases of extreme thrombocytosis, we opt for AI dosing or dose reduction in this setting as an alternative to withholding the drug to avoid a precipitous drop in the platelet count.

Avatrombopag

As avatrombopag is not yet approved for ITP, specific dosing recommendations are not currently available. In a phase II trial of avatrombopag, a daily dose of 5 or 10 mg daily achieved a platelet response (defined as a platelet count $\geq 50 \times 10^9$/l with $\geq 20 \times 10^9$/l increase above baseline) in approximately half of patients, and a dose of 20 mg daily achieved a platelet response in 80%.[47] This 20 mg dose was used in a subsequent phase III trials with similarly robust response rates.[11]

What adverse events occur and how to monitor for them

TPO-RAs are generally well-tolerated agents. In clinical trials of adult patients with ITP, the most commonly observed nonbleeding-related adverse events of eltrombopag were gastrointestinal symptoms (nausea, vomiting, diarrhea), mild transaminase elevations, and headache.[2] In trials of romiplostim, headache, arthralgia, myalgia, dizziness and insomnia were the most commonly reported symptoms.[1] In avatrombopag trials, headache, fatigue, arthralgia and diarrhea were most commonly reported.[11] The most common adverse event overall was mild to moderate headache, which is typically managed with acetaminophen and dose reduction as necessary. Because of the risk of hepatotoxicity with eltrombopag, liver enzymes and bilirubin should be monitored every 2 weeks during dose optimization and monthly thereafter, with discontinuation of the agent for significant transaminase or bilirubin elevations.[14] Many such patients may resume eltrombopag at a lower dose or altered frequency upon recovery from the hepatic insult.

Thrombotic events and bone marrow fibrosis are the potential adverse events of greatest concern with the use of TPO-RAs in patients with ITP.

Although thrombotic events were not observed, the thrombotic potential of pharmacologic administration of thrombopoietic agents was suggested by the marked thrombocytosis observed in otherwise healthy nonhuman primates exposed to recombinant thrombopoietins.[48,49] However, studies examining the function of platelets from human patients with ITP treated with eltrombopag[50] and romiplostim[51] showed no evidence of platelet hyperreactivity or spontaneous platelet aggregation. To the contrary, there appeared to be a defect in the platelet aggregation response to adenosine diphosphate and epinephrine (likely due to platelet autoantibodies rather than the effect of the drug) in the platelets of patients with ITP despite treatment with romiplostim.[51] It is well recognized that ITP is itself a prothrombotic state,[52–54] but the numerous large controlled studies of patients with ITP receiving the TPO-RAs have not demonstrated a significantly increased of arterial or venous thrombotic risk over those treated with placebo.[1,2,55,56] Of note, these trials had relatively short observation periods. Longer-term nonrandomized observational studies have suggested a modestly higher rate of thrombosis in patients with ITP treated with TPO-RAs as compared with similar observational studies of patients with ITP treated with immunosuppressive agents.[57,58] Therefore, the thrombotic potential of TPO-RAs should be a consideration in patients with ITP with significant risk factors for venous or arterial thrombosis.

In the chronic liver disease population, there is stronger evidence of a possible increased propensity to VTE with TPO-RA use. In two studies of eltrombopag use in patients with chronic liver disease (one examining treatment of periprocedural thrombocytopenia[29] and the other examining treatment of hepatitis C-associated thrombocytopenia[5]), there was an apparent increased rate of VTE (and portal vein thrombosis in particular) in patients receiving eltrombopag. This was not seen, however, in studies of avatrombopag and lusutrombopag to treat periprocedural thrombocytopenia in chronic liver disease patients,[59–61] although these studies were not specifically powered to detect a difference in VTE rate between TPO-RA and placebo-treated patients, and treatment was for a brief period of time.

Therefore, if a thrombotic event occurs in an ITP patient receiving TPO-RA treatment, assessment of thrombotic risk factors should occur as in any patient presenting with a new thrombosis. If

provoking risk factors (e.g. atherosclerosis, obesity, surgery, trauma, or prolonged immobility) are not identified, it may be reasonable to switch to another ITP treatment such as immunosuppression, even if the TPO-RA cannot be accountable for the thrombotic event. This is done with the recognition that a stable platelet count is necessary for the anticoagulation of the patient. If other ITP treatments are known to be ineffective and TPO-RAs are required to maintain a safe platelet count for anticoagulation, they should be continued for this purpose with close monitoring. It is not appropriate to forego anticoagulation in patients with ITP with thrombosis because of thrombocytopenia unless the disease is refractory to all treatments and a minimally acceptable platelet count (e.g. $\geqslant 20 \times 10^9$/l) cannot be achieved.

While bone marrow fibrotic complications remain a potential risk of TPO-RAs, examination of a large number of patients treated with these agents for extended periods of time revealed a very low risk of reversible marrow reticulin fibrosis and essentially no increased risk of more serious, usually irreversible collagen fibrosis.[62,63] Therefore, bone marrow biopsy prior to TPO-RA initiation or serial bone marrow biopsies in patients maintained on TPO-RAs for extended periods are not needed. Similarly, while bone marrow blast percentages may rise in patients with myelodysplastic syndromes treated with TPO-RAs, this reverses upon discontinuation of the agent and there is no increased risk of progression to acute myeloid leukemia even with several years of follow up.[64] The risk of myeloid malignancies in patients with ITP receiving treatment with TPO-RAs has not been rigorously studied, although an increased rate has not been observed in currently published randomized or observational studies.

How to define treatment success

As the ultimate objective of TPO-RA treatment is to prevent bleeding, a target platelet count between 50×10^9/l and 150×10^9/l is appropriate in the majority of patients. However, many patients with severe disease rarely or never achieve a platelet count $\geqslant 50 \times 10^9$/l and more modest goals, such as a platelet count $\geqslant 20 \times 10^9$/l, are acceptable in these patients in the absence of bleeding symptoms.

There is rarely a need to normalize the platelet count, but this situation may arise in patients undergoing major cardiovascular or neurological surgery. In the event a surgeon requests normalization of the platelet count in a patient with ITP due to a perceived high surgical bleeding risk, TPO-RA treatment is capable of achieving this in the vast majority of patients with ITP.[7,65] Additionally, fatigue is a very common symptom in patients with ITP, and may correlate with the platelet count.[66] Although fatigue is frequently challenging to assess, validated instruments for this population are available.[67] While data are lacking, normalization of the platelet count with TPO-RA treatment in patients with ITP suffering from severe fatigue may be considered as a therapeutic trial to treat fatigue.[68]

When to consider discontinuation or combination therapy

Discontinuation of TPO-RA management may be considered in the setting of treatment failure, unacceptable adverse events (such as thromboembolism or liver injury), or remission. The prescribing information advises discontinuation of therapy if no hematologic response is seen after 16 weeks of treatment with eltrombopag or 4 weeks of treatment at maximal dose of romiplostim.[13,14] When contemplating TPO-RA discontinuation for nonresponse, two strategies may be attempted. The first is a switch between agents, as for unclear reasons some patients who fail to respond to one TPO-RA may respond to another.[69] The second is the addition of low-dose prednisone, 5–15 mg daily. Addition of low-dose prednisone to TPO-RA treatment may achieve a response in some patients for whom maximal dose TPO-RA alone has failed.[30]

Given the risk of rebound thrombocytopenia following discontinuation of romiplostim in approximately 10–15% of patients with ITP who have demonstrated a response,[70] a gradual wean over 2–4 weeks is reasonable. Despite the lack of more definitive data describing rebound thrombocytopenia with oral TPO-RAs, we also taper responsive patients with ITP receiving eltrombopag or avatrombopag. This practice has not yet been assessed in a clinical study, however.

Determining when a patient has achieved remission while on TPO-RA therapy can sometimes be challenging, especially in patients well controlled for extended periods of time on low-dose therapy. A recent study demonstrated that absence of

direct glycoprotein-specific platelet autoantibodies was 88% sensitive and 91% specific for a clinical remission of ITP (a negative test had a positive likelihood ratio of 9.5 for remission).[71] Despite the fact that TPO-RAs are not immune-modulating agents, there appears to be a small fraction of patients who achieve remission with use of these agents (although it is possible that these are coincidental spontaneous remissions).[24,25] Therefore, the need for continuing TPO-RA therapy should be assessed frequently. Remission should be considered in patients with an increasing platelet count or new thrombocytosis in the setting of repeated dose reductions of the TPO-RA. In this setting, discontinuation *via* a short taper (or the AI dosing protocol for eltrombopag-treated patients, Figure 3) is a reasonable course of action. The opposite scenario, in which a patient on romiplostim loses a response that had been previously maintained over time, should prompt consideration of very rare neutralizing anti-drug antibodies.[72] In this setting, blood samples can be sent to the drug manufacturer (Amgen, Thousand Oaks, CA, USA) for the evaluation of this possibility.

TPO-RAs are an attractive choice for combination therapy in ITP, as their unique mechanism of action among the ITP therapies of augmenting platelet production may synergize with agents that diminish platelet destruction, either via decreased platelet clearance (e.g. glucocorticoids and danazol) or reduction in platelet autoantibody production (e.g. cyclophosphamide, rituximab or azathioprine).[20] Any of the TPO-RAs can be used as part of combination therapy in treatment-resistant or treatment-refractory patients,[13,14,73] but evidence evaluating each of the potential combinations is sparse. Given that romiplostim and the small molecule TPO-RAs act on different domains of the TPO receptor c-Mpl (Table 2), administration of dual-agent TPO-RA therapy could theoretically have additive or synergistic effect and achieve a response in a patient who fails to respond to single-agent therapy. Data are lacking for this approach, however, and it is difficult to justify the financial cost of two expensive agents simultaneously if other viable therapeutic combinations are possible. Finally, combination TPO-RA plus glucocorticoid therapy is under evaluation in the upfront setting, with the aim of increasing early remission rates and lowering the likelihood of progression to chronic ITP.[18] Currently this approach is still experimental.

Conclusion

TPO-RAs currently represent a reliable second-line ITP treatment with a relatively high response rate and few adverse effects. Measurement of the baseline endogenous TPO level prior to TPO-RA initiation can guide selection of TPO-RAs over other treatment as well as selection of one TPO-RA over another. Many other factors, such as route of administration preference, dietary restrictions, and potency considerations may also impact agent selection. The goal of treatment is a platelet count sufficient to prevent bleeding rather than a normalized platelet count. TPO-RAs are generally well tolerated, with headache as the most frequently reported adverse effect. Importantly, large clinical trials have not demonstrated an increased rate of thromboembolism or appreciable risk of bone marrow fibrosis in patients treated with TPO-RAs. Finally, recognition that TPO-RA treatment may be associated with remission in a subset of patients is encouraging and the search for patient or disease characteristics that predict an increased likelihood of remission will allow for further optimization of our use of these agents in clinical practice.

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