Switching thrombopoietin receptor agonist treatments in patients with primary immune thrombocytopenia

Ther Adv Hematol
2019, Vol. 10: 1–9
DOI: 10.1177/2040620719837906

José R. González-Porras, Bertrand Godeau and Monica Carpenedo

Abstract: Primary immune thrombocytopenia (ITP) is a bleeding disorder that conventionally has been treated with steroids or other immunosuppressive treatments. The introduction of thrombopoietin receptor agonists (TPO-RAs), which increase platelet production, dramatically changed the treatment landscape for ITP by providing patients with well-tolerated, long-term treatment options. Two TPO-RAs, eltrombopag and romiplostim, have been approved in the United States and European Union for the treatment of ITP. Some patients do not benefit from the first TPO-RA they receive, so it is assumed that the alternate TPO-RA would have the same outcome. However, eltrombopag and romiplostim have distinct pharmacodynamic and pharmacokinetic properties and may have different tolerability and efficacy in individual patients with ITP. Published retrospective studies showed that >75% of patients who switched to the alternate TPO-RA maintained or achieved a response with the new treatment. Notably, most patients who switched due to lack of efficacy with the first TPO-RA responded to the alternate TPO-RA, which demonstrates an absence of cross-resistance between the two drugs. Therefore, switching to the alternate TPO-RA if the first TPO-RA fails to demonstrate a response should be considered before the use of a less-preferable option.

Keywords: eltrombopag, hemorrhage, immune thrombocytopenia, romiplostim, thrombopoietin

Received: 23 October 2018; revised manuscript accepted: 5 February 2019.

Introduction

The thrombopoietin (TPO) pathway is the primary signaling mechanism driving platelet production.[1] In healthy individuals, the pathway is activated during periods of elevated platelet consumption to maintain platelet levels.[2] However, patients with immune thrombocytopenia (ITP) cannot mount a robust TPO-mediated response to compensate for the immune-mediated destruction of platelets, which leads to a net decrease in platelet counts that may lead to bleeding symptoms.[2–4]

TPO receptor agonists (TPO-RAs) are medications that bind and activate the TPO receptor (TPO-R). Two TPO-RAs, eltrombopag and romiplostim, have been approved in the United States and European Union for the treatment of chronic ITP. Although both TPO-RAs have high tolerability and response rates, a minority of patients do not benefit from their first prescribed TPO-RA.[5] On the basis of the assumption that treatment with the alternate TPO-RA will have the same outcome, these patients are sometimes splenectomized or treated with agents that are not approved for use in ITP. Splenectomy may produce durable responses in many patients with ITP; however, it is associated with short-term surgical complications and lifelong increased risk of infections and thrombosis.[6,7] Treatment with the anti-CD20 antibody rituximab may lead to long-term remission in selected patients with ITP when used concomitantly with steroids but has a limited overall response rate and duration in the general ITP population.[8–10] Other agents, including azathioprine, cyclosporine A, cyclophosphamide, and mycophenolate mofetil, may produce responses that are highly variable in individual patients and are also associated with significant toxicities.[3] However,

Correspondence to:
José R. González-Porras
Department of Hematology, IBSAL-Hospital Universitario de Salamanca, 1ª Planta. Paseo de San Vicente, 58-182, 37007, Salamanca, Spain
jrgp@usal.es

Bertrand Godeau
Henri Mondor University Hospital, Creteil, France

Monica Carpenedo
ASST San Gerardo Hospital, Monza, Italy

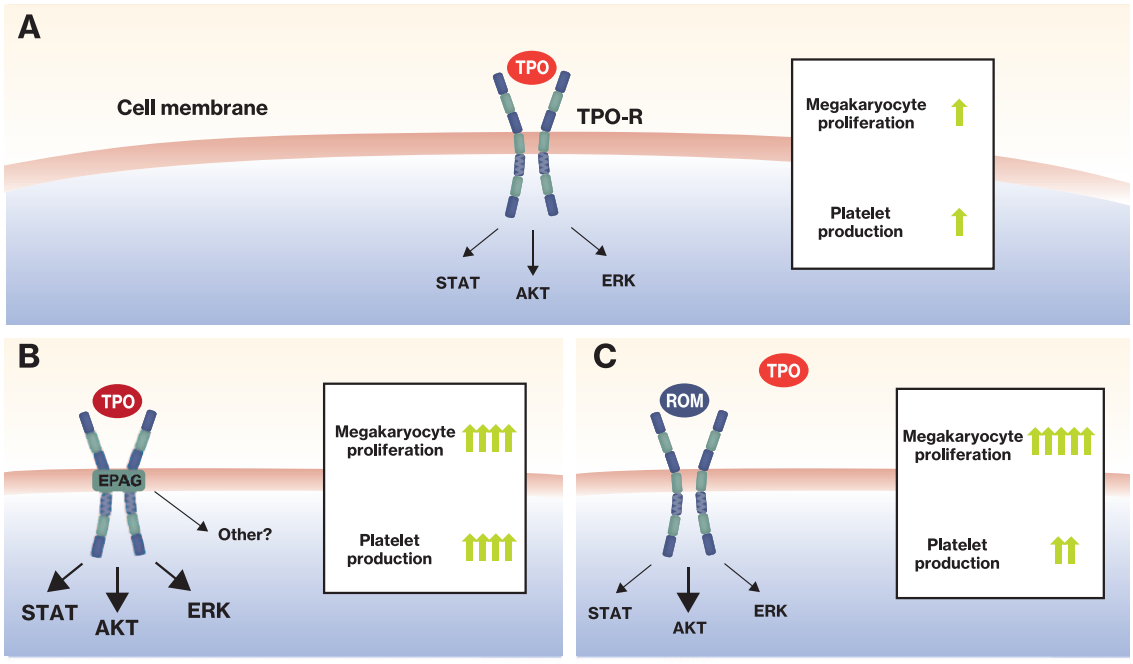

Figure 1. Thrombopoietin receptor (TPO-R) activation by TPO, romiplostim, and eltrombopag. TPO-Rs are found on the cell membranes of multiple cell types in the bone marrow, including multipotent hematopoietic stem cells, common myeloid progenitors, and megakaryocytes.[11] (A) Upon binding to its receptor on the cell membrane, TPO activates the downstream STAT3/5, AKT, and ERK pathways, which may lead to increased megakaryocyte proliferation and increased platelet production.[11] (B) Eltrombopag (EPAG) binds to the transmembrane domain of the TPO-R and strongly activates all TPO-R downstream pathways, leading to a robust increase in both megakaryocyte proliferation and platelet production.[12,13] In addition, eltrombopag has TPO-R-independent activities, such as strong iron chelation, which may confer antileukemic effects;[14,15] however, it is not known whether these activities have any important clinical implications for patients with ITP. (C) Romiplostim (ROM) competes with TPO for the extracellular TPO-R binding site, and it induces stronger activation of the AKT pathway than the STAT and ERK pathways, which favor megakaryocyte proliferation rather than platelet production.[12,13]

because of their distinct pharmacodynamic and pharmacokinetic properties, eltrombopag and romiplostim do not have identical safety and efficacy profiles in individual patients with ITP. Therefore, in patients who are refractory or resistant to their first TPO-RA treatment, switching to the alternate TPO-RA may be a better option than prescribing third-line therapies.

In this review article, we compare the mechanisms of action of eltrombopag and romiplostim, review the clinical data for patients who have switched TPO-RA therapy, and discuss practical considerations.

TPO-RAs: mechanisms of action

The peptide cytokine TPO is a critical regulator of thrombopoiesis and megakaryopoiesis. TPO binds its membrane receptor, found on hematopoietic progenitors, including megakaryocytes, and activates the signal transducer and activator of transcription (STAT) 3/5, AKT, and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways.[11]

The Janus kinase/STAT3/5 pathways are known to promote megakaryocyte differentiation, survival, and expansion. Although balanced activation of the AKT and ERK pathways increases platelet formation, disruption of this balance may have the opposite effect.[12] Endogenous TPO and TPO-RAs act on the same receptor; however, each have notably different effects on megakaryocyte and platelet function (Figure 1).[11–15] Eltrombopag is an oral, small-molecule TPO-RA with a unique transmembrane binding site on the TPO-R.[11–13] Eltrombopag does not compete with endogenous TPO for

receptor binding and, thus, may have additive effects, even in patients with increased endogenous TPO levels.[11] It activates STAT3/5, AKT, and ERK proportionally but at a higher level than TPO and therefore enables marked upregulation of both thrombopoiesis and megakaryopoiesis.[13] In addition, eltrombopag may be able to bypass the interferon γ-mediated blockade of TPO-R signaling, which is thought to be involved in the loss of stem cells in aplastic anemia.[16] Based on preclinical evidence, the proinflammatory cytokine interferon γ forms neutralizing heterodimers with endogenous TPO that block the extracellular binding site of the TPO-R; however, owing to its unique transmembrane binding site, eltrombopag can evade this blockage.[16] If supported by clinical data, these findings could explain why eltrombopag is effective in aplastic anemia, in which endogenous TPO levels are significantly elevated, but also have important clinical implications for other hematologic disorders involving chronic inflammation.[16,17] Independent of its TPO-RA activity, eltrombopag is also a strong iron chelator, able to decrease oxidative stress, and has shown antileukemic effects in preclinical studies.[14,15,18] However, there is no evidence suggesting a therapeutic role for eltrombopag-mediated iron chelation in patients with ITP. Eltrombopag has a half-life of 26–35 h in patients with ITP and is administered orally once daily.[19]

Romiplostim is a peptide TPO mimetic that binds to the TPO-R at the extracellular TPO binding site.[13] Romiplostim induces a stronger activation of the AKT pathway than the STAT and ERK pathways, which leads to proliferation of immature megakaryocytes that have a reduced capacity for platelet production.[13] Romiplostim has a median half-life of 3.5 days (range, 1–34 days) and is administered subcutaneously once weekly.[20]

Switching: clinical data

We identified 18 journal publications that reported retrospective findings in 401 patients with ITP who switched their TPO-RA therapy (Table 1).[21–38] In a pooled analysis of these studies, lack of efficacy was identified as the primary reason for switching in 58% of patients (172/295). Non-efficacy-related reasons for switching included adverse events (AEs), patient preference, and platelet count fluctuations. Response rates after switching were available in 209 patients, and 162 of those (77.5%) achieved or maintained a platelet response. Nearly all patients (93% [87/94]) who switched TPO-RAs due to reasons other than lack of efficacy maintained their response after switching. Importantly, a high response rate (65% [72/111]) and improved platelet counts were observed even if switching was due to lack of efficacy with the first TPO-RA.[21–38]

The outcomes of switching were similar regardless of the direction of the switch (i.e. eltrombopag to romiplostim or romiplostim to eltrombopag); however, the reasons for switching were different for eltrombopag and romiplostim. Although the rate of switching due to safety and tolerability considerations was comparable between the two TPO-RAs (20–30%), switching due to platelet count fluctuations was reported exclusively in patients who received romiplostim. Among 20 patients who switched to eltrombopag due to platelet count fluctuations, 14 (70%) attained a response. Patient preference was a major driver of switching from romiplostim to eltrombopag. Preference for an oral *versus* subcutaneous route of administration, complexity of use of romiplostim vials, and affordability of therapy were reported as considerations prompting patients to request switching to eltrombopag.[24,25,28]

In addition to the aforementioned studies, Cantoni *et al.* recently conducted a statistical analysis on the findings from 106 patients who switched TPO-RA agents at 17 collaborating centers in Italy between 2009 and 2015.[23] The results were consistent with previously published data. In 67% of patients, the switching of TPO-RA was conducted after a lack of efficacy with the first TPO-RA. Overall, 65% of patients responded upon switching; the two TPO-RA switch sequences were equally effective. Patients who switched for non-efficacy-related reasons were more likely to maintain a response than those who switched for efficacy-related reasons (80% *versus* 57.8%; $p = 0.03$). Age, sex, and splenectomy status were not significantly associated with the outcomes of switching, while increased disease duration ($p = 0.066$) and higher number of lines of prior therapy ($p = 0.02$) were negatively associated with the probability of a response. Platelet fluctuations and patient preference resulted in switching from romiplostim to eltrombopag, except for two patients who switched from eltrombopag to romiplostim due to platelet fluctuations.

Overall, the available data clearly demonstrate that switching to the alternate TPO-RA may be a

Table 1. Publications reporting outcomes in patients with ITP who switched their TPO-RA therapy.

Study	Number of patients			Response rate after switching (%)		
	Romiplostim →eltrombopag	Eltrombopag →romiplostim	Total	Romiplostim →eltrombopag	Eltrombopag →romiplostim	Total
Gonzalez *et al.*[21]	17	4	21	77	75	76
Lakhwani *et al.*[22]	17	9	26	94	78	88
Cantoni *et al.*[23]	59	47	106	—	—	65
Depre *et al.*[24]	8	28	36	63	71	69
Gonzalez-Porras *et al.*[25]	51	—	51	80	—	80
Mazza *et al.*[26]	7	2	9	57	100	67
Mori *et al.*[27]	—	1	1	—	100	100
Kuter *et al.*[28]	44	42	86	—	—	—
Sartori *et al.*[29]	1	—	1	100	—	100
Scaramucci *et al.*[30]	1	2	3	100	50	67
Khellaf *et al.*[31]	35	11	46	66	80	70
Meyer *et al.*[32]	—	2	2	—	100	100
Nakazato *et al.*[33]	—	1	1	—	100	100
Piccin *et al.*[34]	—	1	1	—	100	100
Polverelli *et al.*[35]	1	1	2	100	100	100
D'Arena *et al.*[36]	2	—	2	100	—	100
Aoki *et al.*[37]	—	1	1	—	100	100
Tsukamoto *et al.*[38]	—	6	6	—	100	100
Total	243	158	401	76 (107/140)*	80 (55/69)*	78 (162/209)*

*The overall response rates were not specified in the Kuter *et al.*[28] publication and were available only as a combined percentage in the Cantoni *et al.*[23] publication. Hence, these values were not included in the total calculation.

favorable approach, even when the patient did not adequately respond to the initial TPO-RA.

Switching: clinical considerations and recommendations

In clinical practice, the decision to discontinue TPO-RA treatment is made for several reasons (Figure 2).

- Lack of efficacy: platelets $<30 \times 10^9$/l or less than twice the baseline value after 4 weeks of treatment with the highest approved/tolerable dose.[3] Based on the prior response with the treatment, lack of efficacy may involve a treatment failure or loss of response.
- Platelet fluctuations: no standard definition exists but may be empirically defined as more than two weekly platelet counts that are below 30×10^9/l or above 400×10^9/l in a month and a mean change of $>200 \times 10^9$/l in weekly platelet counts in the absence of rescue treatment, and despite best efforts to optimize dosing. For example, romiplostim was given to a 70-year-old patient diagnosed with ITP, and highly fluctuating platelet counts were observed during the first few months of dose adjustments.[39]

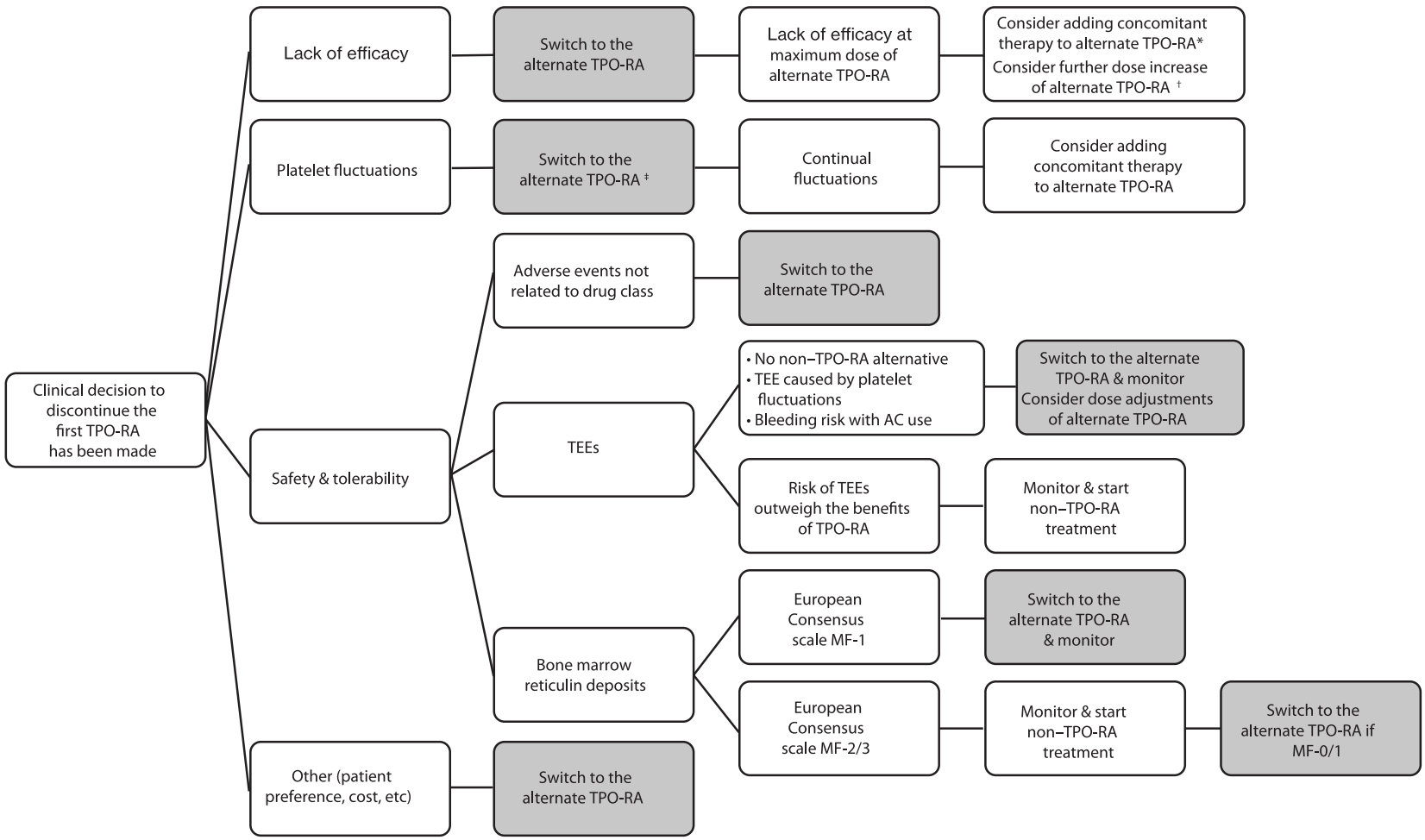

Figure 2. Switching considerations. In clinical practice, the decision to discontinue TPO-RA treatment could be made due to lack of efficacy, platelet fluctuations, safety and tolerability, or other factors. A trial with the alternate TPO-RA is often a plausible next step; however, a careful risk assessment and evaluation of non-TPO-RA options may be needed for patients who needed to discontinue the first TPO-RA due to adverse events related to the TPO-RA drug class.

AC, anticoagulant; MF, bone marrow fibrosis; TEE, thromboembolic events; TPO-RA, thrombopoietin receptor agonist.

*Immunosuppressive therapy with agents such as mycophenolate mofetil, cyclophosphamide, or azathioprine or other drugs, including danazol or vinca alkaloids.

†Doses above 75 mg/day for eltrombopag and 10 μg/kg/week for romiplostim have not been approved for patients with immune thrombocytopenia.

‡Data from reviewed studies were not sufficient to support the reduced platelet fluctuations associated with eltrombopag after switching to romiplostim. Nevertheless, a trial with romiplostim may be considered before switching to a non-TPO-RA option.

Platelet counts increased from 23 × 10^9/l to >50 × 10^9/l with 1–2 μg/kg romiplostim. Platelet counts subsequently dropped and dosage was adjusted to 3 μg/kg; the platelet counts rose to 160 × 10^9/l, but a marked drop to <10 × 10^9/l was observed 1 week later. This large fluctuation occurred another two times after dosage was adjusted to 4 μg/kg. Romiplostim was later discontinued and immunoglobulin G rescue therapy was administered; romiplostim was later re-initiated and the patient's platelet counts steadily increased over the next 3 months. The decision to discontinue treatment upon platelet fluctuations is at the discretion of the treating physician and should be based on the benefits of the treatment and potential risks of bleeding and thrombosis due to fluctuations. For some patients, fluctuations resulting in platelet counts >400 × 10^9/l could be tolerated if the benefits of the treatment outweigh the risk.

- AEs: ⩾1 clinically significant AE that is not manageable by treatment interruption or dose optimization and justifies treatment discontinuation.
- Other: may include patient preference, cost of treatment, or availability.

A trial with the alternate TPO-RA appears to be a plausible next step after discontinuation of the initial TPO-RA, regardless of the cause of discontinuation.

It is important to recognize whether the lack of efficacy is due to drug refractoriness or loss of response, because it can help predict the response to the alternate TPO-RA. Patients who lost their response to the first TPO-RA (i.e. resistant) may be more likely to benefit from switching than patients who never responded (i.e. refractory) to the first TPO-RA.[23] For example, antiromiplostim antibodies that may neutralize romiplostim activity have been detected in patients receiving romiplostim.[40] Patients who are resistant to romiplostim due to the development of neutralizing antibodies may be more likely to respond to eltrombopag. Development of resistance to TPO-RAs may also occur in the absence of neutralizing antibodies through mechanisms that are not fully understood.[40] If the use of a TPO-RA resulted in no increased platelet counts, even at the highest approved dose, a response with the alternate TPO-RA is still feasible, but relatively less likely (33%–59%).[23,25] Some patients who do not respond to either TPO-RA may have a complex disease mechanism that requires a combination treatment approach. The addition of immunosuppressive agents to TPO-RAs has been shown to be effective in multirefractory patients for whom all standard single-agent treatments for ITP had failed.[41]

Platelet fluctuations are more common with romiplostim, possibly due to longer dosing intervals and inconsistent delivery associated with subcutaneous administration.[31] In particular, splenectomized patients may be more prone to platelet fluctuations, as the spleen plays a role in stabilizing platelet counts.[23] Most patients who experience platelet fluctuations with romiplostim may be stabilized by switching to eltrombopag.[24] From our review, two patients were identified who switched from eltrombopag to romiplostim due to platelet fluctuations, and only one had their platelet fluctuations resolved almost completely.[23] Nevertheless, in these patients, a trial with romiplostim may be logical before considering non-TPO-RA options.

For patients experiencing AEs with a TPO-RA that cannot be managed by dose adjustments or interruption, the alternate TPO-RA could be considered. This should be feasible, as eltrombopag and romiplostim have nonoverlapping safety profiles. The most common AEs reported with eltrombopag are nausea, diarrhea, upper respiratory tract infections, vomiting, increased alanine aminotransferase, myalgia, and urinary tract infections.[19] With romiplostim, the most commonly reported AEs are arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia.[20] For certain AEs that may be associated with the TPO-RA drug class, including bone marrow reticulin deposits and thromboembolic events (TEEs), a washout period may be recommended before switching to the alternate TPO-RA. In patients who develop significant bone marrow reticulin deposits (i.e. European Consensus scale MF-2 to MF-3), use of any TPO-RA should be avoided until reticulin deposits and associated clinical symptoms are resolved.

It is not clear whether patients who experience TEEs during TPO-RA therapy should switch to a different medication class. A recent retrospective study suggested that in patients receiving TPO-RAs, a good prognosis with thrombotic events is common and not linked with TPO-RA withdrawal.[42] Thus, if a TPO-RA has been

discontinued after reports of TEEs, the decision to switch to the alternate TPO-RA or start using a different medication class should be made based on a personalized evaluation of benefits and risks. Several factors may favor a trial with the alternate TPO-RA—for example, if the patient was refractory to non-TPO-RA options, if the TEE was considered related to platelet fluctuations, or if the patient has an immediate risk of bleeding due to anticoagulant therapy for the TEE. Switching to the alternate TPO-RA should be avoided if the risk of TEEs outweighs the benefits of TPO-RA treatment or if there are better treatment options available for the patient.

Although there are no clinical data showing that patients remain at high risk for TEEs or bone marrow reticulin deposits after switching to the alternate TPO-RA, it would be prudent to consider this possibility, and patients should continue to be monitored accordingly.

A non-TPO-RA treatment would be the best option in patients who cannot tolerate TPO-RAs or who have no measurable improvement in platelet counts with either eltrombopag or romiplostim. However, if TPO-RAs are well tolerated and partially effective (platelet counts significantly higher than baseline but $<30 \times 10^9$/l), there might be other options to consider before moving on to a non-TPO-RA treatment. First, adding an immunosuppressive therapy, such as mycophenolate mofetil, cyclophosphamide, or azathioprine or other drugs (e.g. danazol or vinca alkaloids), may augment the response to a TPO-RA.[41,43] Second, higher doses of eltrombopag could be considered if romiplostim is not an option, even if higher doses appeared to be noneffective in a retrospective analysis in multirefractory patients.[41] However, preliminary results of an ongoing study ($n = 35$) suggest that eltrombopag at doses >75 mg/day could potentially be used in some patients with ITP who do not respond to doses <75 mg/day. The maximum recommended dose on the label is 75 mg/day for ITP and 150 mg/day for patients with severe aplastic anemia.[44]

Conclusions

The TPO-RAs eltrombopag and romiplostim are effective and well-tolerated treatment options for patients with chronic ITP. Because they belong to the same therapeutic class and have comparable efficacy and safety profiles, there may be a misconception that if one agent fails to demonstrate a response, the alternate will also fail. However, these two TPO-RAs have distinct pharmacokinetic and pharmacodynamic properties and therefore may have different effects in individual patients.

In available studies, >75% of patients who switched to the alternate TPO-RA maintained or achieved a response. The rate of response was higher in patients who switched due to AEs or preference than in patients who switched due to lack of efficacy. There is also a proportion of patients who may be refractory or resistant to both TPO-RAs. The characteristics of these patients and the underlying mechanisms of TPO-RA failure are not well understood. In patients with multirefractory ITP, single-agent treatments may not be sufficient to counter the potent immune response to platelets: adding a concomitant immunosuppressant may be a useful approach.[41,45]

The safety profiles of the two available TPO-RAs do not completely overlap, which allow clinicians to consider switching TPO-RAs due to tolerability issues. In patients who switch due to rare class-related AEs, a drug washout period and careful monitoring are recommended.

In summary, switching to the alternate TPO-RA can be an appropriate treatment strategy in patients with ITP, even if they do not achieve or sustain an adequate response with the first TPO-RA.

Funding

ClinicalThinking, Inc., NJ, USA, provided editorial support for the preparation of this manuscript, which was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. Novartis had no influence on the content of the manuscript, nor did the authors receive financial compensation for authoring the manuscript.

Conflict of interest statement

Dr. González-Porras and Dr. Carpenedo have nothing to disclose. Dr. Godeau reports grants and personal fees from Amgen, personal fees from Novartis, personal fees from LFB, grants and personal fees from Roche, and personal fees from Argenx, outside the submitted work.

ORCID iD

José R. González-Porras https://orcid.org/0000-0003-3266-7996

References

1. Kuter DJ. The biology of thrombopoietin and thrombopoietin receptor agonists. *Int J Hematol* 2013; 98: 10–23.
2. Nichol JL. Endogenous TPO (eTPO) levels in health and disease: possible clues for therapeutic intervention. *Stem Cells Dayt Ohio* 1998; 16(Suppl. 2): 165–175.
3. Neunert C, Lim W, Crowther M, *et al*. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; 117: 4190–4207.
4. Rodeghiero F, Stasi R, Gernsheimer T, *et al*. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009; 113: 2386–2393.
5. Rodeghiero F and Ruggeri M. Treatment of immune thrombocytopenia in adults: the role of thrombopoietin-receptor agonists. *Semin Hematol* 2015; 52: 16–24.
6. Ghanima W, Godeau B, Cines DB, *et al*. How I treat immune thrombocytopenia: the choice between splenectomy or a medical therapy as a second-line treatment. *Blood* 2012; 120: 960–969.
7. Thai L-H, Mahévas M, Roudot-Thoraval F, *et al*. Long-term complications of splenectomy in adult immune thrombocytopenia. *Medicine (Baltimore)* 2016; 95: e5098.
8. Ghanima W, Khelif A, Waage A, *et al*. Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015; 385: 1653–1661.
9. Bussel JB, Lee CS, Seery C, *et al*. Rituximab and three dexamethasone cycles provide responses similar to splenectomy in women and those with immune thrombocytopenia of less than two years duration. *Haematologica* 2014; 99: 1264–1271.
10. Chapin J, Lee CS, Zhang H, *et al*. Gender and duration of disease differentiate responses to rituximab-dexamethasone therapy in adults with immune thrombocytopenia. *Am J Hematol* 2016; 91: 907–911.
11. Kuter DJ. New thrombopoietic growth factors. *Blood* 2007; 109: 4607–4616.
12. Di Buduo CA, Currao M, Pecci A, *et al*. Revealing eltrombopag's promotion of human megakaryopoiesis through AKT/ERK-dependent pathway activation. *Haematologica* 2016; 101: 1479–1488.
13. Raslova H, Vainchenker W and Plo I. Eltrombopag, a potent stimulator of megakaryopoiesis. *Haematologica* 2016; 101: 1443–1445.
14. Roth M, Will B, Simkin G, *et al*. Eltrombopag inhibits the proliferation of leukemia cells via reduction of intracellular iron and induction of differentiation. *Blood* 2012; 120: 386–394.
15. Koumoutsea EV, Cooper N, Psaila B, *et al*. Eltrombopag mobilizes intracellular iron stores at concentrations lower than those required with other clinically available iron chelators. *Blood* 2014; 124: 1353–1353.
16. Alvarado LJ, Andreoni A, Huntsman HD, *et al*. Heterodimerization of TPO and IFNγ impairs human hematopoietic stem/progenitor cell signaling and survival in chronic inflammation. *Blood* 2017; 130: 4.
17. Desmond R, Townsley DM, Dunbar C, *et al*. Eltrombopag in aplastic anemia. *Semin Hematol* 2015; 52: 31–37.
18. Kalota A, Selak MA, Garcia-Cid LA, *et al*. Eltrombopag modulates reactive oxygen species and decreases acute myeloid leukemia cell survival. *PLoS ONE* 2015; 10: e0126691.
19. Novartis. PROMACTA [package insert]. Novartis Pharmaceuticals Corporation, East Hanover, NJ.
20. Amgen. NPLATE [package insert]. Amgen, Inc., Thousand Oaks, CA.
21. González KJ, Zuluaga SO, DaRos CV, *et al*. Sequential treatment with thrombopoietin-receptor agonists (TPO-RAs) in immune thrombocytopenia (ITP): experience in our center. *Ann Hematol* 2017; 96: 507–508.
22. Lakhwani S, Perera M, Fernández-Fuerte F, *et al*. Thrombopoietin receptor agonist switch in adult primary immune thrombocytopenia (ITP) patients: a retrospective collaborative survey involving 4 Spanish centers. *Eur J Haematol* 2017; 99: 372–377.
23. Cantoni S, Carpenedo M, Mazzucconi MG, *et al*. Alternate use of thrombopoietin receptor agonists in adult primary immune thrombocytopenia patients: a retrospective collaborative survey from Italian hematology centers. *Am J Hematol*. 2018; 93: 58–64.
24. Depré F, Aboud N, Mayer B, *et al*. Bidirectional inefficacy or intolerability of thrombopoietin receptor agonists: new data and a concise review. *Blood Transfus* 2018; 16: 307–312.
25. González-Porras JR, Mingot-Castellano ME, Andrade MM, *et al*. Use of eltrombopag

after romiplostim in primary immune thrombocytopenia. *Br J Haematol* 2015; 169: 111–116.

26. Mazza P, Minoia C, Melpignano A, *et al.* The use of thrombopoietin-receptor agonists (TPO-RAs) in immune thrombocytopenia (ITP): a 'real life' retrospective multicenter experience of the Rete Ematologica Pugliese (REP). *Ann Hematol* 2016; 95: 239–244.
27. Mori M, Kato M, Koh K, *et al.* Successful switching from eltrombopag to romiplostim in a pediatric patient with refractory chronic ITP. *Rinsho Ketsueki* 2015; 56: 511–513.
28. Kuter DJ, Macahilig C, Grotzinger KM, *et al.* Treatment patterns and clinical outcomes in patients with chronic immune thrombocytopenia (ITP) switched to eltrombopag or romiplostim. *Int J Hematol* 2015; 101: 255–263.
29. Sartori R, Candiotto L, Ruggeri M, *et al.* Immune thrombocytopenia successfully treated with eltrombopag following multiple therapies including romiplostim. *Blood Transfus* 2014; 12(Suppl. 1): s151–s152.
30. Scaramucci L, Giovannini M, Niscola P, *et al.* Reciprocal absence of cross-resistance between eltrombopag and romiplostim in two patients with refractory immune thrombocytopenic purpura. *Blood Transfus* 2014; 12: 605–607.
31. Khellaf M, Viallard JF, Hamidou M, *et al.* A retrospective pilot evaluation of switching thrombopoietic receptor-agonists in immune thrombocytopenia. *Haematologica* 2013; 98: 881–887.
32. Meyer SC, Rovo A, Tsakiris DA, *et al.* Severe cutaneous toxicity related to Eltrombopag. *Br J Haematol* 2013; 160: 412–414.
33. Nakazato T, Ito C, Mihara A, *et al.* Successful treatment of eltrombopag-resistant refractory immune thrombocytopenia with romiplostim. *Int J Hematol* 2013; 97: 291–293.
34. Piccin A, Amaddii G, Natolino F, *et al.* Idiopathic thrombocytopenic purpura resistant to eltrombopag, but cured with romiplostim. *Blood Transfus* 2014; 12(Suppl. 1): s149–s150.
35. Polverelli N, Catani L, Sollazzo D, *et al.* Platelet fluctuations during thrombopoietin-receptor agonist treatment: correlation with platelet apoptosis. *Ann Hematol* 2015; 94: 339–341.
36. D'Arena G, Guariglia R, Mansueto G, *et al.* No cross-resistance after sequential use of romiplostim and eltrombopag in chronic immune thrombocytopenic purpura. *Blood* 2013; 121: 1240–1242.
37. Aoki T, Harada Y, Matsubara E, *et al.* Thrombopoietin receptor agonists in refractory immune thrombocytopenia: differential responses to eltrombopag and romiplostim: a case report and possible explanations. *J Clin Pharm Ther* 2012; 37: 729–732.
38. Tsukamoto S, Nakaseko C, Takeuchi M, *et al.* Safety and efficacy of romiplostim in patients with eltrombopag-resistant or -intolerant immune thrombocytopenia. *Br J Haematol* 2013; 163: 286–289.
39. Shinohara K and Kambara N. Highly fluctuating thrombocytopenia developing in a patient with immune thrombocytopenia (ITP) while administering romiplostim. *Intern Med* 2012; 51: 1399–1401.
40. Carpenedo M, Cantoni S, Coccini V, *et al.* Response loss and development of neutralizing antibodies during long-term treatment with romiplostim in patients with immune thrombocytopenia: a case series. *Eur J Haematol* 2016; 97: 101–103.
41. Mahévas M, Gerfaud-Valentin M, Moulis G, *et al.* Characteristics, outcome, and response to therapy of multirefractory chronic immune thrombocytopenia. *Blood* 2016; 128: 1625–1630.
42. Weber E, Moulis G, Mahevas M, *et al.* [Thrombosis during thrombopoietin receptor agonist treatment for immune thrombocytopenia. A French multicentric observational study]. *Rev Med Interne* 2017; 38: 167–175.
43. Cuker A and Neunert CE. How I treat refractory immune thrombocytopenia. *Blood.* 2016; 128: 1547–1554.
44. Keefe PJ, Morrissey MC, McGuinn CE, *et al.* Randomized double-blind study of increasing doses of eltrombopag in patients with chronic ITP. *Blood* 2015; 126: 1057.
45. Balduini CL, Savoia A and Seri M. Inherited thrombocytopenias frequently diagnosed in adults. *J Thromb Haemost* 2013; 11: 1006–1019.