




ORIGINAL ARTICLE



Tapering thrombopoietin receptor agonists in primary immune thrombocytopenia: Expert consensus based on the RAND/UCLA modified Delphi panel method

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Abstract

Background: Thrombopoietin receptor agonists (TPO-RAs) are used to treat primary immune thrombocytopenia (ITP). Some patients have discontinued treatment while maintaining a hemostatic platelet count.

Objectives: To develop expert consensus on when it is appropriate to consider tapering TPO-RAs in ITP, how to taper patients off therapy, how to monitor patients after discontinuation, and how to restart therapy.

Methods: We used a RAND/UCLA modified Delphi panel method. Ratings were completed independently by each expert before and after a meeting. Second-round ratings were used to develop the panel's guidance. The panel was double-blinded: The sponsor and nonchair experts did not know each other's identities.

Results: Guidance on when it is appropriate to taper TPO-RAs in children and adults was developed based on patient platelet count, history of bleeding, intensification of treatment, trauma risk, and use of anticoagulants/platelet inhibitors. For example, it is appropriate to taper TPO-RAs in patients who have normal/above-normal platelet counts, have no history of major bleeding, and have not required an intensification of treatment in the past 6 months; it is inappropriate to taper TPO-RAs in patients with low platelet counts. Duration of ITP, months on TPO-RA, or timing of platelet response to TPO-RA did not have an impact on the panel's guidance on appropriateness to taper. Guidance on how to taper patients off therapy, how to monitor patients after discontinuation, and how to restart therapy is also provided.

Conclusion: This guidance could support clinical decision making and the development of clinical trials that prospectively test the safety of tapering TPO-RAs.

Name of institution where study took place: Partnership for Health Analytic Research (PHAR), LLC.

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KEYWORDS

blood platelets, consensus, idiopathic, platelet count, purpura, receptors, thrombocytopenic, thrombopoietin

Essentials

- Thrombopoietin receptor agonists (TPO-RAs) are used to treat immune thrombocytopenia (ITP).
- Some patients with ITP have discontinued TPO-RAs and still maintain a hemostatic platelet count.
- Using a modified Delphi panel method, we developed expert consensus on tapering TPO-RAs.
- This guidance can support patient care and inform clinical trials on tapering TPO-RAs.

1 | INTRODUCTION

Primary immune thrombocytopenia (ITP) is an acquired disorder that affects 2-5 per 100 000 people and is characterized by an increased risk of bleeding, fatigue, and reduced quality of life.^{1,2} ITP results from immune-mediated platelet destruction and impaired platelet production.³ The primary goal of ITP therapy is to reduce the risk of clinically significant bleeding.⁴ Glucocorticoids, with or without intravenous immune globulin, are typically used as first-line therapy but are not recommended for long-term use. Second-line therapies include splenectomy, rituximab, and thrombopoietin receptor agonists (TPO-RAs), such as romiplostim, eltrombopag, and avatrombopag.⁴

TPO-RAs are used to stimulate platelet production. In initial clinical trials, platelet counts returned to pretreatment levels within approximately 2 weeks of discontinuing TPO-RAs.^{5,6} However, some retrospective and prospective cohort studies have shown that 3%-33% of patients with ITP, including those treated early in their ITP course, may go into remission and maintain hemostatic platelet counts after tapering and discontinuing TPO-RAs (although studies differed in their definition of remission and follow-up duration).⁷⁻¹⁷

Most of these cohort studies were not designed to assess the feasibility of TPO-RA discontinuation. The true prevalence of patients able to maintain a hemostatic platelet count off therapy is unknown, and while a gradual tapering to discontinuation has been advised to avoid rebound thrombocytopenia,^{18,19} factors associated with successful discontinuation have not been identified.

Large randomized clinical trials on the management of ITP, including when and how to safely taper or discontinue TPO-RAs, are lacking. As a result, current clinical practice guidelines do not include recommendations on the most appropriate patients for whom tapering may be considered, nor when and how to safely taper TPO-RAs.^{4,20} In these circumstances, guidance based on expert opinion and clinical experience can be helpful in exploring factors that might be associated with successful TPO-RA discontinuation to support clinical care, avoid unnecessary treatment and potential side effects, decrease cost, and inform future clinical trials. Zaja et al²¹ and Cooper et al²² took a similar approach and conducted surveys of international experts to explore these factors.

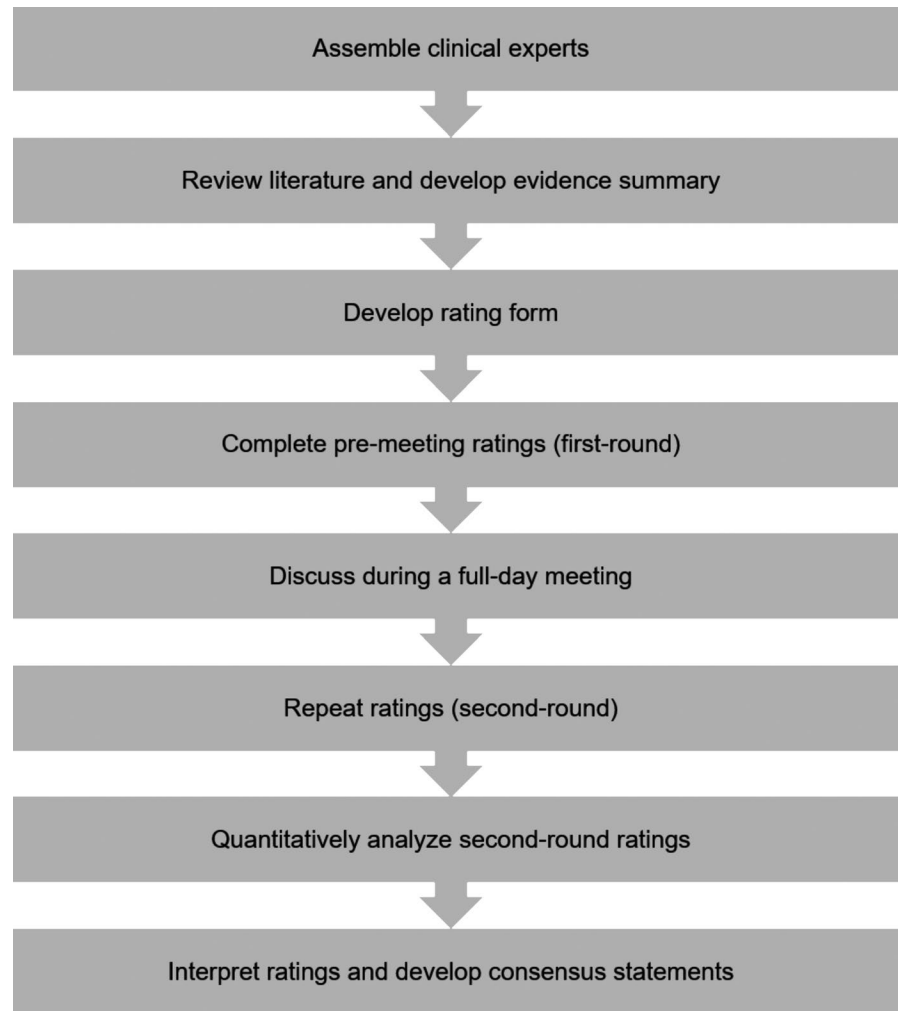
We conducted a study using a standardized method of soliciting expert opinion to develop consensus from experts in the United States on when it is appropriate to consider tapering TPO-RAs in children and adults with persistent or chronic primary ITP, how to taper patients off therapy, how to monitor patients after discontinuation, and how to restart therapy in the event of relapse.

2 | METHODS**2.1 | Study design and participants**

We used the RAND/UCLA modified Delphi panel method, which is fully described elsewhere.²³⁻²⁵ Briefly, this method is a formal group judgment process which systematically and quantitatively combines expert opinion and systematic literature review evidence by asking panelists to rate, discuss, and then rerate various patient scenarios. The primary steps in the process include identification of the question to be answered, a systematic literature review of the evidence, selection of expert panelists, generation of a rating form, first-round survey, a meeting in which panelists discuss areas of disagreement, final ratings and analysis of those ratings, and development of a written summary of areas of agreement and disagreement. A visual representation of this process is provided in Figure 1.

Our expert panel included nine hematologists (six adult hematologists, three pediatric hematologists) with extensive experience treating ITP and one patient representative. The hematologists were from a variety of practice settings (six academic, three community/private practice) and US regions (four Northeast, one Midwest, two South, two West) with an average of 25 years of experience. The panel was double-blinded while work was ongoing: The sponsor (Novartis) did not know the identity of the nonchair experts, and the nonchair experts did not know the identity of the sponsor until a manuscript of the work was drafted and funding sources were disclosed. Nonchair experts received honoraria for their participation. One expert served as the panel chair and was not blinded to the sponsor and did not receive an honorarium. The sponsor did not provide input on study design, methods, results, or interpretation of findings. No human subjects were involved in this research; thus, ethics committee approval was not required.

FIGURE 1 RAND/UCLA modified Delphi panel method. This figure represents the RAND/UCLA modified Delphi panel method we followed to develop our expert consensus statements. In brief, we assembled clinical experts, conducted a literature review of the evidence, developed a rating form (survey), completed the rating form before a meeting, discussed our ratings at a 6-hour virtual meeting, completed the rating form a second time following the meeting, analyzed these second-round ratings, and developed a written summary of areas of agreement and disagreement



We developed a summary of evidence on the cessation of TPO-RA treatment in adults and children with ITP by using PubMed to conduct a targeted search of ITP guidelines and all case reports, observational studies, and clinical trials of TPO-RAs from inception until January 2020. Articles that included patients with ITP, treatment with TPO-RAs, and cessation of TPO-RAs were reviewed and summarized. The summary included evidence from 12 case reports,²⁶⁻³⁷ 11 cohort studies,⁷⁻¹⁷ and two analyses of pooled clinical trial data^{38,39} on sustained remission in patients with ITP after discontinuation of TPO-RAs. We did not formally appraise the quality of evidence using a standard tool.

2.2 | Rating form

We collaboratively developed the rating form through individual telephone interviews with panelists. We began by developing a list of patient characteristics that might affect a clinician's decision to discontinue TPO-RA monotherapy in adults and children. Over several conversations, we added to, clarified, removed, and grouped those characteristics. Early drafts included 19 characteristics; some characteristics (eg, age, sex, fatigue, history of prior

treatments, history of venous thromboembolism or renal impairment) were not included based on feedback from panelists. The final list included the following eight characteristics (defined in Table 1): current platelet count on treatment, history of bleeding, intensification of treatment (between 3 and 6 months ago vs no intensification of treatment in the past 6 months), trauma risk, use of anticoagulants or platelet inhibitors, duration of ITP (persistent versus chronic), months on TPO-RA monotherapy, and early platelet response to TPO-RA. In the rating form, the panel defined intensification of treatment between 3 and 6 months ago versus no intensification of treatment over that time frame. However, the panel decided not to include treatment intensification in the past 3 months in the definition because it was assumed that such recent escalation of therapy would disqualify patients from consideration for tapering.

These eight characteristics were combined to create 432 patient scenarios in the rating form (Table 2). The scenarios were designed to describe a broad patient history as if the patient were entering a clinician's office with these characteristics. For each scenario, we rated how appropriate it would be to recommend tapering (with the aim of discontinuing) TPO-RAs using a scale of 1 to 9, where 1 = inappropriate ("I would not recommend tapering treatment in this

TABLE 1 Definitions of characteristics included in rating form

Characteristics included in patient scenarios	Definition
Current platelet count	
Normal/above normal	Normal/above normal for a patient without ITP (eg, $>150 \times 10^9/L$)
Adequate	Adequate for a patient with ITP (eg, $50-150 \times 10^9/L$)
Responding but still low	Responding but still low (eg, $30-50 \times 10^9/L$)
History of bleeding ⁴	
None	No bleeding other than skin manifestations (eg, minimal bruising or scattered petechiae)
Minor	Any bleeding (other than skin manifestations) not meeting the criteria for “major bleeding”
Major	Bleeding defined as World Health Organization grade 3 or 4, Buchanan severe grade, Bolton-Maggs and Moon “major bleeding,” ITP Bleeding Scale grade 2 or higher, life-threatening or intracerebral
Intensification of treatment ⁴⁹	
No intensification of treatment in the past 6 mo	See definition of intensification of treatment below
Intensification of treatment between 3 and 6 mo ago	Any increase in treatment while on TPO-RA, including rescue therapies or increasing dose of TPO-RA, between 3 and 6 mo ago as a result of a low platelet count
Trauma risk ⁵⁰	
Low	Lifestyle with low trauma risk (eg, primarily sedentary lifestyle, plays sports without bleeding risk [eg, walking, swimming, tennis])
High	Lifestyle with high trauma risk (eg, primarily active lifestyle, plays sports with bleeding risks [eg, basketball, soccer, baseball, American football, skiing, wrestling], holds an occupation associated with high risk of trauma, has a high fall risk, high-energy toddlers)
Use of anticoagulants or platelet inhibitors	For treatment of comorbidity (eg, aspirin, clopidogrel, nonsteroidal anti-inflammatory drugs, heparin, warfarin, direct oral anticoagulants)
Duration of ITP ⁴	
Persistent	Time since diagnosis 3-12 mo
Chronic	Time since diagnosis >12 mo
Months on TPO-RA monotherapy	Defined as ≤ 12 mo or >12 mo

(Continues)

TABLE 1 (Continued)

Characteristics included in patient scenarios	Definition
Platelet response to TPO-RA ⁵	
Early	Platelet count $\geq 30 \times 10^9/L$ and at least doubling of the baseline 1 week after initiating treatment at the standard starting dose
Not early	See definition of early platelet response above

ITP, primary immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonists.

patient because the risks of discontinuing treatment outweigh the benefits”) and 9 = appropriate (“I would recommend tapering treatment in this patient because the benefits of discontinuing treatment outweigh the risks”).

We also defined the setting for these scenarios: we assumed the patient was any age, on TPO-RA monotherapy for some period of time for the treatment of persistent or chronic ITP, was having a successful treatment response (defined as a platelet count $\geq 30 \times 10^9/L$ and at least doubling of the baseline⁴), and was asymptomatic or only had symptoms of petechiae and/or bruising. We also assumed the provider accounted for patient preference, the patient agreed with the provider’s decision on whether to taper, and the patient would be reasonably compliant with the care plan. While there may be a variety of reasons to taper patients off TPO-RAs (eg, bridge therapy to splenectomy or rituximab, adverse effects, lack of treatment response, no longer able to afford treatment), we chose not to focus on these scenarios.

In addition, we discussed how to taper patients off TPO-RA monotherapy, how to monitor patients after discontinuing TPO-RAs, and how to restart TPO-RAs in the event of relapse. In the final rating form, we included all the different ways that panelists reported tapering TPO-RAs (12 items), monitoring patients after discontinuation (11 items), and restarting therapy (5 items). We rated how appropriate each item is for patient care using a scale of 1 to 9, where 1 = inappropriate (“This action represents a significant problem with quality of care”) and 9 = appropriate (“This action represents the best quality of care”).

Ratings were completed independently by each expert before the panel meeting (first-round ratings). While we had originally planned to hold the meeting in person, we ultimately met using a virtual platform due to the COVID-19 pandemic. At the virtual meeting, we discussed the scenarios and items on which there was disagreement (defined below). Ratings were completed a second time at the conclusion of the meeting (second-round ratings).

2.3 | Data analysis

Median ratings were calculated for each item using Microsoft Excel. As is typical in the RAND/UCLA modified Delphi panel method, we defined items with disagreement as single items that had two or

more ratings between 1 and 3 and two or more ratings between 7 and 9.²⁵ Items without disagreement were grouped into three categories based on their median (1 to <4, ≥ 4 to <7, ≥ 7 to 9). Using the second-round ratings, we identified patient characteristics on which there was agreement that it was inappropriate (ratings 1 to <4 without disagreement) or appropriate (ratings ≥ 7 to 9 without disagreement) to taper TPO-RA monotherapy. We also conducted chi-squared tests using SAS version 9.4 (SAS Institute, Cary, NC, USA) to determine which characteristics had a statistically significant impact on ratings (defined as $P < .05$). In addition, we identified actions the panel agreed would be inappropriate (ratings 1 to <4 without disagreement) or appropriate (ratings ≥ 7 to 9 without disagreement) to take to taper TPO-RA monotherapy, monitor patients after discontinuation, and restart therapy in the event of relapse.

3 | RESULTS

The proportion of items with disagreement decreased from 20% to 10% following the panel meeting. Five patient characteristics significantly impacted ratings: platelet count ($P < .001$), history of bleeding ($P = .001$), intensification of treatment (between 3 and 6 months ago vs no intensification of treatment in the past 6 months; $P < .001$), trauma risk ($P < .001$), and use of anticoagulants or platelet inhibitors ($P < .001$). Three characteristics did not influence ratings: duration of ITP (persistent vs chronic) ($P = .43$), months on TPO-RA monotherapy ($P = .96$), and timing of platelet response to TPO-RA ($P = .88$) (Table 3). No scenarios in which patients had low platelet counts (defined as $30\text{--}50 \times 10^9/\text{L}$) were rated as appropriate for tapering TPO-RAs. The panel agreed that most scenarios in which patients required an intensification of treatment between 3 and 6 months ago (63%), had a history of major bleeding (67%), had a high risk of trauma (69%), or were using anticoagulants or platelet inhibitors (73%) were inappropriate for tapering TPO-RAs.

3.1 | Consensus statements on when to taper TPO-RAs

Every clinical situation is different, with its own set of complex characteristics. The consensus statements presented here are in no way intended to supersede clinician decision making and are intended only as general guidance. In developing this guidance, the panel assumed the patient was on TPO-RA monotherapy for treatment of persistent or chronic ITP for some period of time, was involved in the decision-making process, was having a successful treatment response (defined as a platelet count $\geq 30 \times 10^9/\text{L}$ and at least doubling of baseline),⁴ and was asymptomatic or only had symptoms of petechiae and/or bruising, and would be reasonably compliant with the care plan.

The panel identified circumstances when it is inappropriate or appropriate to consider tapering (with the aim of discontinuing)

TPO-RA monotherapy (illustrated in Table 4 and Figure 2). It is usually inappropriate to consider tapering TPO-RA monotherapy in the following circumstances:

- In patients with low platelet counts ($30\text{--}50 \times 10^9/\text{L}$).
- In patients with less than normal but still adequate platelet counts ($50\text{--}150 \times 10^9/\text{L}$) who have a history of major bleeding.
- In patients with less than normal but still adequate platelet counts ($50\text{--}150 \times 10^9/\text{L}$) who have required an intensification of treatment between 3 and 6 months ago and are using anticoagulants or platelet inhibitors.
- In patients who, regardless of platelet count, have a high risk of trauma and are using anticoagulants or platelet inhibitors.

Assuming that there are no contraindications as outlined above, the panel determined that it is usually appropriate to consider tapering TPO-RA monotherapy in the following circumstances:

- In patients with normal or above normal platelet counts ($>150 \times 10^9/\text{L}$), no history of major bleeding, and who have not required an intensification of treatment in the past 6 months.
- In patients with normal or above-normal platelet counts ($>150 \times 10^9/\text{L}$), no history of major bleeding, and have required an intensification of treatment between 3 and 6 months ago, as long as they have a low risk of trauma and are not using anticoagulants or platelet inhibitors.
- In patients with normal or above-normal platelet counts ($>150 \times 10^9/\text{L}$) who have a history of major bleeding, as long as they have a low risk of trauma, are not using anticoagulants or platelet inhibitors, and have not required an intensification of treatment in the past 6 months.
- In a subset of patients with a less-than-normal but still adequate platelet count ($50\text{--}150 \times 10^9/\text{L}$), as long as they have no history of bleeding, have not required an intensification of treatment in the past 6 months, have a low risk of trauma, and are not using anticoagulants or platelet inhibitors.

The circumstances the panel identified as “appropriate” to consider tapering therapy do not mean that therapy must or should be tapered, but rather that tapering could be an acceptable option. There were areas of remaining uncertainty, either because the panel members disagreed about whether tapering should begin in those circumstances (with some experts feeling it was inappropriate and others that it was appropriate) or because the entire panel was uncertain about those circumstances. These areas are illustrated in white in Table 4.

3.2 | Consensus statements on how to taper TPO-RAs

The panel agreed it is inappropriate to discontinue TPO-RA monotherapy without tapering. Eltrombopag and romiplostim can

TABLE 2 Example rating form of patient scenarios

	Early platelet response to TPO-RA ¹		No early platelet response to TPO-RA															
					Intensification of treatment between 3 and 6 months ago		Intensification of treatment between 3 and 6 months ago											
					Current platelet count on treatment (within 2 weeks)		Current platelet count on treatment (within 2 weeks)											
<p>A patient with no history of bleeding*, is having a successful treatment response, and is currently asymptomatic (or has no or mild bleeding[†]):</p> <p>When there is heterogeneity within a scenario, do your best to answer each question for a <u>typical</u> patient with those characteristics.</p>	≤12 months on TPO-RA monotherapy	Persistent ITP ^{§§}	Low trauma risk ^{**}	No	A	B	C	D	E	F	G	H	I	J	K	L		
			High trauma risk ^{††}	Yes	2													
		Chronic ITP ^{¶¶}	Low trauma risk	No	3													
			High trauma risk	Yes	4													
			Low trauma risk	No	5													
			High trauma risk	Yes	6													
	>12 months on TPO-RA monotherapy	Chronic ITP	Low trauma risk	No	7													
			High trauma risk	Yes	8													
		Chronic ITP	Low trauma risk	No	9													
			High trauma risk	Yes	10													
			Low trauma risk	No	11													
			High trauma risk	Yes	12													

Note: ITP = primary immune thrombocytopenia; TPO-RA = thrombopoietin receptor agonists. This table illustrates one part of the rating form experts completed. Each cell represents a unique patient scenario using the combined characteristics in the columns, meta-columns, rows, and meta-rows. This table was repeated three times to produce 432 scenarios.

^aThis table was repeated for patients with no history of bleeding (no bleeding other than skin manifestations [eg, minimal bruising or scattered petechiae]); history of minor bleeding (any bleeding [other than skin manifestations] not meeting the criteria for "major bleeding;" and history of major bleeding [bleeding defined as World Health Organization grade 3 or 4, Buchanan severe grade, Bolton-Maggs and Moon "major bleeding," ITP Bleeding Scale grade 2 or higher, life-threatening or intracerebral]).⁴

^bSkin manifestations only (eg, minimal bruising or scattered petechiae).⁴

^cPlatelet count $\geq 30 \times 10^9/L$ and at least doubling of the baseline 1 week after initiating treatment at the standard starting dose.⁵

^dAny increase in treatment while on TPO-RA, including rescue therapies or increasing dose of TPO-RA, between 3 and 6 months ago as a result of a low platelet count.^{4,9}

^eNormal/above normal for a patient without ITP (eg, $>150 \times 10^9/L$).

^fAdequate for a patient with ITP (eg, $50-150 \times 10^9/L$).

^gResponding but still low (eg, $30-50 \times 10^9/L$).

^hTime since diagnosis 3-12 months.⁴

ⁱTime since diagnosis >12 months.⁴

^jLifestyle with low trauma risk (eg, primarily sedentary lifestyle, plays sports without bleeding risk [eg, walking, swimming, tennis]).⁵⁰

^kLifestyle with high trauma risk (eg, primarily active lifestyle, plays sports with bleeding risks [eg, basketball, soccer, baseball, American football, skiing, wrestling⁵⁰], holds an occupation associated with high risk of trauma, has a high fall risk, high-energy toddlers).

^lFor treatment of comorbidity (eg, aspirin, clopidogrel, nonsteroidal anti-inflammatory drugs, heparin, warfarin, direct oral anticoagulants).

be tapered by decreasing the dose periodically to the minimum available dose but maintaining the time interval between doses. Eltrombopag and avatrombopag can also be tapered by maintaining the dose but increasing the time interval between doses periodically or by first decreasing the dose periodically to the minimum available dose while maintaining the time interval between doses and then increasing the time interval between doses. The panel agreed that it is inappropriate to taper romiplostim by maintaining the dose but increasing the time interval between doses periodically. No additional specific consensus statements about the length of taper or how to monitor patients during the taper were made.

The panel also agreed that it is appropriate to measure the platelet count soon after the patient has discontinued treatment (eg, within 1 to 2 weeks) and with decreasing frequency over time assuming a successful taper. However, we did not reach consensus on a specific schedule for platelet count monitoring over time. The panel also noted that it may be appropriate to measure the platelet count during viral illness and/or vaccine administration; at signs of new bleeding symptoms; before a scheduled invasive procedure; and if the patient is started on therapy that affects bleeding risk (eg, anticoagulants, platelet inhibitors). It is appropriate to ask patients during clinical visits about signs of bleeding and fatigue.

TABLE 3 Distribution of ratings by characteristics included in patient scenarios

Characteristics included in patient scenarios	Median $\geq 7-9$ without disagreement, % (n)	Median ≥ 4 to <7 without disagreement, % (n)	Median 1 to <4 without disagreement, % (n)	Disagreement, ^a % (n)	P value ^b
Current platelet count ^c					<.001
Normal/above normal	32 (46)	40 (58)	17 (25)	10 (15)	-
Adequate	3 (4)	33 (47)	54 (78)	10 (15)	-
Responding but still low	0 (0)	1 (2)	90 (130)	8 (12)	-
History of bleeding					.001
None	17 (24)	27 (39)	48 (69)	8 (12)	-
Minor	14 (20)	27 (39)	47 (67)	13 (18)	-
Major	4 (6)	20 (29)	67 (97)	8 (12)	-
Intensification of treatment					<.001
No intensification of treatment in the past 6 months	18 (38)	28 (60)	45 (97)	10 (21)	-
Intensification of treatment between 3 and 6 months ago	6 (12)	22 (47)	63 (136)	10 (21)	-
Trauma risk					<.001
Low	19 (42)	29 (62)	39 (84)	13 (28)	-
High	4 (8)	21 (45)	69 (149)	6 (14)	-
Use of anticoagulants or platelet inhibitors					<.001
No	19 (42)	29 (63)	35 (75)	17 (36)	-
Yes	4 (8)	20 (44)	73 (158)	3 (6)	-
Duration of ITP					.43
Persistent	14 (20)	21 (30)	54 (78)	11 (16)	-
Chronic	10 (30)	27 (77)	54 (155)	9 (26)	-
Months on TPO-RA monotherapy					.96
≤ 12 months	11 (32)	25 (71)	54 (156)	10 (29)	-
>12 months	13 (18)	25 (36)	53 (77)	9 (13)	-
Platelet response to TPO-RA					.88
Early	12 (25)	26 (57)	52 (113)	10 (21)	-
Not early	12 (25)	23 (50)	56 (120)	10 (21)	-

ITP, primary immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonists.

Percentages may not add to 100 due to rounding.

^a ≥ 2 ratings of 1-3 and ≥ 2 ratings of 7-9.

^b Chi-square tests were conducted to determine whether distribution of ratings differed significantly by characteristic.

^c Refer to Table 1 for definitions of characteristics.

TABLE 4 Circumstances when it is inappropriate or appropriate to consider tapering TPO-RA monotherapy

				No intensification of treatment in the past 6 months			Intensification of treatment between 3 and 6 months ago*		
				Current platelet count on treatment (within 2 weeks)					
				Normal/above normal†	Adequate‡	Responding but still low§	Normal/above normal	Adequate	Responding but still low
No history of bleeding¶	Low trauma risk**	Use of anti-coagulants or platelet inhibitors¶¶	No	Green	Green	Red hash	Green	White	Red hash
			Yes	Green	White	White	White	Red hash	
	No		White	White	White	White	Red hash		
	Yes		Red hash	Red hash	Red hash	Red hash	Red hash		
History of minor bleeding**	Low trauma risk	No	Green	Green	Red hash	Green	White	Red hash	
		Yes	Green	White	White	White	Red hash		
	High trauma risk	No	White	White	White	White	Red hash		
		Yes	Red hash	Red hash	Red hash	Red hash	Red hash		
History of major bleeding††	Low trauma risk	No	Green	Red hash	Red hash	White	Red hash		
		Yes	Red hash	Red hash	Red hash	Red hash	Red hash		
	High trauma risk	No	White	White	White	White	Red hash		
		Yes	Red hash	Red hash	Red hash	Red hash	Red hash		

Key: Red hash marks = inappropriate. Green = appropriate. White = uncertain.

The panel agreed that, in many cases, it is appropriate to consider restarting therapy when the patient’s platelet count is $<30 \times 10^9/L$ and shows any signs of bleeding beyond skin manifestations. However, the panel acknowledged that thresholds for restarting therapy may be different for patients with different characteristics. When resumption of TPO-RA therapy is warranted, we agreed that it may be appropriate to restart the TPO-RA at the baseline dose (the dose of TPO-RA the patient was on when the decision to start the taper was made).

4 | DISCUSSION

We used a validated methodology to develop the first set of consensus statements from US clinical experts on tapering TPO-RA monotherapy in patients with persistent or chronic primary ITP. While it was previously thought that patients with ITP would have to remain on TPO-RAs indefinitely to maintain adequate platelet counts, recent case reports and cohort studies have shown that selected patients with ITP can safely discontinue treatment.^{7-17,26-39} However, to date, no formal guidelines identify which patients can successfully discontinue TPO-RAs.^{4,20} In response to this need, we developed consensus statements on when it is appropriate to consider tapering TPO-RAs; broad guidance on how to taper patients off therapy, how to monitor patients after discontinuation, and how to restart therapy in the event of relapse is also provided. Without large randomized controlled trials, expert opinion can be helpful in exploring patient characteristics and other factors that might be associated with successful TPO-RA discontinuation. We hope this guidance is useful to support patient care. However, as noted earlier, these consensus statements are not intended to supersede clinical judgment or shared clinical decision making.

We recognize that these consensus statements reflect the opinion of a small group of individuals. Nevertheless, a validated method was used to develop these statements. The RAND/UCLA modified Delphi panel method has been used extensively to develop quality

measures and guidance in a variety of clinical areas,⁴⁰ and there is evidence that the resultant measures have content, construct, and predictive validity.⁴¹ In addition, the method has been shown to produce guidance statements that improve health outcomes.⁴²⁻⁴⁴

The panel’s consensus statements are also consistent with another study that used expert opinion to develop guidance on tapering TPO-RAs. Zaja et al²¹ conducted a survey of 11 international experts and concluded that TPO-RAs can be tapered in patients with stable platelet counts $>50 \times 10^9/L$ maintained for at least 6 months without concomitant therapy. This aligns with our panel’s guidance that patients with normal or above-normal platelet counts ($>150 \times 10^9/L$) may be considered for tapering and adds specificity among which patients with adequate platelet counts ($50-150 \times 10^9/L$) can be considered for tapering, including those who have not required an intensification of treatment in the past 6 months. The survey respondents also noted that patients receiving anticoagulant therapies are not eligible for tapering, except in patients with a platelet count of $>100 \times 10^9/L$. In contrast to Zaja et al,²¹ our panel’s guidance includes more patient characteristics that may be considered in a decision to taper as well as how these characteristics may interact.

Our panel’s guidance on how to taper TPO-RA monotherapy (ie, gradually) is also based on both clinical experience and evidence; if TPO-RAs are discontinued abruptly, patients may experience a temporary worsening in thrombocytopenia below baseline and increased potential for bleeding.^{18,19} Therefore, the panel advised that TPO-RAs be tapered rather than abruptly discontinued. The panel also included specific guidance on how to slowly decrease the TPO-RA dose and/or dose interval depending on the type of TPO-RA. Our guidance aligns with the pharmacokinetics of the TPO-RAs: eltrombopag and avatrombopag are taken orally daily and have shorter half-lives than romiplostim, which is administered subcutaneously weekly.⁴⁵⁻⁴⁷ The panel also included guidance for consideration to restart the TPO-RA if the platelet count drops below $30 \times 10^9/L$.

Our study has several limitations. First, we did not use randomized controlled trial results to develop our guidance because such evidence on the discontinuation of TPO-RAs does not exist;

instead, our consensus statements are based primarily on observational studies. The Delphi panel method has been shown to be reproducible but is more reproducible when there is a stronger evidence base. Shekelle et al⁴⁸ conducted six separate panels on coronary revascularization and hysterectomy. The authors found 90% agreement among the panels that used randomized control trial evidence, compared to 70%-80% agreement in the panels that used a weaker evidence base.⁴⁸ Second, our guidance is intended for patients of any age with ITP, even though bleeding risk varies by age and existing clinical guidelines are different for adults versus

children.^{4,20} For example, it may be reasonable to be more aggressive in tapering TPO-RAs in children because of their lower baseline bleeding risk.

Third, we only considered patients with persistent or chronic primary ITP on TPO-RA monotherapy in whom discontinuation of the TPO-RA was being considered to determine whether the patient could maintain a hemostatic platelet count off treatment. Our guidance is not intended to apply to patients with newly diagnosed ITP, patients on combination therapy, and patients in whom discontinuation of a TPO-RA is being considered for another indication.

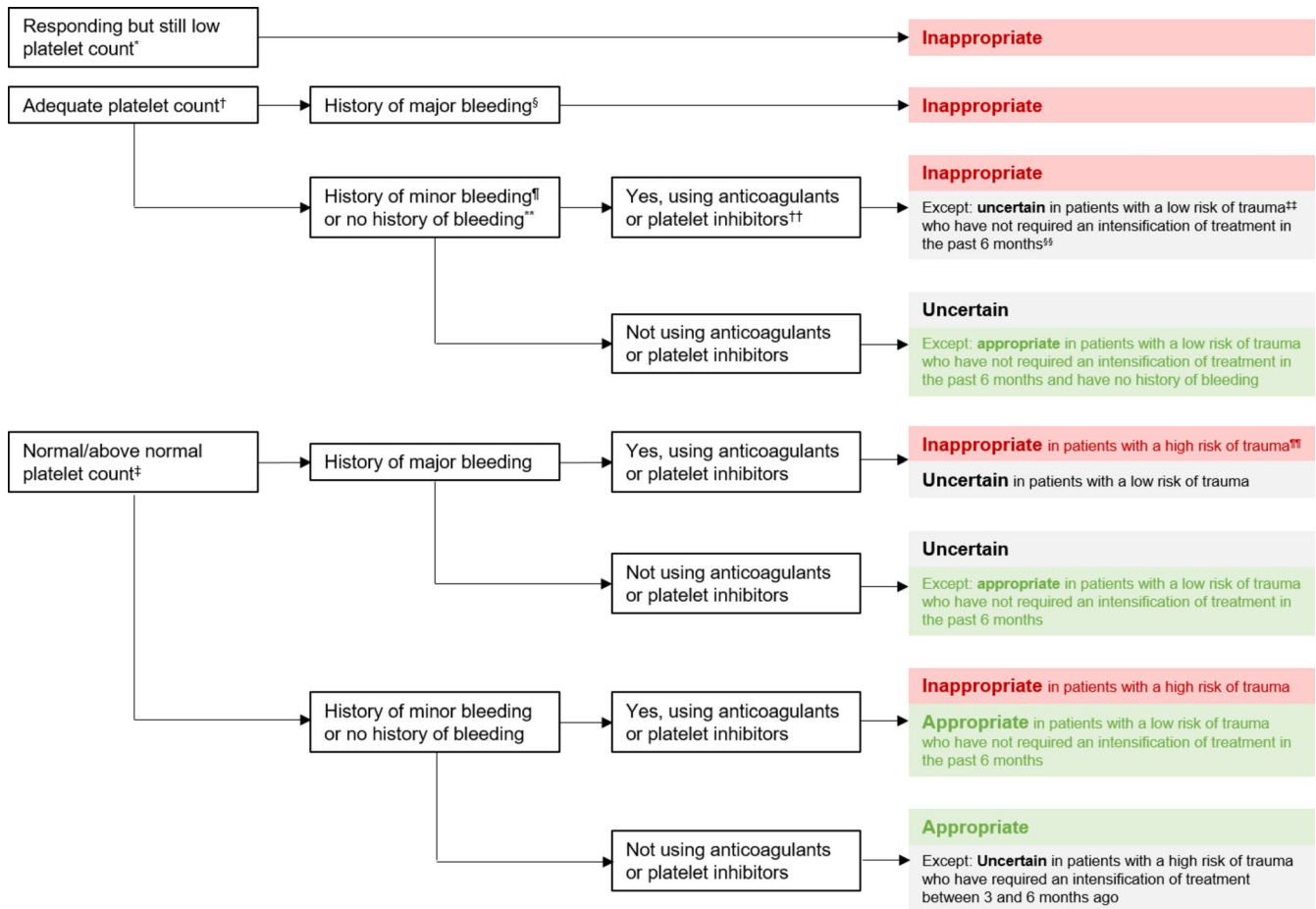


FIGURE 2 Patient flowchart of circumstances when it is inappropriate or appropriate to consider tapering TPO-RA monotherapy. This figure represents circumstances when experts agreed it is inappropriate (red boxes), appropriate (green boxes), or were uncertain (gray boxes) whether to consider tapering (with the aim of discontinuing) TPO-RA monotherapy. To read this flowchart, start by determining the patient’s current platelet count and follow the arrows based on other patient characteristics. *Current platelet count on treatment (within 2 weeks) is responding but still low (eg, $30\text{-}50 \times 10^9/\text{L}$). †Current platelet count on treatment (within 2 weeks) is adequate for a patient with ITP (eg, $50\text{-}150 \times 10^9/\text{L}$). ‡Current platelet count on treatment (within 2 weeks) is normal/above normal for a patient without ITP (eg, $>150 \times 10^9/\text{L}$). §Bleeding defined as World Health Organization grade 3 or 4, Buchanan severe grade, Bolton-Maggs and Moon “major bleeding,” ITP Bleeding Scale grade 2 or higher, life-threatening or intracerebral. ¶Any bleeding (other than skin manifestations) not meeting the criteria for “major bleeding.” **No bleeding other than skin manifestations (eg, minimal bruising or scattered petechiae). ††For treatment of comorbidity (eg, aspirin, clopidogrel, nonsteroidal anti-inflammatory drugs, heparin, warfarin, direct oral anticoagulants). ‡‡Lifestyle with low trauma risk (eg, primarily sedentary lifestyle, plays sports without bleeding risk [eg, walking, swimming, tennis]). §§Any increase in treatment while on TPO-RA, including rescue therapies or increasing dose of TPO-RA as a result of a low platelet count. During the panel meeting, experts agreed it would be inappropriate to consider tapering TPO-RA monotherapy in patients who required an intensification of treatment in the past 3 months. ¶¶Lifestyle with high trauma risk (eg, primarily active lifestyle, plays sports with bleeding risks [eg, basketball, soccer, baseball, American football, skiing, wrestling], holds an occupation associated with high risk of trauma, has a high fall risk, high-energy toddlers). ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist

However, we acknowledge that our guidance on how to taper, how to monitor after discontinuation, and how to restart therapy could be extrapolated to some patients with other indications for TPO-RA discontinuation (eg, adverse event, cost issues).

Fourth, although the analysis is based on realistic clinical scenarios and incorporates elements that could influence a clinician's decision to taper a TPO-RA, we acknowledge that the simplified patient scenarios we used do not fully capture the nuances encountered in real-world practice or individual patient circumstances. Fifth, there remained some areas of uncertainty (illustrated in white in Table 4), either because panel members disagreed about whether tapering was appropriate or because the entire panel was uncertain about the appropriateness of tapering in those circumstances. For example, we were uncertain about most patients with a history of major bleeding and normal platelet counts. We also disagreed on the platelet monitoring frequency after a successful taper and did not attempt to issue specific guidance on how quickly or slowly a taper should be conducted or how to monitor the platelet count while tapering. These are areas where further research is needed to establish clearer guidance. Finally, the panel included only US experts, and therefore our guidance may not be generalizable to other countries. Reassuringly, as described above, a survey of international experts yielded similar guidance.²¹

The guidance described here reflects the areas of greatest agreement among a panel of experts based on currently available evidence. These consensus statements could serve as a guide for clinical care and identify patients who could safely taper and discontinue TPO-RAs. Our results could also inform the design and development of clinical trials, including identifying which patients to enroll, that prospectively test the safety of tapering TPO-RA monotherapy in patients with ITP.

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RELATIONSHIP DISCLOSURE

AC has served as a consultant to Synergy CRO, and his institution has received research support on his behalf from Alexion, Bayer, Novartis, Novo Nordisk, Pfizer, Sanofi, Spark, and Takeda. He did not receive an honorarium for his work on the panel. JMD has served as a consultant to Amgen, Novartis, and Dova, and her institution has received research support on her behalf from Novartis and Amgen. RFG has served on an advisory board for Dova and has received institutional research funding from Agios, Pfizer, and Novartis. CK has served as a consultant to Novartis and UCB; Platelet Disorder Support Association (PDSA) has received consultancy support and honoraria on her behalf from Amgen, and

funding on her behalf from Amgen, Argenx, CSL Behring, Dova, Momenta, Novartis, Octapharma, Pfizer, Principia, Rigel, and UCB; and has served on the board of Thrombosis & Hemostasis Societies of North America. MPL has served on an advisory board for Dova, Principia, and Novartis; has served as a consultant to Dova, Principia, Novartis, Shionogi, Educational Concepts in Medicine, Octapharma, Bayer, and Argenix; has received honorarium from ClinGen; has served as a medical advisor to the Platelet Disorder Support Association (PDSA), 22qSociety, ITP Australia, CdLS Foundation, and the RDMD ITP study; and has received institutional research funding from Sysmex, Novartis, AstraZeneca, and Octapharma. HAL has served as a consultant to Genzyme, BMS, Rigel, Janssen, Portola, and Principia Biopharma; and has received research funding from Amgen, Rigel, Novartis, Kezar, and Argenix. His wife (Dr Ilene Weitz) has served as a consultant to Alexion. RML has no additional conflicts. KRM has served as a consultant to Rigel and Dova. VP has served as a consultant to and received honoraria from Amgen, Novartis, and Dova. JSW has served as a speaker for Novartis; his institution has received research funding on his behalf from Pfizer, Merck, and Incyte; and he has served as a consultant to Amgen. He and his wife have equity ownership in Merck, Biogen, Pfizer, and Eli Lilly. DB, SNG, IY, and MSB are employees of the Partnership for Health Analytic Research (PHAR), LLC, which was paid by Novartis to conduct this research.

AUTHOR CONTRIBUTIONS

AC served as the panel chair. JMD, RFG, CK, MPL, HAL, RML, KRM, VP, and JSW served as panel members. AC, DB, SNG, IY, and MSB designed the study, conducted the research, and drafted this manuscript. All authors critically reviewed and approved the content.

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