

Tapering Thrombopoietin Receptor Agonists in Primary Immune Thrombocytopenia: Recommendations Based on the RAND/UCLA Modified Delphi Panel Method

Adam Cuker¹, Jenny M Despotovic², Rachael F Grace³, Caroline Kruse⁴, Michele P Lambert⁵, Howard A Liebman⁶, Roger M Lyons⁷, Keith R McCrae⁸, Vinod Pullarkat⁹, Jeffrey S Wasser¹⁰, David Beenhouwer¹¹, Sarah N Gibbs¹¹, Irina Yermilov¹¹, Michael S Broder¹¹

¹Perelman School of Medicine, University of Pennsylvania; ²Department of Pediatrics, Baylor College of Medicine; ³Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School; ⁴Platelet Disorder Support Association; ⁵Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania; ⁶University of Southern California, Norris Cancer Hospital; ⁷Texas Oncology, USONCOLOGY; ⁸Cleveland Clinic, Lerner College of Medicine; ⁹City of Hope; ¹⁰University of Connecticut; ¹¹Partnership for Health Analytic Research (PHAR), LLC

Disclosures

This study was funded by Novartis. **JM Despotovic, RF Grace, C Kruse, MP Lambert, HA Liebman, RM Lyons, KR McCrae, V Pullarkat, and JS Wasser** signed research agreements with PHAR and received honoraria from Novartis for their participation on the panel; these panel members were not aware of the identity of the sponsor during the study or manuscript development. Novartis did not provide input on study design, methods, results, or interpretation of findings.

Authors report the following additional conflicts of interest:

- **A Cuker** 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.
- **JM Despotovic** has served as a consultant to Amgen, Novartis, and Dova, and her institution has received research support on her behalf from Novartis and Amgen.
- **RF Grace** has served on an Advisory Board for Dova, and has received institutional research funding from Agios, Pfizer, and Novartis.
- **C Kruse** 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.
- **MP Lambert** 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 Platelet Disorder Support Association (PDSA), 22qSociety, ITP Australia, CdLS Foundation, and RDMD ITP study; and has received institutional research funding from Sysmex, Novartis, AstraZeneca, and Octapharma.
- **HA Liebman** 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.
- **RM Lyons** has no additional conflicts.
- **KR McCrae** has served as a consultant to Rigel and Dova.
- **V Pullarkat** has served as a consultant to and received honoraria from Amgen, Novartis, and Dova.
- **JS Wasser** 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.
- **D Beenhouwer, SN Gibbs, I Yermilov, and M Broder** report other from Novartis during the conduct of the study; other from AbbVie, other from Akcea, other from ASPC, other from Amgen, other from AstraZeneca, other from BMS, other from Boston Scientific Corporation, other from Celgene, other from Eisai, other from Ethicon, other from GRAIL, other from Helsinn, other from Illumina, other from Innovation and Value Initiative, other from Ionis, other from Jazz, other from Kite, other from Novartis, other from Otsuka, other from Pathnostics, other from PhRMA, other from Prothena, other from Sage, other from Verde Technologies, other from Genentech, Inc., other from Greenwich Biosciences, Inc., other from Mirum Pharmaceuticals, Inc., grants and other from Dompe US, Inc., other from Sanofi US Services, Inc., other from Sunovion Pharmaceuticals, Inc. outside the submitted work.

Background & objective



- Thrombopoietin Receptor Agonists (TPO-RAs), such as romiplostim, eltrombopag, and avatrombopag, are approved for the treatment of primary immune thrombocytopenia (ITP).¹
- While it was previously thought that patients would need to remain on TPO-RAs indefinitely, case reports and cohort studies have shown that some patients are able to maintain a hemostatic platelet count off all treatment after discontinuing their TPO-RA.²⁻¹²
- We convened a panel of experts to develop consensus 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
 - How to restart therapy in the event of relapse

RAND/UCLA modified Delphi panel method

- We convened a diverse panel of 9 hematologists and 1 patient representative.
- We developed and reviewed evidence from 12 case reports,¹³⁻²⁴ 11 cohort studies,²⁻¹² and 2 clinical trial analyses²⁵⁻²⁶ on the cessation of TPO-RA treatment in adults and children with ITP.
- The panel was double-blinded while work was ongoing: The sponsor did not know the identity of the non-chair experts and the non-chair experts did not know the identity of the sponsor until publications of the work were drafted.



6 adult hematologists



3 pediatric hematologists



1 patient representative

Rating form development & patient scenarios

- We collaboratively developed the rating form.
- Part I included 432 patient scenarios based on 8 patient characteristics to assess the appropriateness of tapering therapy.
- Part II included the different ways to taper TPO-RAs (12 items), how to monitor patients after discontinuation (11 items), and how we restart therapy (5 items).

Current platelet count on treatment (normal/above normal [$>150 \times 10^9/L$]), adequate [$50-150 \times 10^9/L$], responding but still low [$30-50 \times 10^9/L$])

History of bleeding (none, minor, major)

Duration of ITP (persistent, chronic)

Months on TPO-RA monotherapy (≤ 12 , >12 months)

Platelet response to TPO-RA (early, not early)

Intensification of treatment (between 3 and 6 months ago, none in the past 6 months)

Trauma risk (low, high)

Use of anticoagulants or platelet inhibitors (no, yes)

432 patient scenarios

```
graph LR; A[Current platelet count on treatment] --- H[432 patient scenarios]; B[History of bleeding] --- H; C[Duration of ITP] --- H; D[Months on TPO-RA monotherapy] --- H; E[Platelet response to TPO-RA] --- H; F[Intensification of treatment] --- H; G[Trauma risk] --- H; H[Use of anticoagulants or platelet inhibitors] --- H;
```

Conducted two rounds of ratings, before and after a meeting

- We independently rated each item in the rating form on a 1 to 9 scale.
- Discussed our ratings during a virtual meeting on March 18-19, 2020.



How appropriate is it to recommend tapering (with the aim of discontinuing) TPO-RAs in a patient with these characteristics?

Inappropriate, I would not recommend tapering treatment in this patient because the risks of discontinuing treatment outweigh the benefits

I'm not sure (e.g., due to inadequate data) or the risks and benefits of discontinuing treatment in this patient seem roughly balanced

Appropriate, I would recommend tapering treatment in this patient because the benefits of discontinuing treatment outweigh the risks

Analyzed median ratings and differences in distributions

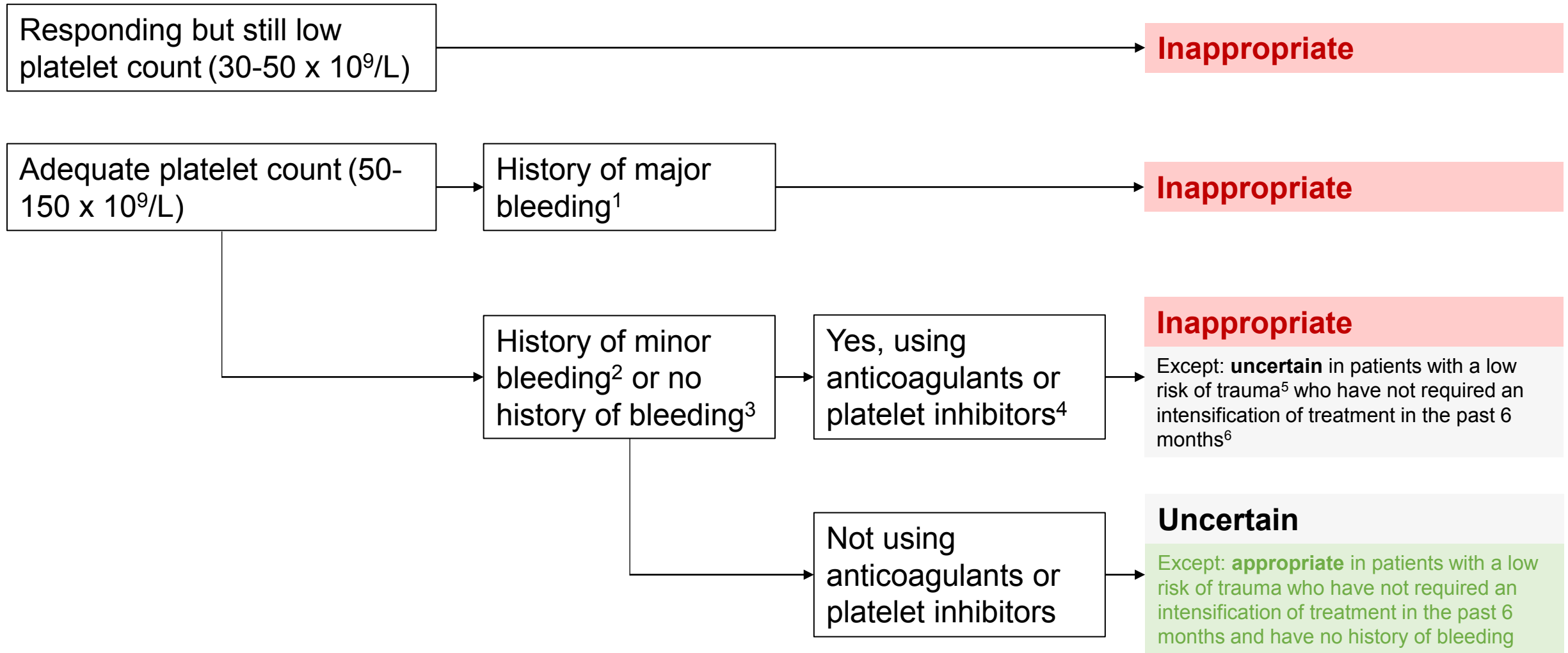
- Median ratings were calculated for each item and classified into 4 groups.
- We conducted Chi-squared tests to determine which characteristics had a statistically significant impact on ratings (defined as $p < 0.05$).
- The proportion of items with disagreement decreased from 20% to 10% following the panel meeting.

% (n)	Median $\geq 7-9$ without disagreement	Median $\geq 4- < 7$ without disagreement	Median $1- < 4$ without disagreement	Disagreement (≥ 2 ratings of 1-3 and ≥ 2 ratings of 7-9)
First-round	13% (59)	15% (68)	52% (241)	20% (92)
Second-round	14% (66)	24% (110)	52% (237)	10% (47)

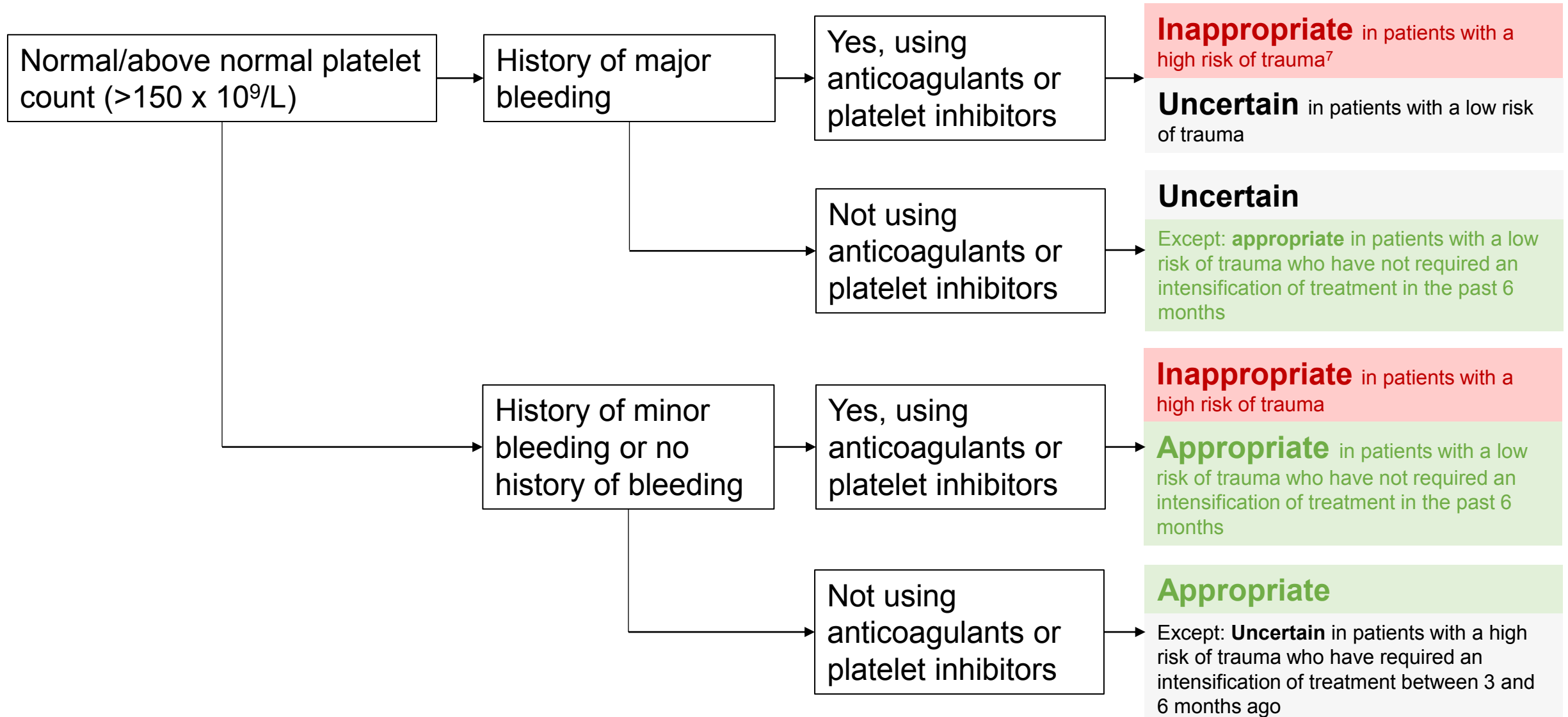
Five characteristics significantly impacted ratings

Characteristics included in patient scenarios	p-value
Platelet count (normal/above normal [$>150 \times 10^9/L$]), adequate [50-150 $\times 10^9/L$], responding but still low [30-50 $\times 10^9/L$])	<0.001
History of bleeding (none, minor, major)	0.001
Intensification of treatment (between 3 and 6 months ago, none in the past 6 months)	<0.001
Trauma risk (low, high)	<0.001
Use of anticoagulants or platelet inhibitors (no, yes)	<0.001
Duration of ITP (persistent, chronic)	0.427
Months on TPO-RA monotherapy (≤ 12 , >12 months)	0.964
Platelet response to TPO-RA (early, not early)	0.881

Consensus about when to taper TPO-RAs



Consensus about when to taper TPO-RAs



Example consensus statements about how to taper TPO-RAs



- It is inappropriate to discontinue TPO-RA monotherapy without tapering.
- Eltrombopag and romiplostim can be tapered by decreasing the dose periodically to the minimum available dose but maintaining the time interval between doses.
- It is appropriate to measure the platelet count soon after the patient has discontinued treatment (e.g., within 1-2 weeks) and with decreasing frequency over time assuming a successful clinical taper.
- 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. Thresholds for restarting therapy may be different for patients with different characteristics.

Conclusions



- 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.
- The guidance reflects areas of greatest agreement among a panel of experts based on currently available limited evidence.
- These consensus statements could serve as a guide for clinical care and could inform the design and development of clinical trials that prospectively test the safety of tapering TPO-RA monotherapy in patients with ITP.

Thank you

References



1. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv.* 2019 Dec 10;3(23):3829–66.
2. Ghadaki B, Nazi I, Kelton JG, Arnold DM. Sustained remissions of immune thrombocytopenia associated with the use of thrombopoietin receptor agonists: Sustained ITP Remissions after TPO Receptor Agonists. *Transfusion (Paris).* 2013 Nov;53(11):2807–12.
3. Mahévas M, Fain O, Ebbo M, Roudot-Thoraval F, Limal N, Khellaf M, et al. The temporary use of thrombopoietin-receptor agonists may induce a prolonged remission in adult chronic immune thrombocytopenia. Results of a French observational study. *Br J Haematol.* 2014 Jun;165(6):865–9.
4. Provan D, Taylor L, Nandigham R, Doobaree U, Kalkur P, Newland C A. Sustained Responses following Treatment with Romiplostim in Immune Thrombocytopenia: A Single-Centre Experience. *J Hematol Thromboembolic Dis [Internet].* 2014 [cited 2020 May 13];02(04). Available from: <http://www.esciencecentral.org/journals/sustained-responses-following-treatment-with-romiplostim-in-immune-thrombocytopenia-a-singlecentre-experience-2329-8790.1000147.php?aid=28250>
5. Kim Y-K, Lee S-S, Jeong S-H, Ahn J-S, Yang D-H, Lee J-J, et al. Efficacy and safety of eltrombopag in adult refractory immune thrombocytopenia. *Blood Res.* 2015;50(1):19.
6. González-López TJ, Pascual C, Álvarez-Román MT, Fernández-Fuertes F, Sánchez-González B, Caparrós I, et al. Successful discontinuation of eltrombopag after complete remission in patients with primary immune thrombocytopenia: Discontinuation of Eltrombopag in Primary ITP. *Am J Hematol.* 2015 Mar;90(3):E40–3.
7. Carpenedo M, Cantoni S, Coccini V, Fedele M, Morra E, Pogliani EM. Feasibility of romiplostim discontinuation in adult thrombopoietin-receptor agonist responsive patients with primary immune thrombocytopenia: an observational retrospective report in real life clinical practice. *Hematol Rep [Internet].* 2015 Feb 24 [cited 2020 May 13];7(1). Available from: <http://www.pagepress.org/journals/index.php/hr/article/view/5673>
8. Červinek L, Mayer J, Doubek M. Sustained remission of chronic immune thrombocytopenia after discontinuation of treatment with thrombopoietin-receptor agonists in adults. *Int J Hematol.* 2015 Jul;102(1):7–11.
9. Janssens A, Rodeghiero F, Anderson D, Chong BH, Boda Z, Pabinger I, et al. Changes in bone marrow morphology in adults receiving romiplostim for the treatment of thrombocytopenia associated with primary immune thrombocytopenia. *Ann Hematol.* 2016 Jun;95(7):1077–87.
10. Eser A, Toptas T, Kara O, Sezgin A, Noyan–Atalay F, Yilmaz G, et al. Efficacy and safety of eltrombopag in treatment-refractory primary immune thrombocytopenia: a retrospective study. *Blood Coagul Fibrinolysis.* 2016 Jan;27(1):47–52.
11. Newland A, Godeau B, Priego V, Viallard J-F, López Fernández MF, Orejudos A, et al. Remission and platelet responses with romiplostim in primary immune thrombocytopenia: final results from a phase 2 study. *Br J Haematol.* 2016 Jan;172(2):262–73.
12. Marshall AL, Scarpone R, De Greef M, Bird R, Kuter DJ. Remissions after long-term use of romiplostim for immune thrombocytopenia. *Haematologica.* 2016 Dec 1;101(12):e476–8.
13. Bussel JB, Saleh MN, Vasey SY, Mayer B, Arning M, Stone NL. Repeated short-term use of eltrombopag in patients with chronic immune thrombocytopenia (ITP). *Br J Haematol.* 2013 Feb;160(4):538–46.

References



14. Contis A, Lazaro E, Greib C, Pellegrin J-L, Viallard J-F. Romiplostim as early treatment for refractory primary immune thrombocytopenia. *Int J Hematol*. 2013 Nov;98(5):520–4.
15. Katsutani S, Tomiyama Y, Kimura A, Miyakawa Y, Okamoto S, Okoshi Y, et al. Oral eltrombopag for up to three years is safe and well-tolerated in Japanese patients with previously treated chronic immune thrombocytopenia: an open-label, extension study. *Int J Hematol*. 2013 Sep;98(3):323–30.
16. Khalafallah AA, Rahman Z, Ogden K, Hannan T. Successful treatment with eltrombopag in avoiding splenectomy for patients with chronic refractory immune thrombocytopenia. *Mediterr J Hematol Infect Dis*. 2012 Jan 18;4(1):e2012003.
17. Khellaf M, Michel M, Quittet P, Viallard J-F, Alexis M, Roudot-Thoraval F, et al. Romiplostim safety and efficacy for immune thrombocytopenia in clinical practice: 2-year results of 72 adults in a romiplostim compassionate-use program. *Blood*. 2011 Oct 20;118(16):4338–45.
18. Mingot-Castellano M-E, Grande-García C, Valcárcel-Ferreiras D, Conill-Cortés C, de Olivar-Oliver L. Sustained Remission in Patients with Primary Immune Thrombocytopenia after Romiplostim Tapering and Discontinuation: A Case Series in Real Life Management in Spain. *Case Rep Hematol*. 2017;2017:1–8.
19. Noronha V, Philip SD, Joshi A, Prabhaskar K. Prolonged remission from eltrombopag in chronic refractory idiopathic thrombocytopenic purpura. *Int J Hematol*. 2012 Sep;96(3):380–2.
20. Perera M, Suarez A, Luzardo H, Lopez J, Molero T. Spontaneous remission after a year of romiplostim in an adult patient with refractory primary immune thrombocytopenia. *Ann Hematol*. 2012 Sep;91(9):1497–8.
21. Santoro C, Volpicelli P, Baldacci E, Ferrara G, Di Rocco A, Ferretti A, et al. Repeated successful use of eltrombopag in chronic primary immune thrombocytopenia: description of an intriguing case. *Clin Case Rep*. 2017 Aug;5(8):1385–8.
22. Thachil J, Salter I, George JN. Complete remission of refractory immune thrombocytopenia (ITP) with a short course of Romiplostim. *Eur J Haematol*. 2013 Jul;n/a-n/a.
23. Vlachaki E, Papageorgiou V, Klonizakis F, Spandonidou M, Chisan S, Vetsiou E, et al. Total remission of severe immune thrombocytopenia after short term treatment with romiplostim. *Hematol Rep Former Hematol Rev*. 2011 Oct 21;3(3):e20.
24. Wang X, Liu X, Wang L, Wang J-Y, Li A. Successful discontinuation of eltrombopag in one child with refractory primary immune thrombocytopenia and literature review: *Blood Coagul Fibrinolysis*. 2019 Mar;30(2):71–4.
25. Bussel JB, Wang X, Lopez A, Eisen M. Case study of remission in adults with immune thrombocytopenia following cessation of treatment with the thrombopoietin mimetic romiplostim. *Hematology*. 2016 Apr 20;21(4):257–62.
26. Kuter DJ, Newland A, Chong BH, Rodeghiero F, Romero MT, Pabinger I, et al. Romiplostim in adult patients with newly diagnosed or persistent immune thrombocytopenia (ITP) for up to 1 year and in those with chronic ITP for more than 1 year: a subgroup analysis of integrated data from completed romiplostim studies. *Br J Haematol*. 2019 May;185(3):503–13.