

Letters to the Editor**Early Use of Thrombopoietin Receptor Agonists (Tpo-Ras) in Clinical Practice: Results from an Italian Survey on Behalf of the Gimema Working Group Anemia and Thrombocytopenia****Keywords:** Tpo-Ras; Gimema.**Published:** May 01, 2025**Received:** September 19, 2024**Accepted:** April 15, 2025

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To the editor.

Thrombopoietin receptor agonists (TPO-RAs) are currently part of the second-line treatment of primary immune thrombocytopenia (ATP). Since their initial availability, TPO-RAs have been administered earlier in accordance with the most recent evidence and drug indication.¹⁻⁶ However, the optimal timing of administration, tapering, and discontinuation of these drugs has not yet been clearly defined. We have performed a nationwide survey specifically focused on the early administration of TPO-RAs in the current Italian clinical practice. The current survey was performed in Italy to evaluate the opinions and behaviors of expert hematologists in ITP care; it was based on their experience and not specifically focused on a patient category. Survey results show that early use of TPO-RAs is frequently adopted in common clinical practice, also immediately after a first-line therapy with corticosteroids plus immunoglobulins; the main driver for the early use is always the clinical condition, in particular, an absent or unsatisfactory response. The choice of the ideal candidate for early treatment with

TPO-RAs is mainly defined on the basis of comorbidities, aiming to avoid corticosteroid-related toxicities, while it is unrelated to age. We have recently published a nationwide survey on the use of TPO-RA among Italian hematologists,⁷ but it was not merely related to the early use of TPO-RAs. The current work was developed in the frame of a scientific project (ITP-NET) in partnership with the National GIMEMA working party on ITP. It was conceived within the study group and focused on the early use of TPO-RA. The survey was structured as a 13-item questionnaire, with an accurate definition of the clarity of questions. Survey items were structured as close-ended or multiple-choice-style questions. The main topics of the proposed questions on TPO-RAs referred to: timing and schedule of administration, ideal candidate profile, perceived risk factors for their early administration, main factors in favor or against their early use, the confidence of administration in case of thrombotic events, pregnancy or other immune-mediated thrombocytopenias. A full list of the proposed questions is reported in **Table 1**.

The survey was launched among hematologists from

Table 1. Full list of questions and proposed answers.

List of Questions	List of Answers
1) Has the clinical experience you gained with TPO-RAs changed your approach to using these drugs compared to the time of their initial marketing?	• No; • Yes, both for the timing of the start and for tapering of TPO-RAs; • Yes, but only for the timing of the therapy start; • Yes, but only for the tapering of TPO-RAs therapy; • Yes, for reasons other than the timing of starting therapy and tapering (specify which ones).
2) Has the recent availability of new ITP treatments changed your approach to the choice of second-line treatment?	• Yes; • No; • Only in selected cases (specify which ones).
3) With reference to the available evidence and your current clinical practice, do you think that TPO-RAs can be administered very early? (i.e., within four weeks) after the first diagnosis of ITP?	• Yes; • No; • I don't know.

4) Where do you place treatment with TPO-Ras today?	• First-line therapy, in combination with steroids; • First-line therapy, as an alternative to steroids; • First-line therapy in selected cases (i.e, diabetic or elderly or septic patient); • Immediately after a short course (up to two weeks) of appropriately dosed steroid therapy with a scarce or absent increase in platelet count (PLT<30,000/mm³); • Second-line therapy in all patients; • Second-line therapy, evaluating case by case, pros/cons and patient characteristics.
5) Which features/factors can promote early/extremely early administration of TPO-RAs?	• Home administration/delivery, availability of the molecules; • Non – early response to first-line therapy (corticosteroids +/- Ig) with or without bleeding symptoms; • Age; • Frequent contact with patients; • Time required to reach a safe platelet count; Easy dose definition; • Intolerance; • Platelet count fluctuations; • Comorbidities/concomitant therapies/patient compliance; • Other (specify what other characteristics/factors could favor the administration of TPO-RA).
6) You Indicate TPO-RAs early more often	• In young patients; • In elderly patients; • Regardless of age.
7) Do you think that the administration of TPO-Ras should take place earlier or later in relation to an age above or below 65 years?	• Yes, I administer TPO-RAs earlier for age > 65 years; • Yes, I administer TPO-RAs earlier for age < 65 years; • No, actually, I administer TPO-RAs earlier only in the absence of relevant cardiovascular risk factors and comorbidities, regardless of age; • I define the early administration of TPO-Ras based on other criteria (not age and cardiovascular risk) - specify which ones.
8) What features/factors can disadvantage early/extremely early administration of TPO-RAs?	• Costs; • Risk of overtreatment for some patients; • Diagnostic doubts (for patients treated in the first line); • Comorbidity; • Risk of extreme fluctuations in platelet count; Difficult supply; • Interactions with other drugs/food habits;
9) In your opinion, which is the “ideal” candidate for first-line administration of TPO-RAs?	• Patient not responding within 5 days to steroid therapy + /- Ig; • Patient with major bleeding who does not respond within 1-2 days to steroid therapy + Ig; All patients with new diagnosed ITP that experience hemorrhagic syndrome at onset; Patients with ITP and diabetes, as steroid- sparing agents; • If I could, I would use them all on the first line, with the aim of avoiding the side effects of steroid therapy; • None of the above;
10) In the light of the experience gained with the TPO-RAs, you use them with more confidence:	• In the event of thrombosis occurring outside treatment with TPO-RAs because of the need to establish anticoagulant/antiplatelet therapy; • In case of thrombosis occurring during the treatment with TPO-RAs because of the need to start anticoagulant/antiplatelet therapy (continue treatment); • No, I do not use TPO-RAs more confidently, but in light of the introduction of new molecules I preferentially use those, in case also discontinuing previous treatment with TPO-RAs; • In both cases of thrombosis that occurred before or during TPO-RAs treatment.
11) In light of the experience gained with the TPO-RAs, do you use them with more confidence in pregnancy?	• Yes; • No.
12) If you answered yes to the previous question	• First quarter; • Second quarter; • Third quarter; • Indifferently during the course of pregnancy
13) You have had experience using TPO-RAs in the following patient settings:	• Oncology during chemotherapy/radiotherapy; • Onco-hematology during chemotherapy; • Post-autotransplant or allo-transplant to promote recovery of platelet values; • Septic patients.

thirty-eight Italian hematological centers participating in the GIMEMA Foundation between Jul 3, 2023, and Jul 31, 2023, with a reminder sent to non-respondents after 2 and 3 weeks. The respondents' anonymity was guaranteed. Institutional information

was not included. Thus, institutional permission to participate was not required. Overall, 41 participants answered the survey. The whole cohort of patients affected by primary ITP, followed by the Centers participating in the survey, was composed of 4588

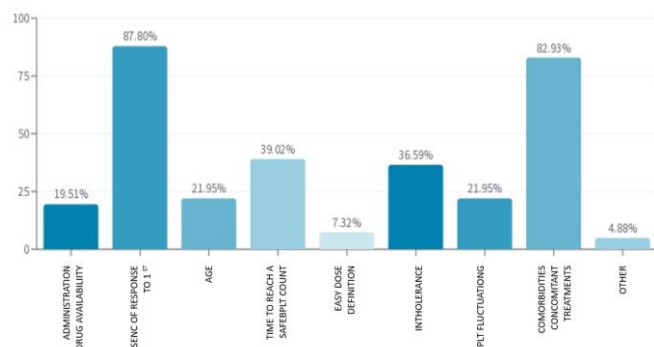


Figure 1. Factors supporting an early administration of Tpo-Ra

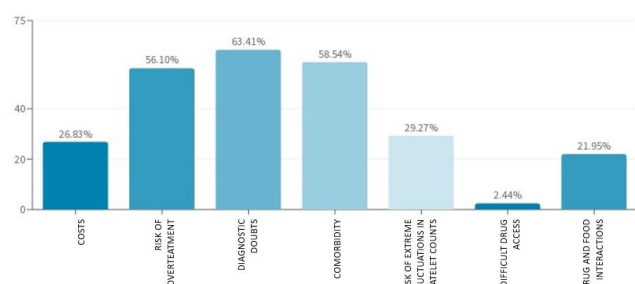


Figure 2. Driving reasons against early use of Tpo-Ra

subjects: 20,69% affected by newly diagnosed ITP, 19,53% with persistent ITP, and 59,78% with chronic ITP.

The main results show that the choice of the ideal candidate for early treatment with TPO-RAs is mainly defined on the basis of comorbidities, including cardiovascular risk factors and corticosteroid-related toxicities, while it seems unrelated to age. The opinions of the survey participants were quite heterogeneous regarding some items, such as the choice of the specific timing of early use and driving reasons in favor or against early use (**Figure 1** and **2**). The most relevant factors against the early administration of TPO-RAs are diagnostic uncertainty, the risks of over-exposure, and comorbidities. A front-line treatment with TPO-RAs can be taken into account in cases of severe bleeding unresponsive to steroids and immunoglobulins or for a clear need for a “steroids-sparing” approach. Increased awareness has furthermore emerged among respondents on the management of thrombotic events requiring the contemporary administration of anticoagulants or

antiplatelet agents. Nowadays, eltrombopag and romiplostim may be administered to patients affected by primary ITP, refractory to other treatments (corticosteroids and immunoglobulins), without consideration of the time from diagnosis. The Italian Society of Hematology (SIE) recommends their administration 6 months after ITP diagnosis.⁸ Early use of TPO-RA allows, on one side, to reduce exposure to steroids, thus avoiding serious adverse events, and on the other side, to control the risk of severe bleeding. The current results have confirmed what was already perceived among Italian hematologists during the previous evaluation performed by our group, in particular, to be desirable for an earlier and much more flexible administration of TPO-RA. Available data suggest that even if TPO-RAs show overlap efficacy during the different phases (newly diagnosed, persistent, or chronic) of ITP, the early administration of eltrombopag and romiplostim may be associated with improved clinical outcomes,⁹⁻¹⁴ particularly referred to as the sustained response off therapy.^{15,16} In a recently published real-world study from the UK, the administration of TPO-RA early after diagnosis, before other treatment lines, including rituximab and splenectomy, without concomitant steroids administration, was predictive of an increased platelet count of $\geq 100 \times 10^9/L$.¹⁷ Similar real word evidence, confirming a reduced exposure to corticosteroids and improved bleeding control after early use of TPO- RAs were also reported by other groups.¹⁸ Furthermore, TPO-RA administration soon after an unsatisfactory response to steroids resulted in safe and effective.^{17,18} The results of the present survey confirm that Italian hematologists adopt early therapy with TPO-RAs if necessary. However, they also support the need to define better the concept of “early use” of TPO-RAs in up-to-date management of ITP, redefining platelet response to better evaluate clinical benefits.

Moreover, the concept of refractoriness to TPOra and the management of patients at high risk for thrombosis that could benefit from this category of drugs should be reconsidered in light of the results obtained in real-life experiences and the availability of new drugs.

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