

# Second-line administration of thrombopoietin receptor agonists in immune thrombocytopenia: Italian Delphi-based consensus recommendations

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## Abstract

**Introduction:** In patients with primary immune thrombocytopenia (ITP), a short course of steroids is routinely given as first-line therapy. However, the response is often transient and additional therapy is usually needed. Thrombopoietin receptor agonists (TPO-RAs) are frequently used as second-line therapy, although there is little clinical guidance on the timing of their administration and on tapering/discontinuation of the drug. To provide clinical recommendations, we used the Delphi technique to obtain consensus for statements regarding administration and on tapering/discontinuation of second-line TPO-RAs among a group of Italian clinicians with expertise in management of ITP.

**Methods:** The Delphi process was used to obtain agreement on five statements regarding initiation and on tapering/discontinuation of second-line TPO-RAs. Agreement was considered when 75% of participants approved the statement. Eleven experts participated in the voting.

**Results:** Full consensus was reached for three of the five statements. The experts held that an early switch from corticosteroids to a TPO-RA has the dual advantage of sparing patients from corticosteroid abuse and improve long-term clinical outcomes. All felt that dose reduction of TPO-RAs can be considered in patients with a stable response and platelet count  $>100 \times 10^9/L$  that is maintained for at least 6 months in the absence of concomitant treatments, although there was less agreement in patients with a platelet count  $>50 \times 10^9/L$ . Near consensus was reached regarding the statement that early treatment with a TPO-RA is associated with an increase in clinically significant partial or complete response. The experts also agreed that optimization of tapering and discontinuation of TPO-RA therapy in selected patients can improve the quality of life.

**Conclusion:** The present consensus can help to provide guidance on use of TPO-RAs in daily practice in patients with ITP.

*Ther Adv Hematol*

2021, Vol. 12: 1–9

DOI: 10.1177/  
20406207211048361

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## Plain language summary

### Second-line administration of thrombopoietin receptor agonists in immune thrombocytopenia

- There is little guidance on the timing of administration and tapering/discontinuation of thrombopoietin receptor agonists (TPO-RAs) in patients with primary immune thrombocytopenia (ITP).

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- The Delphi technique was used to obtain consensus for five statements.
- The present consensus among Italian clinicians aims to provide guidance on second-line use of TPO-RAs for patients with ITP in daily practice.

**Keywords:** consensus, Delphi, immune thrombocytopenia, management, second line, therapy, thrombopoietin receptor agonists

Received: 16 April 2021; revised manuscript accepted: 6 September 2021.

## Introduction

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by reduced platelet counts related to increased peripheral destruction of platelets and diminished production.<sup>1</sup> ITP may have strong negative impact on the patient's quality of life, which is mainly related to the significant burden of therapy, bleeding events, and fatigue.<sup>2</sup> Diagnosis of primary ITP is usually made following exclusion of underlying and/or precipitating causes of the thrombocytopenia and is classified based on duration as newly diagnosed, persistent (3–12 months), and chronic ( $\geq 12$  months).<sup>3</sup> In adults, ITP often has a chronic course.<sup>2,4</sup>

The main goals of therapy are to terminate any active bleeding events and to limit future hemorrhage. In a newly diagnosed patient with ITP, the guidelines of the American Society of Hematology (ASH) suggest that patients with a platelet count of  $<30 \times 10^9/L$  and asymptomatic should be treated with first-line corticosteroids [prednisone (0.5–2.0 mg/kg per day) or dexamethasone (40 mg per day for 4 days)].<sup>5</sup>

Even if the majority of patients will initially respond to corticosteroids, unfortunately the response is often transient and additional therapy is needed.<sup>6</sup> Repeated or sustained administration of corticosteroids is not recommended given the potential for adverse effects and negative impact on quality of life such as weight gain, hypertension, osteoporosis, hyperglycemia, mood alterations, and infections.<sup>5,7</sup> Moreover, prolonged treatment will not improve the patient's response, but will likely worsen adverse events. The high rates of recurrence further demonstrate that corticosteroids reduce symptoms, but do not change the course of the disease.<sup>8</sup> Importantly, all guidelines and consensus recommendations suggest a short course of corticosteroid therapy ( $\leq 6$  weeks) and limited to 1–2 cycles, while carefully

monitoring for adverse effects.<sup>3,5,7–9</sup> However, the administration of corticosteroids is not always in line with these recommendations. For example, in the 472 physicians from 13 countries participating in I-WISH (ITP World Impact Survey), 75% referred that they commonly prescribe corticosteroids or steroids at first relapse.<sup>10</sup> In addition, in a German survey of 1023 patients, 62% of patients receiving steroids as first-line treatment received them for up to 6 months, and 29% received them for more than a year during second- and even third-line treatment.<sup>11</sup>

In many patients, ITP becomes persistent or chronic, and second-line treatment may thus be warranted.<sup>5,12,13</sup> In this regard, it should be considered that limiting corticosteroids to the first line of therapy allows earlier transition to second-line therapy. Second-line therapy should have the same purpose as first-line treatment and aim to achieve long-term remission. The standard options for second-line therapy comprise splenectomy, thrombopoietin receptor agonists (TPO-RAs), and rituximab.<sup>5</sup> Splenectomy has been historically considered as the main option for second-line management of ITP given its potential to provide long-term remission. Splenectomy is associated with high initial response rate, although about one-third of patients will experience relapse over long-term follow-up and there are no reliable predictors of long-term response.<sup>14</sup> Moreover, splenectomy is associated with potentially serious long- and short-term risks due to loss of hematological and immunological functions.<sup>14,15</sup> These include reduced Fc $\gamma$  R-mediated opsonization of microorganisms, reduced interaction of memory B-cells and helper T-cells, impairment of contact between abnormal particulates, and a densely populated reticulum of macrophage.<sup>16</sup> Splenectomy is also associated with an increased risk of thrombosis, with the highest incidence of venous thromboembolism in the perioperative period and during the first year after

the procedure with a cumulative prevalence ranging from 1.4% to 16% depending on the length of follow-up.<sup>17</sup>

Rituximab has been associated with long-term remission in a proportion of patients, although there are no clear indications on which patients and when it should be administered.<sup>18</sup> Moreover, given the current CoVID-19 pandemic, there are also concerns about the use of rituximab since patients receiving it will be unlikely to make antibodies to SARS-CoV-2.<sup>19</sup>

TPO-RAs are often the preferred agent for second-line medical therapy, and some authors have suggested postponing splenectomy as long as possible, or at least up to 1 year.<sup>14</sup> Indeed, a recent consensus approach from a Spanish group reported that 97.5% of these experts consider TPO-RAs as the class of choice for second-line therapy of patients with ITP.<sup>9</sup> TPO-RAs also have the most evidence demonstrating their long-term effectiveness.<sup>5,7-9</sup> While there is convincing consensus on the use of TPO-RAs as second-line therapy, the optimal timing for their administration has not been universally defined. The 2019 ASH guidelines, for example, state that TPO-RAs can only be considered for ITP lasting  $\geq 3$  months in adults.<sup>5</sup>

Another clinically relevant aspect regards tapering of TPO-RAs. Tapering represents a key issue since up to 30% of patients with ITP maintain a sustained response after dose reduction or discontinuation of the TPO-RA.<sup>3</sup> Indeed, a scheme has recently been proposed for tapering and discontinuation of TPO-RA.<sup>20</sup> However, this is limited to expert opinion and at present, there is little evidence-based guidance on the timing of TPO-RA administration and on tapering/discontinuation of the drug. To provide clinical practice recommendations for these aspects, we used the Delphi technique to obtain consensus for statements regarding administration and on tapering/discontinuation of second-line TPO-RAs among a group of Italian clinicians with expertise in management of ITP.

## Materials and methods

The Delphi process is a widely adopted technique that is used to achieve expert consensus. The method adopts a survey type format, where

statements undergo successive rounds of voting until consensus is reached.<sup>21</sup> The Delphi approach thus combines the evidence-based medicine with an iterative and anonymous voting process. Moreover, the Delphi approach avoids problems in group dynamics as the experts can provide their opinions freely and anonymously.<sup>22</sup>

The steering committee was composed of four experts (FB, MC, SMS, FZ) who drafted five statements on administration and on tapering/discontinuation of second-line TPO-RAs. Committee members were identified by criteria that included their expertise in management of ITP, publications, and attendance at international meetings.

An expert panel consisting of 11 Italian hematologists was invited to participate in the Delphi process based on their interest and expertise in the management of patients with ITP. The experts were identified from all geographic regions in order to be representative of clinical practice of ITP in Italy. The process used herein was composed of four steps: (a) establishment of a scientific steering committee who reviewed the relevant literature and developed the statements to be ranked; (b) first round of online voting by the expert panel; (c) modification and/or second round of voting for unmodified statements not reaching consensus by the steering committee based on comments by expert panel; (d) second round of online voting by the expert panel.

The experts were required to express their level of agreement with each statement, using a 5-point Likert-type scale (1 = disagree; 2 = somewhat disagree; 3 = neither agree nor disagree; 4 = somewhat agree; 5 = agree). Consensus was considered if either the sum of answers 1 and 2 (negative agreement), or 4 and 5 (positive agreement) exceeded 75% in line with previous studies with the Delphi method.<sup>23-26</sup> The results are expressed as a percentage of agreement with each statement.

## Results and discussion

The Delphi process described was used to vote upon five statements regarding initiation and on tapering/discontinuation of second-line TPO-RAs in patients with ITP (Table 1). Eleven experts participated in the voting. In the first round of voting, consensus was reached for

**Table 1.** Statements on administration and on tapering/discontinuation of second-line TPO-RAs for treatment of ITP.

	Statement	% agreement
1	An early switch from corticosteroids to a TPO-RA has the dual advantage of sparing patients from corticosteroid abuse and improve long-term clinical outcomes.	100%
2A	Dose reduction (tapering) of TPO-RAs can be considered in patients with a stable response and platelet count $>50 \times 10^9/L$ (PR) that is maintained for at least 6 months in the absence of concomitant treatments.	54.5%
2B	Dose reduction (tapering) of TPO-RAs can be considered in patients with a stable response and platelet count $>50 \times 10^9/L$ (PR) that is maintained for at least 6 months in the absence of concomitant treatments.	63.6%
3	Dose reduction (tapering) of TPO-RAs can be considered in patients with a stable response and platelet count $>100 \times 10^9/L$ (CR) that is maintained for at least 6 months in the absence of concomitant treatments.	100%
4A	If TPO-RA treatment is given early, there is a greater chance of achieving partial or complete response.	72.7%
4B	Early treatment with a TPO-RA is associated with an increase in clinically significant response (partial or complete).	72.7%
5	Optimization of tapering and discontinuation of TPO-RA therapy in selected patients can improve the quality of life.	90.1%

CR, complete response; ITP, immune thrombocytopenia; PR, partial response; TPO-RA, thrombopoietin receptor agonists.

statements 1, 3, and 5. Statement 2 was voted upon again in the original form, while statement 4 was modified and voted upon again. Consensus was not reached for either.

**Statement 1:** An early switch from corticosteroids to a TPO-RA has the dual advantage of sparing patients from corticosteroid abuse and improve long-term clinical outcomes.

Unanimous consensus was reached on this statement. ASH guidelines recommend against a prolonged course of corticosteroids, stating that while there is possibly ‘trivial benefit’ an alternative therapy should be preferred.<sup>5</sup> Nevertheless, the 6 weeks of corticosteroid treatment may be used to understand if the patient will enter remission or will need additional treatment. The guidelines further consider that prolonged (more than 6 weeks) administration of corticosteroids will be likely associated with an increased occurrence of adverse events. Indeed, the long-term side effects are well known and may involve many organs.<sup>27–30</sup> Moreover, since patients with ITP already have a high disease burden, long-term use of corticosteroids does not seem reasonable due to their well

known adverse events. However, the extended use of corticosteroids is common practice as highlighted in a real-world analysis on almost 8000 patients with ITP, wherein long-term, high-dose corticosteroid use was seen for up to 7 lines of therapy and frequently as monotherapy.<sup>31</sup> The expert panel fully agreed that the early use of a TPO-RA is a safe approach, can spare patients glucocorticoid toxicity, and, as such, improve long-term clinical outcomes.

**Statement 2:** Dose reduction (tapering) of TPO-RAs can be considered in patients with a stable response and platelet count  $>50 \times 10^9/L$  [partial response (PR)] that is maintained for at least 6 months in the absence of concomitant treatments.

Dose reduction (tapering) of TPO-RAs can be considered in patients with a stable response and platelet count  $>50 \times 10^9/L$  (PR) that is maintained for at least 6 months in the absence of concomitant treatments. We defined complete response (CR) as a platelet count  $>100 \times 10^9/L$  and response as a platelet count  $>30 \times 10^9/L$  and at least twofold increase in the baseline count as

described in Rodeghiero *et al.*<sup>1</sup> Nonetheless, in recent years, many authors have considered a platelet response defined as a platelet count  $>50 \times 10^9/L$  at a given assessment on treatment with TPO-RA or placebo<sup>32</sup> or a target platelet range variable from  $50 \times 10^9/L$  and  $200 \times 10^9/L$  or higher.<sup>33</sup> This variability in definitions makes comparison among results in different studies difficult both in term of response during ongoing treatment and even more so during and after tapering of TPO-RAs.

No consensus was reached for statement 2 after two rounds of voting. The main reasons leading to this lack of consent were that (a) only a relatively small proportion of patients with a platelet count  $>50 \times 10^9/L$  will maintain response after discontinuation; and (b) the evidence was adequate for patients with CR, but not with PR. Other authors claimed that tapering can be attempted in patients with a platelet count  $>50 \times 10^9/L$  that is sustained for at least 6 months, with the caveat that the tapering can be interrupted if the platelet count drops below  $30 \times 10^9/L$  or  $50 \times 10^9/L$  if a bleeding event is documented.<sup>20</sup> These suggestions were based on the analysis of the published literature documenting delayed responses after discontinuation of a TPO-RA.<sup>20</sup> The trial by Cervinek reported on 46 patients being treated with a TPO-RA.<sup>34</sup> In patients achieving a platelet count  $\geq 50 \times 10^9/L$  for 24 consecutive weeks, the drug was tapered over a period of 3 weeks. Eleven of the 46 patients discontinued the TPO-RA, and all maintained response for a median of 33 months. In the very recent trial by Lucchini *et al.*,<sup>35</sup> 13 of 51 (25%) patients considered as responders (platelet count  $\geq 30 \times 10^9/L$  and at least a twofold increase from the baseline count) were able to taper and discontinue eltrombopag and maintain remission for 24 weeks, while another 13 of the remaining 34 patients (38%) had started tapering. In addition, in both studies a proportion of patients who achieved a treatment-free response were also partial responders. Most recently, Cooper *et al.*<sup>36</sup> published a UK hematologist survey about tapering and discontinuation of TPO-RA in patients with ITP, stating that approximately 30% of patients are eligible for tapering and discontinuation, which may be considered after 6–12 months for patients demonstrating an adequate treatment response (platelet count  $>50,000/\mu L$  at  $\geq 75\%$  of assessments in the preceding 6 months).

Sustained remission off-treatment is possible in a proportion of patients. However, the available data in patients achieving a PR and discontinuing a TPO-RA are somewhat limited. Among the group of expert panelists, there was no agreement that discontinuation of the TPO-RA should be considered in patients with a PR.

Statement 3: Dose reduction (tapering) of TPO-RAs can be considered in patients with a stable response and platelet count  $>100 \times 10^9/L$  (CR) that is maintained for at least 6 months in the absence of concomitant treatments.

For reference, the main published studies on discontinuation of TPO-RAs in patients with ITP are summarized in Table 2. The experts agreed that dose reduction (tapering) of TPO-RAs can be considered in patients with a stable response and platelet count  $>100 \times 10^9/L$  (CR) that is maintained for at least 6 months in the absence of concomitant treatments. Gonzalez-Lopez reported on a cohort of 49 evaluable patients discontinuing eltrombopag; of these, 26 maintained a sustained response after a median of 9 months.<sup>39</sup> In the study by Marshall *et al.*,<sup>41</sup> 12 of 43 patients (28%) who discontinued romiplostim maintained an elevated platelet response after a median of more than 6 years, thus demonstrating that long-term off-treatment response can be attained. In the study by Mahevas *et al.*<sup>40</sup> on 54 patients, a total of 20 patients with CR discontinued TPO-RA and of these 8 maintained sustained response after a median of 13.5 months. Similar results have been reported by other authors, suggesting that discontinuation of a TPO-RA is associated with sustained platelet responses in a subset of patients who achieve a CR.<sup>42–44</sup> Accordingly, tapering and discontinuation can be considered in these patients.

Statement 4: If TPO-RA treatment is given early, there is a greater chance of achieving partial or complete response.

Near consensus was reached after two rounds of voting for statement 4 regarding the possibility that early treatment is associated with higher rates of PR or CR. The agreement of 72.7% *versus* 75% needed for full consensus was obtained twice in two consecutive rounds of voting repeated on the same rephrased statement. In published studies, as noted in a recent review by Zaja *et al.*, CR or PR with TPO-RAs are more often observed

**Table 2.** Main published studies on discontinuation of TPO-RAs in patients with ITP.

Study	Number of patients	Patients who discontinued TPO-RA (n, % from all pts)	Patients in sustained remission (n, % of all patients)	Median follow-up (months)
Newland <i>et al.</i> <sup>37</sup>	75	31 (41)	24 (32)	6
Ghadaki <i>et al.</i> <sup>38</sup>	31	9 (29)	5 (16)	9.5
González-Lopez <i>et al.</i> <sup>39</sup>	201	80 (39)	42 (21)	9
Mahevas <i>et al.</i> <sup>40</sup>	54	20 (37)	8 (15)	13.5
Cervinek <i>et al.</i> <sup>34</sup>	46	11 (24)	11 (24)	33
Marshall <i>et al.</i> <sup>41</sup>	43	12 (28)	12 (28)	33

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

when initiated early, especially before splenectomy, or before early switch from first-line treatments.<sup>20,39,44,45</sup> These results might suggest that early use of a TPO-RA can be associated with improved responses, which would lead to better long-term outcomes.<sup>20</sup> In order to find predictors of remission, Newland *et al.*<sup>37</sup> presented a pooled analysis of 13 studies involving 911 adults with ITP being treated with romiplostim; treatment-free responses were observed in 61 patients. In multivariate analysis, shorter duration of ITP was significantly associated with a higher odds ratio of achieving a treatment-free response for both newly diagnosed and persistent ITP (<3 months *versus* >12 months, OR=4.275,  $p < 0.0001$ ; 3–12 months *versus* >12 months, OR=2.171,  $p = 0.0408$ ). Previous splenectomy and bleeding were not predictors of treatment-free response. Early use of TPO-RAs has also been observed in other studies. As reported by Gonzalez-Lopez in a study of 220 adults with ITP, PR, and CR rates were higher in those treated earlier.<sup>46</sup> The study by Lucchini *et al.*<sup>35</sup> on eltrombopag mentioned in statement 2 enrolled patients with early-stage ITP (i.e. not responsive or in relapse after a full course of corticosteroid therapy and no second-line therapy). As suggested by the authors, TPO-RAs could help to maintain platelet counts until the immune system reestablishes an equilibrium, further supporting their early administration.<sup>35</sup>

Statement 5: Optimization of tapering and discontinuation of TPO-RA therapy in selected patients can improve the quality of life.

Consensus was reached for statement 5 that optimization of tapering and discontinuation of

TPO-RA therapy in selected patients can improve the quality of life. While some studies have shown TPO-RAs can improve the patient's quality of life through reduction of bleeding events and emergency treatments,<sup>47,48</sup> there is limited data on the quality of life in patients who successfully discontinued a TPO-RA. However, it should be noted that among the goals of treatment, a positive effect on the quality of life should be a primary objective.<sup>3</sup>

A general improvement of QoL can be reasonably expected in patients who achieved a complete discontinuation of the drug. Nonetheless, even a simple reduction of the dosage (i.e. tapering of the dose) in many patients might be related to better tolerability of treatment and eventually to improvement of QoL. One panelist referred that the statement can be considered valid only in patients who achieve optimal levels of platelet counts, and that patients with lower levels may continue to feel insecure. Another commented that balance is needed between frequent clinical evaluations and effective long-term control of platelet counts. In addition, the common feeling was that the physician–patient relationship is important, as well as the patient's view, individual clinical history, and duration of disease. Finally, if the patient is rid of the burden of therapy with good disease control, his or her quality of life will be improved.

## Conclusions

The present Delphi method consolidates the current consensus on administration and tapering/discontinuation of second-line TPO-RAs in patients with ITP. Specifically, the evidence

regards the benefits of an early switch from corticosteroids to a TPO-RA and dose tapering of TPO-RAs in patients with a stable response and platelet count  $>100 \times 10^9/L$  for at least 6 months in the absence of concomitant treatments. For treatment discontinuation in patients with lower platelet counts ( $50 \times 10^9/L$ ), consensus was not achieved, and clinicians should decide according to the bleeding risk of each individual patient. It should be mentioned that the present recommendations are only applicable in countries where TPO-RAs are available at any stage in the treatment of ITP, although where available the recommendations could be useful to advocate early reimbursement of TPO-RA. Furthermore, the consensus highlighted areas where further studies are needed, namely the possibility to taper the TPO-RA in patients with PR and the potential benefits of early treatment with a TPO-RA in achieving clinically meaningful responses. Near consensus was obtained on the first issue, whereas on the second further studies are warranted.

#### Author contributions

All authors contributed to the design of the research, to the analysis of the results and to the writing of the manuscript. MC and FZ discussed the results and commented on the manuscript.

#### Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CM received honoraria from Amgen and Novartis for serving on advisory boards; SS received honoraria from CSL, AMGEN, Novartis, Novo Nordisk, SOBI, and Bayer; ZF received honoraria and funding from Novartis, Amgen, and Grifols; PF received honoraria from Novartis; FB received consultation honoraria from Amgen, Novartis, and Momenta; BC received honoraria from Novartis and Amgen; BA has received honoraria from Amgen, Novartis, Novo Nordisk, Bayer, and Takeda; GG, SPR, BE, CF, CG, RE, VA have no conflict of interest to declare.

#### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Editorial support was provided by Content Ed Net, with the helpful assistance of Dr. Patrick Moore. The authors thank Novartis Farma Italy for funding the editorial support.

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