Review

Tapering and discontinuation of thrombopoietin receptor agonists in immune thrombocytopenia: Real-world recommendations

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ABSTRACT

Thrombopoietin receptor agonists (TPO-RAs) are currently indicated for continuous treatment of chronic primary immune thrombocytopenia (ITP). However, there is growing evidence that TPO-RAs can also trigger sustained response in 10–30% of cases after treatment tapering and discontinuation. Therefore, at least for selected responding patients, it might be rational to plan TPO-RA interruption to exploit off-treatment response. Intriguingly, complete or partial responses with TPO-RAs are frequently observed when treatments are initiated early, suggesting that unknown immune-related mechanisms may be involved in this phenomenon. The sustained responses observed after interruption of TPO-RAs may be interpreted as a recovery of immunological tolerance; thus, the re-establishment of immunological equilibrium might be primarily responsible for the observed off-treatment effect. Importantly, these findings may indicate that anticipated TPO-RA usage can lead to improved responses, and that optimized tapering and interruption in selected patients can furthermore improve prognoses. On the base of this rationale, a series of real-life considerations have been generated by a panel of Experts to elucidate possible novel criteria and modalities to identify subgroups of patients who can benefit from tapering and/or discontinuation of TPO-RAs. Towards this aim, the results of a survey of ITP experts are herein reported, reflecting a snapshot of current real-life experience on early discontinuation of TPO-RA-based therapy. The present manuscript also highlights the importance of future translational studies on novel prognostic and predictive biomarkers that can stratify patients and facilitate the clinical choice for second-line treatment of ITP.

1. Introduction

During the past decade, the clinical management of immune thrombocytopenia (ITP), a disease characterized by highly heterogeneous manifestations, has advanced considerably. Thanks to the development of novel therapeutic approaches and the improvement of diagnostic criteria, ITP treatment can now be supported by a more robust, systematic approach as compared with the past. Among major advances, the development of thrombopoietin receptor agonists (TPO-RAs) represents a significant therapeutic improvement that already allowed optimization of disease management; TPO-RAs, thanks to their ability to mimic the physiological activity of thrombopoietin, can effectively trigger sustained platelet counts. TPO-RAs are currently indicated as a continuous second-line treatment for chronic ITP patients who do not respond to first-line therapies or splenectomy. However, evidence of important off-treatment activity after their tapering and discontinuation has been accumulating, indicating that up to 30% of ITP patients receiving TPO-RAs can obtain sustained responses lasting

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for months after discontinuation [1,2]. The most significant benefits have been reported when TPO-RAs are administered prior to splenectomy or as an early switch from first-line therapies [3–5]. This suggests that an *on-demand* schedule of administration of TPO-RA can be the ideal regimen and that the observed off-treatment responses may be due to a drug-independent mechanism that persists after treatment discontinuation, thereby opening novel research questions while offering new therapeutic possibilities. Furthermore, it has been demonstrated that TPO-RA usage appears to be both safe and effective for the treatment of early-stage ITP, posing the basis for an even more upfront adoption of this therapeutic approach [6].

Currently, data from randomized studies are lacking, and therefore the creation of guidelines and/or recommendations based on real-life clinical practice is strongly needed. Real-life clinical experience represents a unique source of objective data that allows to retrieve a snapshot of current clinical practice. Nonetheless, literature and real-life observations can contribute to the identification of patients who may benefit the most from the discontinuation of TPO-RAs. The present manuscript focuses on the potential long-term benefits from *on-demand* administration of second-line TPO-RAs for the treatment of adult ITP patients and offers several recommendations for the best modalities to perform successful tapering and/or discontinuation of these drugs according to literature and observations arising from daily clinical practice.

2. First-line therapeutic failure

2.1. Corticosteroids

Corticosteroids, including prednisone and high-dose dexamethasone, are commonly administered in adult ITP patients as first-line therapy in order to rapidly achieve safe platelet counts, to prevent or interrupt bleeding events, and to ensure an acceptable quality of life [7,8]. Corticosteroids can also be associated with immunoglobulins for the treatment of severe cases of thrombocytopenia with high bleeding risk. Although initial responsiveness is observed in about 60–80% of patients, sustained responses are seen only in 20–40% of cases, highlighting an important loss of efficacy in the long-term [9]. Prolonged exposure to corticosteroids can trigger the onset of severe adverse events (AEs) such as weight gain, cataract, mood alterations, hypertension, and infections. The onset of hyperglycemia represents another important AE, especially in elderly patients and in individuals who receive CS-based treatments during the persistent phase of ITP [10–14]. Excessively prolonged use of corticosteroids can also lead to the development of osteoporosis (more severe in elderly patients) [15,16].

As of today, ITP treatment is supported by several second-line medications that show a safer profile as compared to corticosteroids [17]. It has been recently highlighted that tapering and interruption of corticosteroids in favor of an early switch towards a second-line treatment such as TPO-RA can lead to substantially improved clinical benefits. In particular, patients who require *on-demand* administration of corticosteroids after completing first-line induction treatment should be considered as non-responders and should be promptly switched to alternative therapy. It is possible to switch to a different option even in case of a suboptimal response to a continuous corticosteroid-based treatment regimen. Generally, initial corticosteroid treatment should be administered for no longer than 6–8 weeks. In addition, excessively fast tapering should never be performed as it can lead to undesired effects [17,18].

3. Second-line treatments

Second-line therapeutic approaches for ITP include splenectomy, rituximab, and TPO-RAs, and discussion about the best ways to adopt these approaches is still ongoing [10]. Consensus guidelines do not provide a preferential recommendation about which specific drugs should be employed, nor do they indicate possible schedules of administration [10,19].

According to published data, splenectomy is associated with initial response in 85% of cases, although durable responses are documented in about 60–65% of patients [20,21]. Splenectomy is also associated with an increased chance of relapse in 20–30% of responding patients, especially within ten years from the initial observed response (more frequently within two years). Moreover, 10% of patients develop short-term (within 30 days from surgery) and long-term complications. Then, prognostic factors allowing for patient stratification who may benefit from splenectomy are currently lacking [20,21].

Rituximab, a monoclonal antibody targeting CD-20, is approved for the treatment of several hematological pathologies, as well as for ANCA-positive vasculitis and rheumatoid arthritis [20,21]. Although the drug is not currently indicated for the treatment of ITP, several authors are contemplating its possible utilization for the treatment of this disease especially in the relapsed/refractory setting: the use of rituximab has been demonstrated to trigger short-term responses in 50–60% of patients, with long-term responses documented in 20–30% of cases. Utilization of rituximab has also been considered as feasible in young women with a short history of ITP, in whom the drug led to positive long-term clinical outcomes [22].

Although rituximab is characterized by infusion-related toxicities such as cytokine storms, the drug is overall well-tolerated, and the risk of developing hypogammaglobulinemia tends to increase only after several cycles of therapy. However, the use of rituximab reduces the efficacy of concomitant vaccinations and is associated with rare but lethal complications, including hepatitis B reactivation and multifocal leukoencephalopathy, especially in patients who are exposed to immunosuppressant medications [22,23].

TPO-RAs, among which eltrombopag (oral administration) and romiplostim (subcutaneous administration) represent the most widely studied agents, are therapeutic options approved for second-line treatment of ITP. The mechanism of action of TPO-RAs involves agonistic activity on the thrombopoietin receptor, which in turn triggers an increase of megakaryopoiesis and platelet production [24,25]. The chemical structure of TPO-RAs differs from recombinant human thrombopoietin, resulting in improved activity on the thrombopoietin receptor and a remarkably reduced incidence of severe thrombocytopenia [24,26].

In clinical trials, TPO-RAs have been shown to be highly effective, with initial responses observed already after 1–2 weeks of treatment, while significantly reducing bleeding events and emergency hospitalizations. Importantly, response rates of 70–80% were documented (85–95% in long-term extension studies), with a median exposure time of 2 years. TPO-RAs are also well tolerated, especially in the long-term, and are not linked to increased thrombotic risk. [27–33]. However, the correlation between TPO-RA usage and thrombotic is today under debate, as some authors have pointed out recently [34]. In the absence of clear evidence, further investigations are strongly awaited.

Moreover, the long-term use of TPO-RAs does not affect bone marrow tolerability: as recently reported, long-term use of TPO-RAs was not associated with the development of medullary fibrosis, augmentation of collagen deposits, or onset of clinically-relevant medullary aberrancies, although some bone marrow alterations were reported in a few cases [35,36]. Not less importantly, the introduction of TPO-RAs has a positive impact on the quality of life of ITP patients.

4. Can sustained responses be achieved after tapering and discontinuation of TPO-RAs?

In the following section, we overview a panel of recently published studies supporting the achievement of long-term responses after TPO-RA tapering/discontinuation (Table 1). Although results here presented have been generated by generally retrospective, single-arm studies,

Table 1
Published clinical trials documenting off-treatment responses after discontinuation of thrombopoietin receptor agonists (TPO-RAs).

Study	Number of patients (n)	Number of patients who discontinued TPO-RA (n, % of all patients)	Number of patients documenting off-treatment responses (n, % of all patients)	Median follow-up (months)
Leven et al. [2]	15	5 (33%)	5 (33%)	6+
Mahevas et al. [38]	54	20 (37%)	8 (15%)	13.5
Cervinek et al. [39]	46	11 (24%)	11 (24%)	33
Gonzalez-Lopez et al. [40]	12	12 (100%)	12 (100%)	7
Newland et al. [41]	4	3 (75%)	3 (75%)	29.5
Marshall et al. [42]	43	12 (28%)	12 (28%)	20
Bussel et al. [43]	302	10 (3%)	9 (3%)	6+
Carpenedo et al. [45]	27	13 (48%)	13 (48%)	26
Mazzucconi et al. [5]	39	7 (18%)	7 (18%)	N/A

they can nonetheless provide an outline of valuable literature achievements.

On the base of published evidence and clinical experiences, a series of real-life recommendations is furthermore provided.

4.1. Published evidence

The use of TPO-RAs as a continuous type of treatment was decided subsequently to the results of a study comparing eltrombopag to placebo, in which clinical responses were obtained in 10 days and maintained over the course of treatment, but lost when eltrombopag was discontinued [37]. However, subsequent studies highlighted that stable responses could be achieved even after treatment interruption: in an early study by Leven et al. in 2012, treatment-free remission (platelets ≥3 0,000/μl and ≥ 20,000/μl) was documented in 33% of chronic ITP patients and was maintained for > 6 months after eltrombopag discontinuation, even in the absence of concomitant medications. Therefore, the study highlighted that achieving safe platelet counts may be the main requirement for obtaining favorable clinical outcomes after discontinuation of a TPO-RA [2].

In 2014, an observational retrospective study from France highlighted that prolonged response could be induced by a transient use of a TPO-RA in adult primary ITP patients [38]. The study, performed on 54 patients treated with romiplostim and eltrombopag over 5 years, documented the achievement of complete response (CR)in 20 of 28 patients. After a median follow up of 13.5 months, 8 patients maintained the initially documented response in the absence of treatment. All these 8 patients had a history of chronic ITP, with a median duration of disease prior to receiving a TPO-RA of 103 months and had received a median of five treatment lines. Three of the 8 patients had received a TPO-RA for < 1 month, and one had undergone splenectomy [38].

Stable responses after TPO-RA discontinuation were also reported in a retrospective analysis comprising 46 relapsing/remitting ITP patients, in whom medications were discontinued in 11 cases (7 romiplostim, 4 eltrombopag) due to achievement of response to treatment. Notably, stable patients received 1–3 prior therapy lines, and splenectomy was performed in 6 cases. The study did not document any side effects related to the use of TPO-Ras, and none of the 11 responders relapsed over a follow-up time of 33 months [39].

A retrospective analysis from Spain on a total of 260 adult primary ITP patients receiving eltrombopag documented the achievement of CR (defined as platelet counts > 100 × 10^9/L) in 201 individuals. The TPO-RA was discontinued in 33 cases due to stable response, with sustained responses in 26 patients over a median follow-up of 9 months (6–25 months) [40].

The perspective analysis by Newland et al. also reported stable responses after discontinuation of a TPO-RA. The study enrolled 75 recently-diagnosed (within 6 months) ITP patients and evaluated the response to romiplostim as a second-line treatment for a maximum of 12 months. Subsequently, patients documenting platelet counts of at least 50 × 10^9/L were selected for treatment tapering. Remission, defined as the documentation of a minimum of 50 × 10^9/L platelets for 24 consecutive weeks without concomitant ITP medications, was achieved in 24 patients, or 32% of the total population. Responses were rapidly reached, with a median of about 2 weeks and remarkably high response rates (90%). Unfortunately, the study did not identify any predictive factors associated with remission [41].

A retrospective study performed by Marshall et al. in 2016 investigated the real-life use of romiplostim in 43 patients with ITP, among whom 12 (28%) were able to interrupt treatment and maintained a clinical response over a median of 2.8 years (0.5–9.2 years) [42].

Moreover, a case study published in 2016 examined the results of 8 clinical trials on the of romiplostim. Overall, remissions (defined as platelet counts ≥50 × 10^9/L for at least 26 weeks in the absence of concomitant medications) were documented in 27 patients. However, the study did not find any predictive factors of remission after treatment discontinuation [43].

The study by Mazzucconi et al. (2017) presented a real-world case series on the achievement of CR after interruption of a TPO-RA in 39 patients with primary ITP [5]. The study also introduced two new definitions of clinical response: durable response, defined as simple response or CR lasting for at least 4 weeks with a stable dose of TPO-RA and sustained response, defined as the achievement of a platelet count of at least 30 × 10^9/L after > 4 weeks from TPO-RA discontinuation, in absence of concomitant treatments. These two new types of responses were added to the standard ones identified by Rodeghiero et al.: simple response, defined as a platelet count of at least 30 × 10^9/L and at least a twofold increase in the initial count and CR, defined as a platelet count of at least 100 × 10^9/L in absence of bleeding events [44]. The study documented treatment response in 74% of patients, with 28% of CR and 55% of durable response. Sustained responses were observed in 18% of cases (7 of 39), and 5 of 7 following initial durable responses. Moreover, obtaining CR was associated with a significantly greater probability of achieving a durable response. These findings suggest that CR is a positive prognostic factor for achieving a subsequent durable response, which can, in turn, be prognostically correlated with achieving a sustained response [5].

4.2. How should successful tapering of TPO-RAs be performed?

A survey focusing on unmet needs in ITP and real-life observations was compiled by the panel of 11 authors who were selected on the basis of their expertise in the clinical management of ITP and significant research activity in the field. After completing the survey, the experts met to discuss the results and established an Expert Panel (EP) with the aim of obtaining a snapshot of current real-life clinical practice, with particular focus on long-term remissions after tapering and discontinuation of TPO-RAs.

At present, establishing a tapering regimen is problematic since ad hoc studies are lacking, and individual patient responses are characterized by a high level of uncertainty. Tapering modalities of TPO-

RAs are, therefore, empirical, and there are no recommendations generated by proper Consensus. For instance, it may sometimes be necessary to perform re-administrations or limited *on demand* recalls, even months after interruption and remission. Empirically, some patients can benefit from the modification of the treatment schedule by reducing the frequency of drug administration. In this complex scenario, updated guidelines are particularly awaited.

In general, slow tapering should be performed to increase overall outcomes, and to minimize the administration of alternative therapies. The initial dose should be administered according to the Summary of Product Characteristics (SPC): i.e., SPC for eltrombopag indicates 50 mg once a day for patients older than 6 years and 25 mg per day for those 1–5 years old. The dose should then be individualized according to the specific characteristics of the patient, and the lowest dose that allows obtaining and maintaining a safe platelet count of at least 50 $\times$ 10^9/L, which is necessary to reduce the risk of bleeding, should be used. A dose of 75 mg/day should never be exceeded.

Based on the experience of the EP, a different customized tapering scheme for eltrombopag and romiplostim is proposed, due to their different pharmacokinetic and pharmacodynamic profiles.

The EP recommended a reduction of eltrombopag by 25 mg every 2 weeks. Then, it is advised to switch to a schedule of administration based on eltrombopag 25 mg every other days for 2 weeks and then every 4 days prior to initiating treatment interruption (Fig. 1). Tapering of romiplostim should be performed with a reduction of 1 mcg/kg/week every 2 weeks until a dose of 1 mcg/kg/week is reached. It is then suggested to give the same dose every other week for two or three administrations, based on the stability of platelet counts; a 1 mcg/kg dose should be administered once every three weeks before discontinuation.

Except for patients showing a CR with low doses of TPO-RA, the panel suggested that tapering timing should not exceed the proposed scheme; however, tapering can be performed in a slower fashion (6–12 months) in some circumstances, such as in patients with suboptimal responses. In any case, tapering should be performed if clinical response is maintained.

4.3. When can successful tapering of TPO-RA be performed?

In clinical practice, approximately 40% of patients are estimated to undergo TPO-RA tapering after achieving an acceptable response. Before considering a patient as eligible for tapering and interruption, a stable response should be documented. Platelet counts of 50 $\times$ 10^9/L (referred to as partial response, PR) and 100 $\times$ 10^9/L (referred to as CR) can be considered as indicators of stable response. The response should be maintained for at least 6 months in the absence of concomitant treatments and hemorrhagic events. In parallel to the documentation of a stable response, tapering can be indicated when specific characteristics are met. The absence of symptoms with low-dose TPO-RA represents a significant positive prognostic factor, and the absence of bleeding events is generally associated with improved clinical outcomes after tapering. However, symptomatic bleeding at treatment initiation does not necessarily contraindicate tapering; in this case, strict monitoring is advised. During tapering, stable platelet counts are associated with favorable clinical outcomes. These features can also be associated with the obtainment of long-term clinical benefits after tapering and discontinuation.

However, after tapering is initiated, some patients may never reach full discontinuation of therapy: if an unstable platelet count is documented at tapering initiation, the patient should not be considered as eligible for therapy discontinuation, and pharmacological treatment should be maintained. In these cases, it is possible to continue therapy at the lowest dose that is able to trigger a clinical response, and tapering can be considered as soon as a stable response is achieved. Moreover, patients requiring the administration of a maximal dose of TPO-RA for a prolonged time to reach a stable platelet count should not be considered as ideal candidates for treatment tapering. Additional criteria driving the choice of *not* performing tapering include comorbidities and concomitant therapies: in particular, patients receiving anticoagulant therapies should not be eligible for tapering, unless a platelet count of at least 100 $\times$ 10^9/L is reached.

The authors of the present manuscript recommend interrupting tapering of TPO-RA if platelet levels fall below 30 $\times$ 10^9/L or below 50 $\times$ 10^9/L if the onset of bleeding events is documented or if patient's quality of life is reduced due to stress, anxiety, or other factors. In this scenario, it is advised to re-introduce pharmacological treatments at the minimum dose needed to trigger a response. Most frequently, re-introduced medications are based on the same TPO-RA, but it is possible to switch from eltrombopag to romiplostim or vice-versa. In support of this statement, two recent publications described cases of ITP that underwent successful tapering and discontinuation of TPO-RA, documenting stable response for long periods of time before relapsing. Of note, re-exposure to the same TPO-RA at relapse for a limited period (*on-demand* administration) re-triggered a durable CR [45,46]. More rarely, in particular circumstances, treatment can be restarted with a different type of medication.

In brief:

Tapering can be performed if the following criteria are met:

- Stable platelet count/stable response (50 $\times$ 10^9/L - 100 $\times$ 10^9/L)

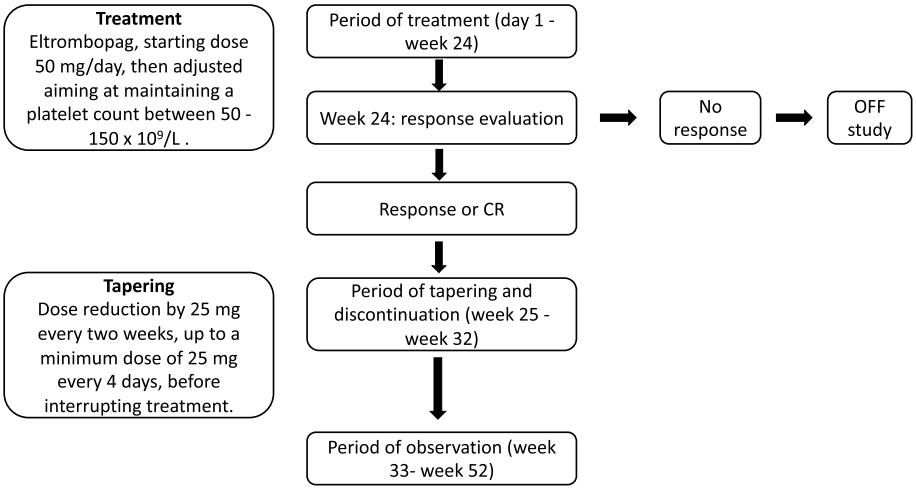

Fig. 1. Proposed scheme of eltrombopag tapering and discontinuation. CR: Complete Response.

- Response maintained for at least 6 months without concomitant treatments and haemorrhagic events

Tapering is not advised if:

- An unstable platelet count is observed: platelet counts fall below 30 × 10^9/L or below 50 × 10^9/L if the onset of bleeding events is documented as well
- A maximal dose of TPO-RA for a prolonged time is required to reach stable platelet counts
- One patient has comorbidities impacting the quality of life
- Concomitant therapies are being administered

4.4. Novel immune-related insights

The loss of so-called self-tolerance is thought to be one of the main mechanisms at the basis of the etiopathogenesis of ITP, arising as a consequence of immunological imbalance generated by external antigenic stimulation (molecular mimicry) or an inflammatory process. In addition, altered equilibrium among different T-lymphocyte populations appears to be in play, with selective activation of CD4 + type-1 helper T-lymphocytes (Th1) and functional inhibition of FOXP3 + CD4 + T-regulatory lymphocytes (Tregs) [47–50]. As a result, both uncontrolled proliferation and activation of cytotoxic CD8 + T lymphocytes are triggered, in parallel with the aberrant production of plasma cells and generation of self-antibodies directed against the host's platelets, leading to macrophage-mediated phagocytosis and induction of apoptosis [51].

In this complex scenario, Tregs are thought to exert a critical pathological role, as the same cell population is restored during the remission phase. However, platelets may be responsible for a successful clinical response after discontinuation of a TPO-RA [52]; the immunomodulation observed during remission may be the result of a self-sustaining platelet-mediated process. Proliferating platelets have been documented to release large amounts of TGF- β in response to pharmacological treatments: it has been demonstrated that the levels of TGF-β1, an anti-inflammatory cytokine, can increase during the pre-treatment phase in active ITP patients; conversely, the same molecule has been observed to significantly increase upon pharmacological therapy in responding patients with platelet recovery. In these individuals, platelets eventually reach homeostatic levels, emphasizing the prognostic importance of TGF-β1 [53].

Moreover, the platelet-mediated release of ectosomes and microvesicles, molecules with important roles in cell communication, plays a major immunoregulatory role, fueling a likely domino effect sustaining the off-treatment phenomena observed in clinical practice [54] (Fig. 2).

Another important pathophysiological mechanism involved in ITP is related to immunoglobulin Fcγ receptors (FcγRs), which exist in three variants: FcRI, IIa, and III. It is known that all three subtypes exert an activating effect on the immune system, while FcγRIIb has been documented to trigger the inhibitory effects on immune cells. Recent evidence indicates that polymorphisms in these receptors are associated with ITP and the observed response to pharmacological treatments. Thus, the disrupted balance between the different polymorphic forms of FcγRs might be correlated with the grade of disease. A recent biological study highlighted that response to TPO-RA treatment eliminates the displacement between the inhibitory and activating state of the immune system by stimulating the expression of FcγRIIb, which can, in turn, exert an immunosuppressive effect that antagonizes the pathological immunostimulation at the basis of ITP [55].

Therefore, TPO-RAs may exert the most benefits during early phases of ITP, and the sustained response observed in the literature and in clinical practice may be due to self-sustaining restoration of the immune cell populations of the host. From a physio-pathological point of view, the benefits arising from an early administration of TPO-RAs (prior to splenectomy or as an early switch from first-line therapy) can be explained considering that during ITP's early phases immune-dysregulation may still be reversible. Thus, the efficacy of eltrombopag and romiplostim on re-establishing immune equilibrium can be maximized.

5. Conclusions and future directions

The present manuscript focuses on the potential benefits related to tapering and discontinuation of TPO-RAs and shows how patient stratification and tapering strategies can impact clinical outcomes; it also provides a snapshot of current best practice to perform tapering/discontinuation of a TPO-RA based on real-life experience and published data. Additionally, a series of practical recommendations to select patients who may be most eligible for TPO-RA tapering is proposed. The information provided herein can help for the future to optimize the management second-line therapeutic approaches for ITP, highlighting that improved utilization of currently-available medications (especially corticosteroids and TPO-RA) can lead to remarkable clinical benefits.

Practice points

- An early switch from corticosteroids to TPO-RAs may be associated with improved clinical outcomes in the long-term [3,4].
- Tapering of TPO-RAs is recommended after a stable response is achieved (platelet count > 50 × 10^9/L [PR] or > 100 × 10^9/L

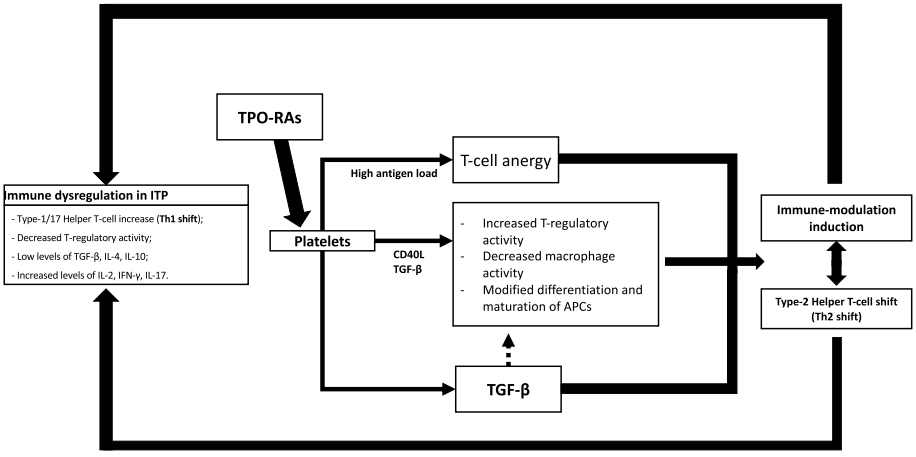

Fig. 2. - Simplified representation of TPO-RA mechanism of action. TGF-β: transforming growth factor; IL: interleukin; IFN-γ: interferon-γ; APCs: Antigen-Presenting Cells; TPO-RAs: Thrombopoietin Receptor Agonists.
Adapted from [54].

[CR]) and maintained for at least 6 months in the absence of concomitant treatments.
- Tapering of TPO-RAs is advised in those patients who obtain a stable clinical response with low doses.
- Tapering is not advised for patients with comorbidities or requiring anticoagulant or antiaggregant-based treatments unless a count of at least 100×10^9/L is documented.
- Tapering should be interrupted if a platelet count between 30×10^9/L and 50×10^9/L is reached; patients should resume pharmacological treatments at the lowest dose of the drug that is able to trigger a response.

Research agenda

- Improved management of second-line therapeutic options for the treatment of ITP.
- Selection of patients who can better benefit from TPO-RA tapering and discontinuation.

Author contributions

The survey was completed by the following authors: C. Baratè*, A. Borchiellini, M. Carpenedo*, F. Chiurazzi*, G. Finazzi, A. Lucchesi*, F. Palandri, A. Ricco*, C. Santoro*, P.R. Scalzulli*, F. Zaja*.

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Declaration of Competing Interest

The authors declare potential conflict of interest with Novartis Corp.

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