The old definition of “idiopathic thrombocytopenic purpura” was recently replaced by “primary immune thrombocytopenia” (primary ITP) by an International Working Group (IWG). Primary ITP (hereafter abbreviated as ITP when the primary context is clear) identifies an autoimmune disorder characterized by an isolated platelet count < 100 × 10⁹/L with or without bleeding manifestations, in the absence of other causes or disorders that may be associated with thrombocytopenia. The term “immune” emphasizes the immune-mediated mechanism of the disease. The diagnosis of primary ITP remains one of exclusion and “secondary ITP” has been proposed to broadly include all forms of immunemediated thrombocytopenias due to recognizable underlying disease or drug exposure. The distinction of primary from secondary forms is clinically relevant, since in secondary forms the treatment should often be direct towards the associated disease and the response to standard treatments proposed for primary ITP is less favorable.

Many comprehensive reviews have been published, focusing on the current understanding of the pathogenetic mechanisms of ITP. Experimental evidences show that, in addition to autoantibody or direct T-cell–mediated platelet destruction, megakaryopoiesis is also impaired and unable to compensate for the accelerated removal of platelets from circulating blood. Moreover, a relative deficiency of circulating thrombopoietin (TPO) has been demonstrated.

**Epidemiology**

Incidence in adults has been estimated between 1.6 and 3.95 × 100,000 subjects per year, depending on the selected diagnostic cut-off, ranging from < 150 to < 50 × 10⁹/L. The incidence tends to increase with age, doubling in subjects over 60 years. Moreover, females have shown a higher incidence than males in patients younger than 60 years. Prevalence estimates were obtained analyzing administrative data from healthcare databases in the United States, with conflicting results and estimates ranging from 9.5 to 20/100,000 subjects, perhaps reflecting a nonstandardized and heterogeneous methodology in
TREATMENT OF ITP

The IWG identifies three different phases of ITP (Figure 1): “newly diagnosed” (once called “acute”) from diagnosis to 3 months thereafter; “chronic” for patients still affected after 12 months; and a new category, called “persistent”, for patients with ITP between 4 and 12 months from diagnosis. The term “severe ITP” should be reserved to cases with clinically relevant bleeding symptoms demanding active treatment. The term “refractory ITP” defines a disease not responsive to (or relapsed after) splenectomy and requiring treatment for severe ITP or at high risk of bleeding. Complete response (CR) was defined as platelet count ≥100 × 10⁹/L and doubling the pretreatment count and response (R) as platelet count ≥30 × 10⁹/L and doubling the pretreatment count, in the absence of bleeding and concomitant treatment. The identification of these phases may improve communication among investigators and facilitate comparability among clinical trials, particularly considering that different therapeutic goals should be pursued (Table 1).

Treatment in Newly Diagnosed and Persistent ITP

The major goal in the treatment of these patients is to provide a safe platelet count, sufficient to prevent major bleeding, and avoiding as much as possible unnecessary toxicity and major side effects from over-treatment with the available therapies. Most guidelines suggest that treatment should be considered with platelet counts <30 × 10⁹/L and/or in the presence of bleeding symptoms. Treatment of newly diagnosed patients is aimed at rapidly increasing the platelet count to prevent or stop hemorrhages and to ensure a good quality of life. This is often accomplished with a short course of corticosteroids, usually at 1 mg/kg body weight (BW) for 2–3 weeks followed by a rapid tapering and/or high-dose intravenous immunoglobulins (IVIg) infusion (1g/kg BW per day for 2 days) in cases with major open bleeding or at exceedingly high risk of hemorrhage. In newly diagnosed and persistent patients not responding to or relapsing after this first-line treatment, there is still a significant probability of obtaining some improvement or remission, even without further treatment. For this reason, “on demand” short courses of therapy (often with low-dose corticosteroids or IVIg) are often warranted to manage bleeding or high-risk of bleeding and to defer or avoid more toxic treatments such as splenectomy or immunosuppression to the chronic phase of disease (see Figure 1). However, it should be emphasized that the treatment of persistent ITP is still a neglected, poorly investigated area, burdened by uncertainty and not sufficiently addressed in the current guidelines, which extensively discuss splenectomy and newer treatments like rituximab or TPO-R agonists, without a clear distinction between persistent and truly chronic disease.

Table 1. Therapeutic Goals in the Different Phases of ITP or for Unresponsive Patients Irrespective of the Phase

<table>
<thead>
<tr>
<th>Phase of Disease</th>
<th>Aim of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial treatment</td>
<td>Obtain a safe platelet count to rapidly reduce bleeding manifestations or bleeding risk and to improve quality of life</td>
</tr>
<tr>
<td>Persistent disease</td>
<td>Defer/avoid toxic immunosuppression or splenectomy</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>Curative aim</td>
</tr>
<tr>
<td>Unresponsive severe patients (after splenectomy or several lines of treatment)</td>
<td>Minimize the risk of bleeding and treatment-related toxicity; increase platelet count is not the main goal</td>
</tr>
</tbody>
</table>

Figure 1. Phases of ITP according to the IWG.

Thrombopoietin-receptor agonists in ITP

In adult patients with chronic ITP, who require more than minimal doses of corticosteroids or need frequent administrations of IVIg or immunosuppressive drugs to maintain a safe platelet count, splenectomy has been considered the undisputed standard treatment. The rate of CR or partial response (PR) after surgery is higher than 80%, with low frequencies of relapse (around 15%) and severe complications or death (0.2%–1.5%). Splenectomy remains the most effective single therapy in ITP and
the only treatment able to potentially cure the disease in approximately 60% of patients as shown in a multicenter study in which patients were monitored for a minimum of 10 years. However, there is a general tendency to avoid or delay this intervention. The rate of splenectomy in older cohorts was around 50%–60% (probably reflecting the real evolution rate into chronic ITP), while a significant decrease is evident in more recent studies, with a rate of surgery of approximately 20%–25% or lower, indicating that most patients with chronic ITP are no longer splenectomized. This trend could be explained in part by the reluctance of some patients to have a healthy organ removed and the fear among patients and physicians of possible surgical complications (such as sepsis, thrombosis, bleeding, or death), and in part by the availability of new drugs, such as anti-CD20 antibodies (rituximab). About 50%–60% of patients show an initial response to anti-CD20 antibodies, but the long-term response after 5 years is no more than 20%. TPO-R agonists (romiplostim and eltrombopag) have shown solid evidence of efficacy and have a good safety profile when used in chronic ITP patients. In the absence of direct comparison studies for second-line therapy in chronic ITP patients (see Table 2 for an indirect comparison), the International Consensus Report (ICR) did not provide a clear flow-chart of preferred sequential treatments for patients failing to respond to corticosteroids, and assigned equivalent places to the different treatment options, including splenectomy, TPO-R agonists, and rituximab. For patients failing any second-line treatment, TPO-R agonists were graded “A” with a preference over rituximab and splenectomy. On the other hand, the guideline provided by the American Society of Hematology (ASH) recommends splenectomy before using TPO-R agonists, on the basis of its curative effects and of the extensive published experience in chronic patients failing corticosteroid treatment. These discrepancies have been addressed in a recent review.

### TPO-R AGONISTS

#### Consolidated Experience

More than 5 years of extensive clinical use of TPO-R agonists in the treatment of adult ITP has shown that these agents can produce a sustained increase of platelet count, a reduced use of concomitant ITP-specific therapies, and a global reduction of bleeding episodes with a general improvement of the quality of life, substantially confirming the efficacy and safety profile of registra
tive and extension studies (Tables 3 and 4).

<table>
<thead>
<tr>
<th>Table 2. Pros and Cons of New Treatments Compared to Splenectomy</th>
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<tbody>
<tr>
<td><strong>Type of treatment</strong></td>
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<tr>
<td>ITP-specific</td>
</tr>
<tr>
<td>Response rate</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Response prediction</td>
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<tr>
<td>Curative potential</td>
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<tr>
<td>Short-term toxicity</td>
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<tr>
<td>Medium- and long-term toxicity</td>
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<tr>
<td>Follow-up after response</td>
</tr>
<tr>
<td>Cost</td>
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Specific structural differences and distinctive features of these two agents are described in more detail elsewhere in this issue of *Seminars*.

Romiplostim is a peptibody that interacts with the extracellular domain of the TPO-R. It requires parental administration and it is given weekly by subcutaneous infusion at a dose ranging from 1 to 10 \( \mu \)g/kg BW. Eltrombopag is an oral, synthetic non-peptide agonist that binds to the trans-membrane domain of the TPO-R. Fasting patients require daily doses ranging from 25 to 75 mg. Doses are adjusted to maintain a platelet count usually above \( 50 \times 10^9/L \) and not higher than \( 150 \times 10^9/L \). A lower dose is required for patients of East Asian descent.\(^{36} \) The clinical outcome is similar with the two agents. With both agents, rebound thrombocytopenia may occur in up to 10% of patients after stopping treatment. They received identical indications from the US Food and Drug Administration (FDA) as second-line treatment in patients with primary ITP not responsive to or relapsing after corticosteroid treatment and at risk of bleeding. The European Medicine Agency (EMA) restricted their use to patients who had already undergone splenectomy or for whom surgery is contraindicated. A third oral, synthetic non-peptide TPO-R agonist (avatrombopag) is undergoing clinical studies.\(^{37} \)

Romiplostim was extensively investigated in a registra-
tive pivotal phase III placebo-controlled study,\(^{25} \) in which patients were randomized 2:1 to romiplostim or placebo, including 63 splenectomized and 62 nonsplenectomized patients with a diagnosis of chronic ITP and a platelet count at enrollment \( <30 \times 10^9/L \). The active (weekly romiplostim 1–10 \( \mu \)g/kg BW) and placebo arms were followed for 24 weeks. A durable response (platelet count \( \geq 50 \times 10^9/L \) during 6 or more of the last 8 weeks of treatment) was achieved by 16 of 42 splenectomized patients who received romiplostim versus none on 21 who received placebo (proportion difference 38%; 95% confidence interval [CI], 23.4–52.8, \( P = .0013 \)) and by 25 of 41 non-splenectomized patients in the romiplostim arm versus one of 21 in the placebo (proportion difference 56%; 95% CI, 38.7–73.7; \( P < .001 \)). A platelet count of at least \( 50 \times 10^9/L \) was maintained for a mean of 15.2 and 12.3 weeks for non-splenectomized and splenectomized patients treated with romiplostim, compared respectively with 1.3 and 0.2 weeks for placebo. Most of romiplostim-treated patients were able to discontinue or reduce concomitant ITP therapies (87% \( v \) 38% of placebo-treated patients). Rescue medications were administered to 14% of romiplostim recipients and to 50% in the placebo arm (\( P < .001 \)). Bleeding symptoms were observed in 16% of romiplostim- and 34% of placebo-treated patients (\( P = .018 \)). In an open-label, 52-week study, 234 nonsplenectomized adults were randomized to receive standard of care (77 patients) or romiplostim (157 patients), confirming the clear superiority of romiplostim also in reducing the splenectomy rate.\(^{26} \) Regarding the latter, the follow-up of the study seems inadequate to

<table>
<thead>
<tr>
<th>Table 3. Romiplostim Efficacy Data in Main Studies</th>
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<tbody>
<tr>
<td><strong>No. of Patients</strong></td>
</tr>
<tr>
<td><strong>Romiplostim Dose and Schedule</strong></td>
</tr>
<tr>
<td>Open-label phase I-II(^61)</td>
</tr>
<tr>
<td>Open-label dose escalation(^62)</td>
</tr>
<tr>
<td>Double blind v placebo(^62)</td>
</tr>
<tr>
<td>Double blind v placebo(^25)</td>
</tr>
<tr>
<td>Open-label, single-arm, &quot;long-term&quot;(^29)</td>
</tr>
</tbody>
</table>

*According to the study definition, differs from the IWG response criteria.

**NA** = not applicable.
definitely outplace splenectomy. In a long-term, single-arm, open-label study, a cohort of 292 patients treated with romiplostim was monitored for a mean of 110 weeks (range, 1–277). Ninety-five of 292 (33%) had a splenectomy prior to study entry; the median time since ITP diagnosis was 4.9 years (range, 1–46); baseline platelet count was $35 \times 10^9$/L (interquartile range, 15–100). Overall, 284/291 (98%) patients experienced a total of 6,933 adverse events; the most common were headache (38% patients), nasopharyngitis (34%), fatigue (32%), and contusion (31%). Twenty-four of 291 (8%) had rebound thrombocytopenia (4/291, 1.4%) and increased bone marrow reticulin (4/291, 1.4%). Sixteen deaths occurred during the study and 19/291 (6.5%) patients experienced 25 thrombotic events. These data were substantially confirmed in a more extensive review including 718 patients exposed to romiplostim in 13 company-sponsored studies. Rebound thrombocytopenia may occur in up to 10% of patients after stopping treatment. A non-negligible rate of thrombosis was confirmed. A total of 921.5 patient-years for romiplostim and 110 patient-years for placebo or standard of care (SOC) were analyzed. Thrombotic events occurred in 5.9% of patients in the romiplostim group versus 3.6% in the placebo/SOC group. However, the annualized rates of first occurring events, either venous or arterial, were 4.2 and 4.5 per 100 patient-years for romiplostim and placebo/SOC, respectively. In a non–company-sponsored retrospective observational French multicenter study, safety and efficacy of romiplostim were evaluated in a nation-wide compassionate-use program enrolling 72 patients failing two or more lines of therapy. After 2 years of follow-up, sustained responses were observed in 51% of patients with an additional 14% of cases with a clinical benefit. No major side effects were recorded apart from transient ischemic cerebral attacks in two elderly patients with cardiovascular risk factors.

Eltrombopag was licensed after publication of the results of the RAISE trial (Randomized Placebo-controlled ITP Study with Eltrombopag), evaluating its efficacy and safety in adult patients with chronic ITP. A total of 197 patients (baseline median platelet count $\sim 16 \times 10^9$/L) were randomized (2:1) to eltrombopag ($n = 135$, starting dosage 50 mg/d) or placebo ($n = 62$), and followed for 6 months. The primary endpoint was the odds of responding with platelet counts between 50 and $400 \times 10^9$/L at least once during the study period. Patients receiving eltrombopag were eight times more likely to achieve this endpoint compared with those in placebo group (odds ratio 8.20; 95% CI, 3.5–18.7; $P < .001$). In the placebo group, no patients had a platelet count $>30 \times 10^9$/L during the study, whereas in the eltrombopag group the median platelet count increased to $36 \times 10^9$/L after 1 week of treatment and stayed around $50–90 \times 10^9$/L during the subsequent study weeks. Splenectomy status, baseline platelet count, and concomitant specific medication did not affect the pattern of response. Of the 63 patients in the eltrombopag arm requiring concomitant ITP treatment, 37 (59%) were able to discontinue or reduce these additional therapies. Rescue medications were administered in 24/135 (18%) eltrombopag-treated

### Table 4. Eltrombopag Efficacy Data in Main Studies

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Eltrombopag Dose and Schedule</th>
<th>Response No. (%)</th>
<th>Response Criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eltrombopag</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-blind v placebo^63</td>
<td>29/27</td>
<td>30-75 mg/d for 42 days</td>
<td>8 (28)</td>
</tr>
<tr>
<td></td>
<td>26/27</td>
<td>50 mg/d for 42 days</td>
<td>19 (70)</td>
</tr>
<tr>
<td></td>
<td>76/38</td>
<td>75 mg/d for 42 days</td>
<td>21 (81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 → 75 mg/d for 42 days</td>
<td>43 (59)</td>
</tr>
</tbody>
</table>

*According to the study definition, differs from the IWG response criteria. ^NA: not applicable.
patients, in comparison to 25/62 (40%) placebo-treated patients ($P = .001$). Bleeding symptoms were fewer in eltrombopag group than in placebo (79% vs 93%, grade 1–4 World Health Organization [WHO] scale). In a long-term, open-label multicenter study, 299 patients treated with eltrombopag (starting dose 50 mg/d, then adjusted from 25–75 mg/d to maintain a platelet count of at least $50 \times 10^9/L$) were followed for a median of 100 weeks (days 698; range, 2–1,267). Adverse events were reported in 262 patients (88%) while in therapy (59% of patients with grade 1 or 2). The most common were headache (26%), nasopharyngitis (23%), upper respiratory tract infection (21%), and fatigue (15%). Severe (grades ≥3) adverse effects were 83; the most common were thrombocytopenia ($n = 7$) and increase of alanine aminotransferase ($n = 7$); 15 patients reported cataracts. Eleven patients had a second bone marrow biopsy after being treated for more than 2 years (among 147 bone marrow biopsies while on treatment): eight had no change in reticulin grade (modified European consensus myelofibrosis [MF] scale$^{40}$), one experienced an increase from MF grade 1 to MF grade 2, and two had a decrease (MF grade 2 to 0 and grade 1 to grade 0). Five deaths occurred during the study period; 16/299 (5%) patients experienced 20 thromboembolic (TE) events, with an annualized thrombotic rate of 3.2 per 100 patient-years, calculated as number of events, not patients. The percentage of patients with at least one TE event reported for eltrombopag, 5.3% (16/299), was similar to that recorded in patients treated with romiplostim.

The possibility of an increased risk of thrombosis with TPO-R agonists remains unsettled.$^{41}$ Finally, it should be mentioned that in randomized trials the quality of life of patients treated with both TPO-R agonists showed a significant improvement compared to placebo or standard of care.$^{42}$ Notwithstanding this very impressive amount of clinical data, which demonstrate the favorable impact of TPO-R agonists, a recent meta-analysis by the Cochrane Collaboration has challenged their efficacy, underlining the lack of definite evidence of a significant, positive effect in comparison with placebo, in terms of mortality rate and reduction of major hemorrhages.$^{43}$ Furthermore, in main trials with TPO-R agonists the response criteria proposed by the IWG$^1$ were not or could not be adopted. A debate followed the Cochrane Collaboration publication, highlighting the conflictual co-existence of regulatory rules, medical needs, and methodological aspects in designing registrative randomized clinical trials.$^{44–47}$

Recently the EMA published an updated guideline for the clinical development of medicinal products intended for the treatment of chronic primary ITP, adopting the terminology and definitions of the IWG$^1$ and also the recently proposed standardized assessment of bleeding manifestations in skin, mucosal, and organ domains and their severity grading (SMOG system)$^{48}$ (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/03/WC500164168.pdf). Key aspects include relevant target population, the definition of the therapeutic goal, identification of an optimal dose, relevant aspects for consideration in the design of confirmatory studies and requirements for pediatric development.

**New Clinical Therapeutic Strategies With TPO-R Agonists**

**Switching to a Second TPO-R Agonist**

Romiplostim and eltrombopag bind to different sites of the TPO-R on megakaryocyte membrane and thus in case of failure with one of them, an attempt with the other agent could be potentially warranted. Some case reports have been published, confirming the effectiveness of this approach.$^{40–51}$ This strategy has been more comprehensively explored in a retrospective French pilot study.$^{52}$ Among 46 cases included in the study, 23 patients who started with romiplostim ($n = 13$) or eltrombopag ($n = 10$) as a first option were then switched to the second agent in case of failure. Response rate to eltrombopag after romiplostim was 46% with one CR and five R after 3 months of follow-up, according to the IWG response criteria.$^1$ The rate of response of romiplostim after eltrombopag was 80%. Moreover, eltrombopag was able to stabilize the platelet count in six of 11 (55%) patients with excessive platelet count fluctuation that required stopping romiplostim. In a few cases, the switching was motivated by side effects and was successfully accomplished in both directions.

Thus, there is a good probability of a favorable outcome when, in the absence of efficacy or in the presence of other impeding factors related to the administration of one of the two available TPO-R agonists, the patient is switched to the other.

**Temporary Use**

During the long-term, single-arm study with romiplostim, nine of 292 patients were able to discontinue the TPO-R agonist after 8.5 months to 2.7 years of treatment, maintaining a platelet count $>50 \times 10^9/L$ off all ITP specific treatments for at least 0.5–3.2 years.$^{31}$ A similar finding was recorded during the EXTEND study with eltrombopag: 13/299 (4%) patients had a prolonged response (platelet count $\geq 50 \times 10^9/L$) sustained for $\geq 12$ weeks after the last dose of TPO-R agonist without rescue treatments.$^{52}$ The median treatment duration with eltrombopag before this prolonged response was 160 days (range, 14–1,107). However, these studies were not designed to explore the patient outcome after stopping the treatment. In an observational multicenter study on 54 consecutive patients treated with TPO-R agonists (22 romiplostin, 18 eltrombopag, 14 both agents) for previous failure to several lines of therapy including splenectomy and/or rituximab 28 (52%) obtained a CR and treatment was discontinued in 20 for a variety of reasons.$^{53}$ Overall, a sustained response was obtained in eight patients (40%) and could be attributed to
TPO-R treatment. In a single-center case series of 31 patients with chronic ITP treated with TPO-R agonists, nine patients achieved a platelet count response that was maintained after stopping all medications. In three of them (10%) the sustained response could be attributed solely to the previous treatment with TPO-R agonists. Tentative hypotheses to explain these unexpected results could be generated. Increased exposure to platelet antigens could restore immune tolerance, like in patients with hemophilia A and inhibitory allo-antibodies to exogenous factor VIII treated with massive doses of the factor for prolonged periods. It is also conceivable that TPO-R agonists themselves have a direct effect on restoring normal T-regulatory cell function, often defective in ITP. However, during the natural history of their disease some patients reach a long-lasting remission, even in chronic phase of ITP and remain off-treatment. So, it cannot be excluded that at least some of these purported TPO-R agonist-induced remissions are part of the course of this unpredictable disease. Prospective, randomized trials are required to demonstrate if TPO-R agonists induce a true sustained response in a significant proportion of responsive patients.

**Use as First-Line Therapy**

The standard first-line treatment in newly diagnosed ITP is represented by corticosteroids, with or without infusion of IVIg. Pulsed high doses of dexamethasone have not been proven to be more effective and are probably more toxic. Given the high rate of relapse, high-dose dexamethasone combined with rituximab has been proposed, but without consistent results or with excessive toxicity. TPO-R agonists, not currently registered for first-line therapy, could represent an attractive alternative, taken into account the high rate of success in term of platelet response, and their short-term good safety profile. A single-arm, open-label study using eltrombopag plus high-dose dexamethasone in previously untreated patients was recently published. Twelve adult ITP patients (median baseline platelet count $7 \times 10^9/L$; range, 2–28) were treated with dexamethasone, 40 mg/d for 4 days and with eltrombopag, 50 mg/d for 28 days (from day +5). At day 34, 10/12 (83%) patients had a CR and 2/12 (17%) had a R, according to the IWG response criteria. Relapse-free survival was calculated from the day of initial response. At 6 months, six of 12 patients (50%) were in CR and three (25%) in R, without rescue therapy, whereas three patients relapsed. At the last evaluation (7–18 months) another patient relapsed; thus, the overall response (CR + R) was 66%, with a probability of relapse-free survival of 66.7% at 12 months. No adverse events occurred and the combination of two drugs was well tolerated. These results suggest an opportunity for a future, larger clinical study in this setting.

**FUTURE PERSPECTIVES**

The decision on the best treatment option after the failure of first-line therapy usually based on corticosteroids remains among splenectomy, rituximab, and TPO-R agonists. Evidence-based data to set a preferred sequential order among these treatments are not yet available. Indeed, individual factors such as personal preferences, age, gender, type of job, lifestyle, and comorbidities may become determining elements in the choice. The lack of reliable patient-specific response markers, either clinical or genetic, for the different therapeutic options is a major drawback and future studies are eagerly needed to identify clinical and biological predictive factors of prolonged response.

The most appropriate treatment for patients with persistent ITP and at risk of bleeding should be investigated with ad hoc designed clinical trials. In this neglected area, TPO-R agonist (presently still off label in this setting) could be a valuable choice in order to spare these patients the toxicity often experienced after prolonged use of even low doses of corticosteroids to sustain platelet counts after the failure of the first full dose course of treatment. Indeed, they still have a significant possibility to obtain a prolonged remission or even no further need of treatment, making the choice of splenectomy or rituximab hazardous. ITP itself could be a pro-thrombotic condition, particularly in splenectomized patients and thus any increased risk linked to TPO-R agonists should be better explored in order to appropriately select patients for this treatment avoiding additional risk. This could apply to aged patients with or without additional cardiovascular risk factors or women taking hormonal substitutive therapy or contraceptives. Some adverse effects of TPO-R agonists, like induction of bone marrow fibrosis, may require more extensive follow-up to be definitely ruled out and their indefinite use seems a difficult choice for most cases.

The use of these new agents in some forms of secondary ITP, for example, concomitantly with indolent lymphoproliferative disorders, or even in other diseases that may be complicated by severe thrombocytopenia like aplastic anemia or myelodysplastic syndromes is being increasingly explored (see also other articles in this issue of Seminars).

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**REFERENCES**


