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Original Article

Nationwide Survey on the Use of Thrombopoietin Receptor Agonists (TPO-RA) for the Management of Immune Thrombocytopenia in Current Clinical Practice in Italy

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Abstract. ***Background:*** **Two thrombopoietin receptor agonists (TPO-RA), romiplostim and eltrombopag, are currently widely adopted as second-line ITP therapy even in the absence of robust evidence on their comparative advantages over rituximab or splenectomy or their preferential use in some specific clinical contexts.**
Methods**: An online survey was distributed between May 2021 and June 2021 to collect standardized information on TPO-RA use in Italy.**
Results**: Eighty-eight hematologists from 79 centers completed the survey. Eighty-four percent would use TPO-RA earlier than formally indicated, without a preference for young or elderly in 82% of respondents. No clear preference for either romiplostim or eltrombopag was indicated. Seventy-two percent would use TPO-RA in young patients aiming at a complete response followed by tapering, a strategy considered by only 16% in the elderly. Switching between the two agents was considered appropriate in case of insufficient response or intolerance. Tapering schedule by reducing the dosage and prolonging the intervals between administrations was preferred by 73% of respondents. TPO-RA was considered a risk factor for thrombosis by only 35%, and 94% would administer TPO-RA in elderly patients also in the presence of other thrombotic risk factors. Thirty-three percent of respondents would withdraw TPO-RA in case of thrombosis. The TPO-RA administration has been reported to be preferred over anti-CD20 or splenectomy by about half of the participants due to the ongoing COVID-19 pandemic.**
Conclusions**: Significant discrepancies in TPO-RA use emerged from the survey, and participants would appreciate consensus-based specific guidance on the practical use of TPO-RA.**

Keywords: thrombocytopenia, TPO-RA.

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Introduction. Immune thrombocytopenia (ITP) is an autoimmune disease characterized by isolated thrombocytopenia with a platelet count <100x10^9/L caused by a dysregulation of the immune response, which promotes the production of autoreactive antibodies and the proliferation of abnormal T-cells, leading to the destruction of circulating platelets and a defective megakaryopoiesis, unable to compensate the continued increased platelet consumption.[1] Where other causes of thrombocytopenia have been excluded, ITP is defined as primary (simply referred to as ITP in this paper) and, based on its duration, is classified as newly diagnosed (< 3 months), persistent (3–12 months), and chronic (> 12 months).[2] This latter form is the most prevalent in adults, with around 70-80% of new cases evolving into chronicity.[3] Recently, an International Consensus Report (ICR)[4] and ASH evidence-based guidelines[5] have defined the aims of ITP treatment and the role of the main therapeutical agents, including corticosteroids, as the preferred option for first-line treatment and rituximab, thrombopoietin receptor agonists (TPO-RA) and splenectomy, variably indicated as second- or third-line treatments. Both documents have largely adopted the terminology, definitions, and outcome criteria proposed by an International Working Group more than a decade ago[2] and are still most frequently used in investigator-driven collaborative studies,[6] thus facilitating the comparison among the different clinical scenarios and related outcomes.

The overall picture emerging from available real-life studies is one of heterogeneity, particularly beyond the initial corticosteroids treatment, which is unanimously recommended by the most recent international guidelines for newly diagnosed patients with a platelet count of <20-30x10^9/L even if asymptomatic or even at higher platelet counts in the presence of bleeding manifestations. However, since the clinical benefit often is transient and adjunctive therapies are needed, both ICR and ASH guidelines[4,5] recommend keeping the corticosteroid administration as short as possible and not prolonged beyond 6-8 weeks, including tapering. Unfortunately, this recommendation is often unattended in common practice.[7,8] Hence, there is a major interest in analyzing the attitude of treating physicians in the management of corticosteroid-refractory patients at a time when TPO-RA, romiplostim and eltrombopag, introduced in clinical practice more than 10 years ago,[9] allowed to postpone or even avoid splenectomy,[10-14] with its significant burden of morbidity, mainly secondary to infections and thrombosis. To some extent, TPO-RA are also replacing rituximab due to its limitation in inducing long-term responses.

Nevertheless, after the advent of TPO-RA, new challenges and several issues regarding this therapeutic option is still debated, including their potential to increase the thrombotic risk of ITP[15] and other relevant practical management aspects. These latter include selecting the most appropriate TPO-RA, reaching and maintaining optimal platelet count before attempting tapering or discontinuation, switching between TPO-RA agents, and use in patients with advanced age and/or concomitant risk factors for thrombosis.[16-19] Indeed, a tailored approach in the management of ITP involves an accurate evaluation of many aspects, such as actual platelet count, bleeding symptoms, duration of the disease, lifestyle, age, thrombotic risk, potential adverse events, potential drug interactions, and response to previous treatments.

TPO-RA use in real-life clinical practice has been the subject of limited investigations, with some national surveys showing variable attitudes toward their use.[16,20] In Italy, limited unpublished information from national or regional meetings sponsored by interested companies reverberated the opinion of a widespread but not uniform use of TPO-RA. To further expand the knowledge of the real-life use of these agents, the Hematology Project Foundation (HPF) promoted and founded a nationwide survey aimed at obtaining a more comprehensive understanding of the real-life use of TPO-RA (romiplostim and eltrombopag) in an unbiased and independent manner. The survey was designed to collect standardized data based on self-reported information by hematologists treating ITP of adults concerning the TPO-RA use in the various clinical scenarios encountered by practicing hematologists.

We report the results emerging from this nationwide survey involving 88 respondents and discuss them in the light of approved indications, international guidelines,

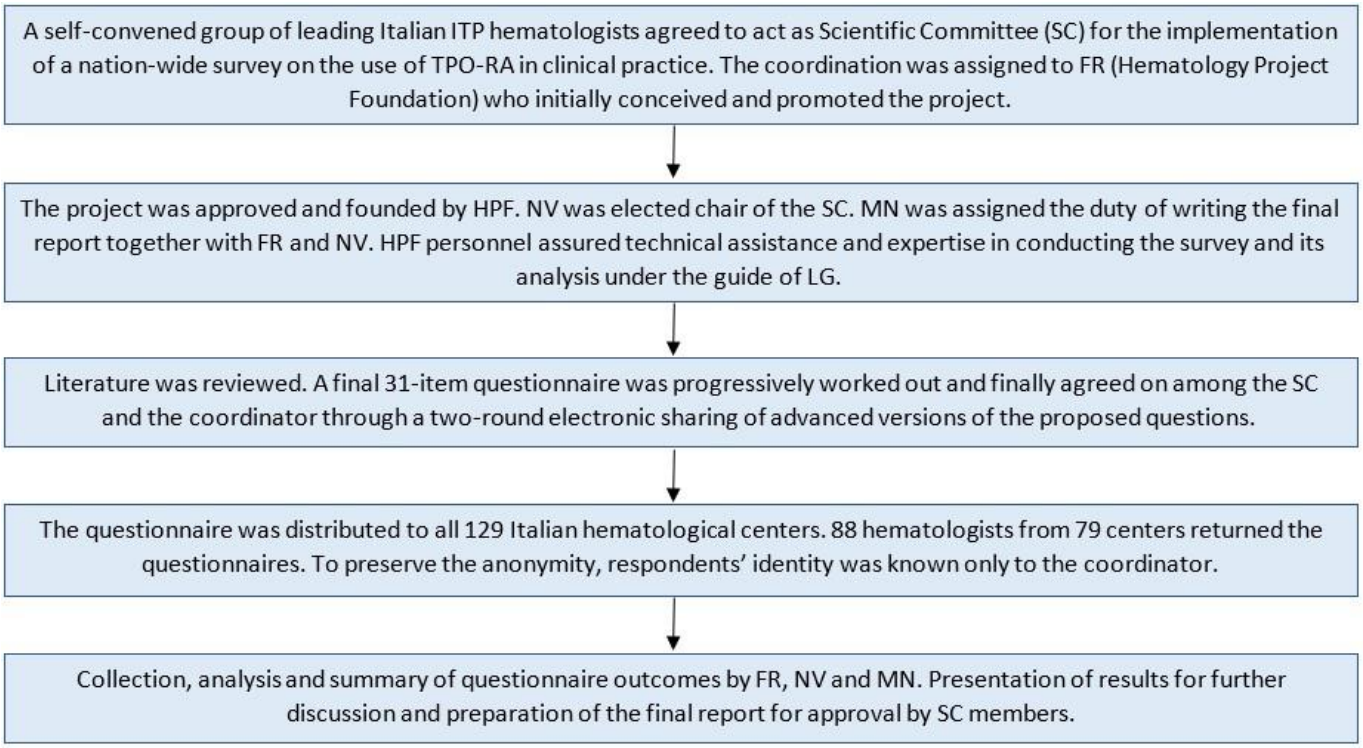

Figure 1. Main operational steps of the survey.

other national reports, and literature data.

Material and Methods. Hematologists charged for managing ITP in adults were identified through the largest Italian hematology collaborative network maintained at GIMEMA Foundation (https://www.gimema.it/la-fondazione/centri-gimema/), which includes all private and public Italian hematological centers. All of them were invited to complete a cross-sectional survey. **Figure 1** shows the several operational steps of the whole process, from its conception to final analysis.

The project was conceived and coordinated by FR (HPF) and included several phases (**Figure 1**). A scientific committee chaired by NV and including 12 hematologists (SC, GC, MC, VC, UC, GG, EL, MN, ER, CS, FR, NV) with recognized experience in the treatment of ITP was convened to prepare a provisional list of questions. Through a two-round sharing of advanced versions of the proposed questions, the scientific committee and the coordinator developed a final 31-item questionnaire with due attention to equipoise, completeness, and clarity of questions. Survey items were close-ended or multiple choice-style questions, with, in some cases, open-ended questions for specifications. Each set of questions on a particular topic always included also open-ended questions. The respondent's anonymity was preserved so that only the coordinator knew his/her identity.

Survey items addressed the following 9 domains: timing of administration of TPO-RA and preferred agent; modality and purpose of treatment in young and elderly patients; parameters evaluated to discontinue treatment in young and elderly patients; switching and tapering of TPO-RA; perceived thrombotic risk associated with TPO-RA; perceived incidence of thrombosis during TPO-RA treatment and its management; TPO-RA during COVID-19 pandemic; administration of TPO-RA in combination or associated with other agents; selected challenging scenarios (including treatment duration, patients requesting to change treatment with TPO-RA, pregnancy, and detection of antiphospholipid antibodies).

The survey was conducted and managed using REDCap (Research Electronic Data Capture),[21] a secure web-based data capture software, and distributed in May 2021, with a reminder sent to non-respondents after 2 and 3 weeks. The survey was distributed exclusively by the coordinator, with technical support from LG (HPF). No incentives were offered to participants. All participants gave consent to the use of their data. Since no institutional informations were required, institutional permission to participate was not required. The list of participants is reported in **Appendix 2**.

Received questionnaires were preliminarily examined by the coordinator to check for inconsistencies and require further information. Subsequently, expert personnel at HPF (LG) summarized the answers as percentages and collected all text comments in an orderly manner for examinations by the coordinator and scientific committee chair. All analysis and graphics were carried out using R (v4.1.0).

Finally, a draft paper was prepared by FR, NV, MN, and LG and circulated among all panel members for further revision and final approval.

Results. A total of 88 hematologists from 79 centers, among the 129 identified, responded to the survey and returned the questionnaire, with only 2% leaving partially unanswered questions. Therefore, all respondents were considered participants and included in the analysis.

Timing of administration of TPO-RA and preferred agent. As to the optimal timing of TPO-RA administration and preferred agent, 84% of participants reported that they would administer either romiplostim or eltrombopag at an earlier stage than defined by the specifications of the marketing authorization of EMA, which, at the time of this survey, still limited the use of eltrombopag, but not of romiplostim, only after at least 6 months from diagnosis at variance with the latest marketing authorizations.[22,23] More precisely, the majority (71%) would prescribe them immediately after steroids failure, and 17% propose TPO-RA administration as front-line treatment in specific subsets of patients (e.g., diabetic, septic, or very aged subjects). See questions 1 and 2 in **Appendix 1**.

Modality and purpose of treatment in young and elderly patients. Eighty-two percent of participants in the survey stated that they would indifferently use romiplostim and eltrombopag, with the same frequency among young and elderly patients. See question 5 in **Appendix 1**. Fifty-six percent of the respondents reported that they do not adopt different approaches for young and elderly patients. On the contrary, the perceived increased thrombotic risk, the higher incidence of comorbidities in elderly patients, and the difficult hospital access associated with advanced age were considered factors negatively influencing the use of TPO-RA, respectively, for 23%, 22%, and 17% of the respondents (**Figure 2B**).

Several specific factors may influence the choice of second-line therapies by treaters. In our survey, the possibility of home administration, TPO-RA manageability, the time interval needed to reach a safe platelet count, comorbidities, certain concomitant therapies, and patient compliance and age were considered the main factors which may favor the administration of TPO-RA. On the contrary, costs, fluctuations in platelet count levels, and the need for frequent contact with the patient were identified as the main limitations of TPO-RA prescription (**Figure 2A**). Forty-four percent of participants did not consider initiating TPO-RA administration at different time points (earlier or later) in patients aged ≥ 65 years compared to

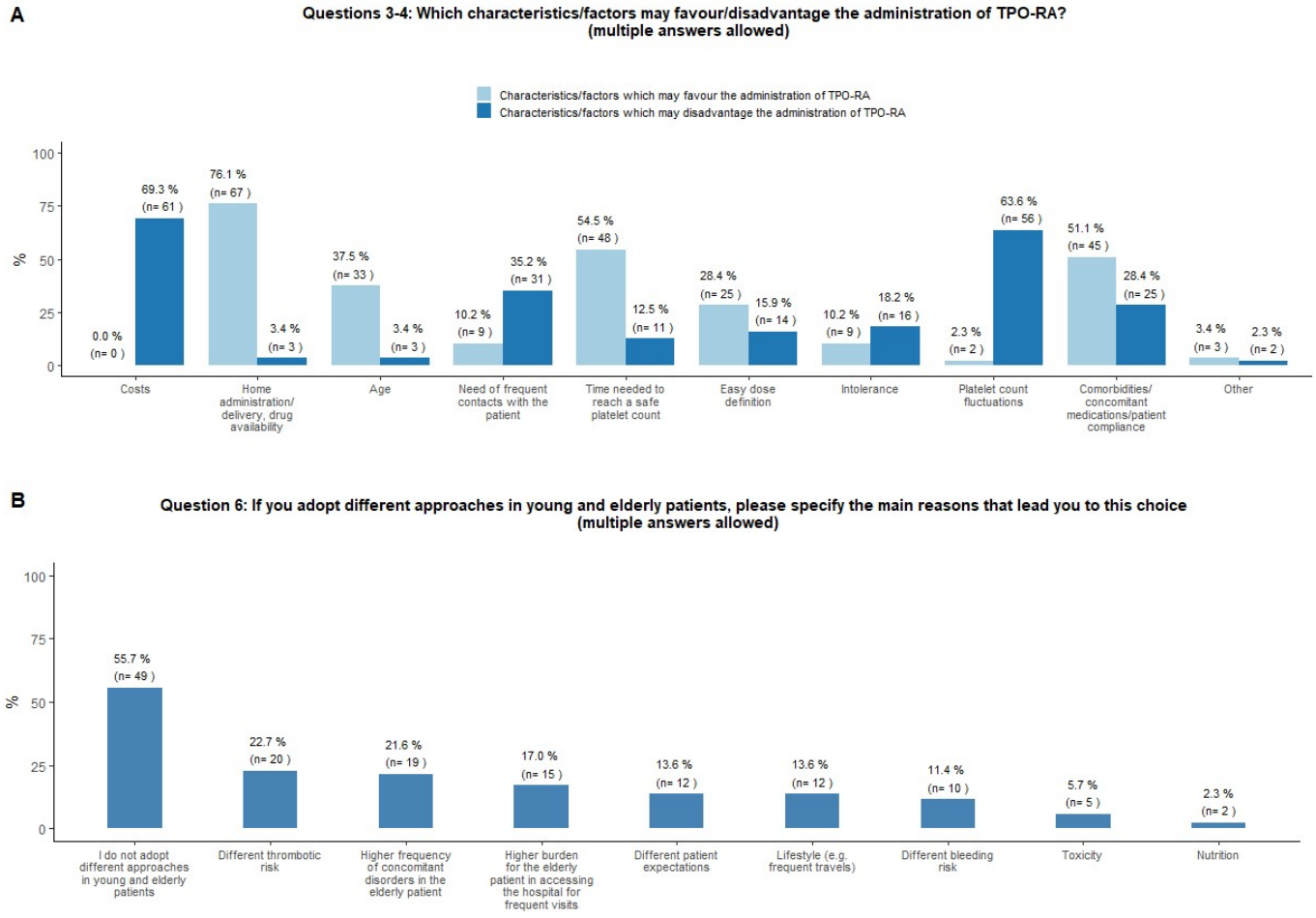

Figure 2. Frequency distribution of the different answers to questions 3, 4 and 6.

the younger ones, 32% considered TPO-RA as appropriate as a second line treatment option after cortisone in aging subjects, independently from concomitant cardiovascular risk factors or comorbidities and 24% considered TPO-RA use as a second line treatment option only in the absence of comorbidities that may negatively impact the cardiovascular system. See question 7 in **Appendix 1**.

Parameters evaluated to discontinue treatment in young and elderly patients. Seventy-two percent of participants would use TPO-RA in young patients aiming at reaching a complete response followed by subsequent tapering and treatment discontinuation in order to obtain a Treatment Free Response (TFR); a couple of hematologists have highlighted the possibility of administering TPO-RA as a bridge to splenectomy, allowing patients to reach the chronic phase of the disease and then receive vaccinations before splenectomy. On the other hand, in the context of elderly patients, 83% of the involved hematologists would use TPO-RA to obtain a stable and safe platelet count, and only 16% would explore the possibility of reaching a complete response and treatment discontinuation (**Figure 3A**).

Approximately one-third of participants reported having observed patients with TFR in 5-10% of their cases, while 30% and 24% of participants stated that in their experience, a TFR was possible in 10-20% and 20-30% of cases respectively (**Figure 3B**).

Thirty-five percent of participants would attempt to withdraw TPO-RA to obtain TFR when the platelet count is $\geq 100x10^9$/L for at least 12 months, while 32% and 13% would try to discontinue TPO-RA treatment aiming to achieve TFR when the platelet count is $\geq 100x10^9$/L for at least 6 and 3 months, respectively (**Figure 3C**).

Switching and tapering of TPO-RA. Regarding the main factors governing switching from one TPO-RA to the other, the vast majority would consider this option in the following clinical scenarios: loss of the response to the first TPO-RA (90%); occurrence of significant toxicity (75%); failure to increase the platelet count above 20-$30x10^9$/L or to double the basal count despite the highest allowed dosage for four consecutive weeks (67%); stable platelet count not reached, due to large fluctuations in platelet counts (57%) (**Figure 4A**).

Regarding the different tapering modalities, 77% of participants stated that they would not adopt a pre-defined scheme that they apply consistently for both

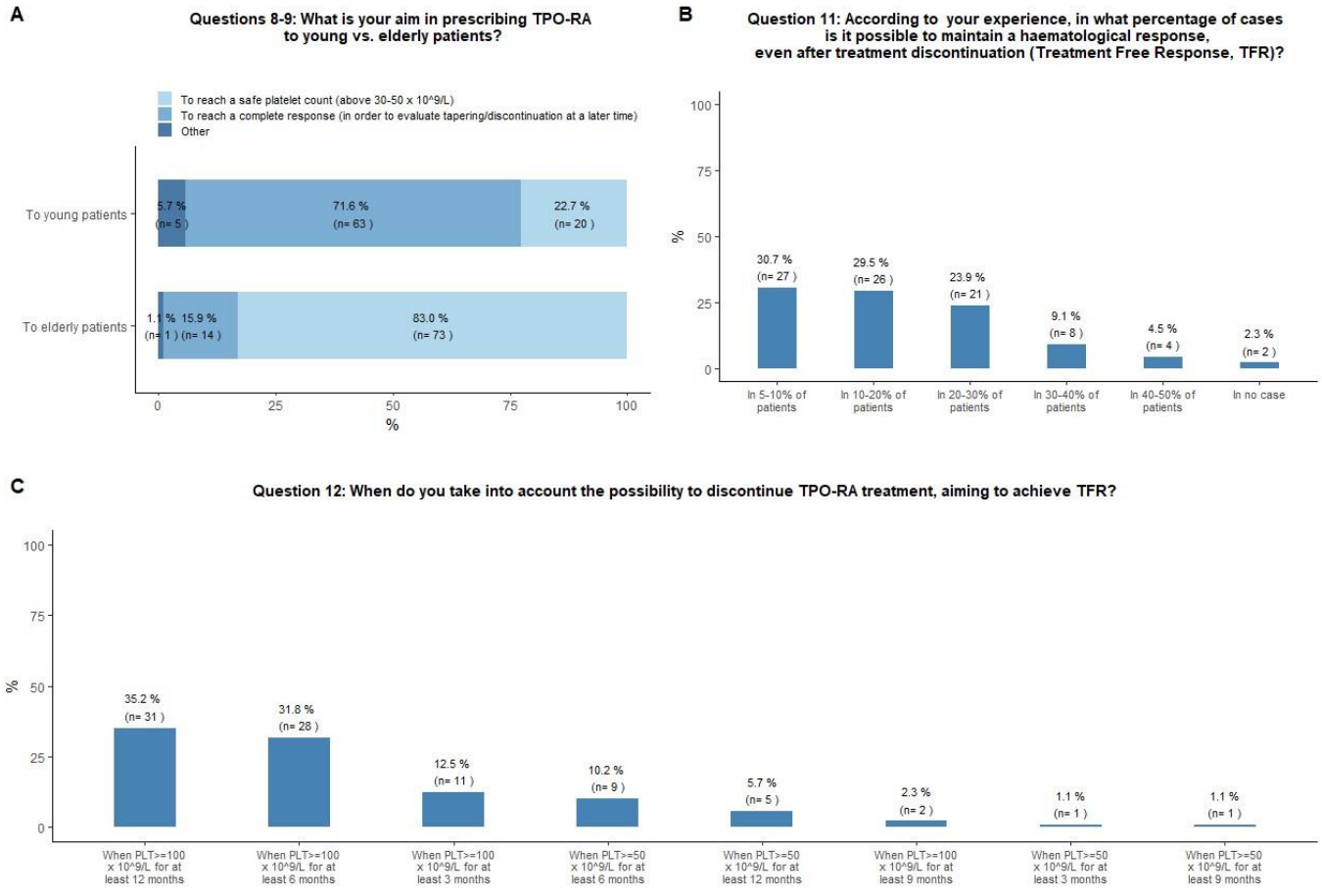

Figure 3. Frequency distribution of the different answers to questions 8, 9, 11 and 12.

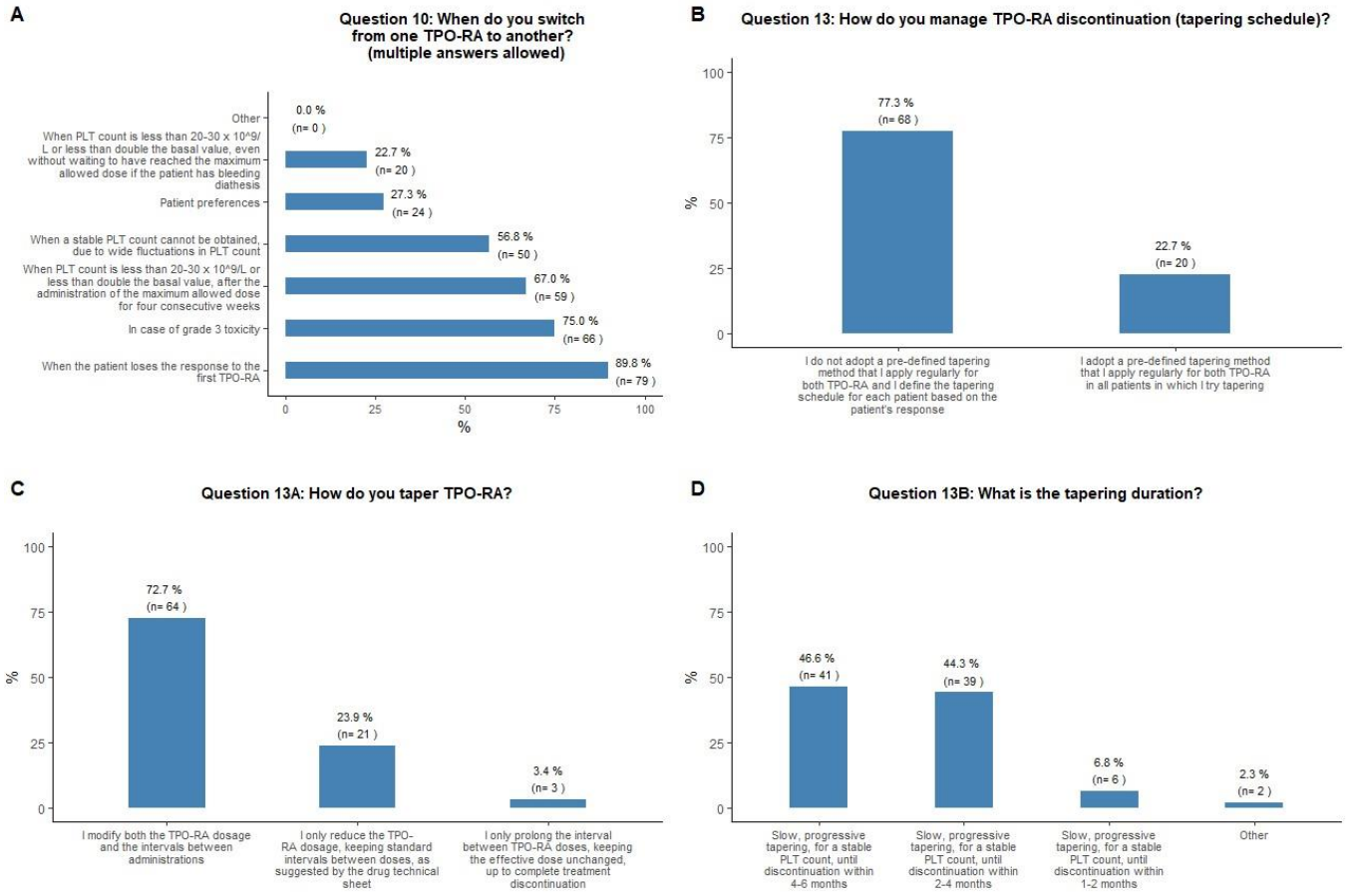

Figure 4. Frequency distribution of the different answers to questions 10, 13, 13A and 13B.

TPO-RA but would prefer to decide on the basis of individual patient platelet count trends (**Figure 4B**).

TPO-RA tapering schedules would be mostly carried out by reducing the dosage and prolonging the intervals between administrations (73% of participants). Alternatively, some participants (27%) would prefer to either reduce the dose or prolong the intervals (**Figure 4C**).

As to the duration of the tapering phase, we observed some heterogeneity. Forty-seven percent of participants would prefer a slow, progressive tapering lasting up to 4-6 months until a stable platelet count is maintained, before the suspension, while 44% would choose a more rapid tapering within 2-4 months. A small proportion stated that they would apply tapering within an even shorter time (1-2 months) or, on the contrary, during a much longer time (up to twelve months) (**Figure 4D**). Once tapering of TPO-RA is initiated, it would be strictly guided by platelet count. Several tapering choices were proposed when platelets decreased below $50x10^9$/L without bleeding diathesis. Most participants (82%) indicated that they would prefer to restore the drug dosage immediately preceding the last one and slow down the tapering phase. On the other hand, 14% of participants would prefer to restore the pre-tapering effective TPO-RA dosage without further attempting another tapering. Finally, a small number of participants (4%) would temporarily associate low doses of steroids to TPO-RA while continuing the planned tapering schedule. See question 14 in **Appendix 1**.

Perceived thrombotic risk associated with TPO-RA. This section explored the participants' concern about a possible increased thrombotic risk associated with TPO-RA and the treatment preferences for patients with a recent history of thrombosis or experiencing thrombosis while on TPO-RA.

Approximately 35% of participants reported that, in their opinion, the administration of TPO-RA could represent a thrombotic risk factor for patients. In comparison, 64% of them consider that TPO-RA are associated with a higher risk of thrombotic complications only in the presence of other concomitant risk factors for thrombosis (**Figure 5A**). Almost all participants consider the possibility of prescribing TPO-RA also in patients with a history of thrombosis. Half of them report the need to evaluate coexisting additional clinical and laboratory thrombosis risk factors accurately. Most participants (84%) believe that romiplostim and eltrombopag have a similar potential to induce thrombotic complications. A minority of respondents (13%) attribute a higher thrombotic risk to eltrombopag. The vast majority (94%)

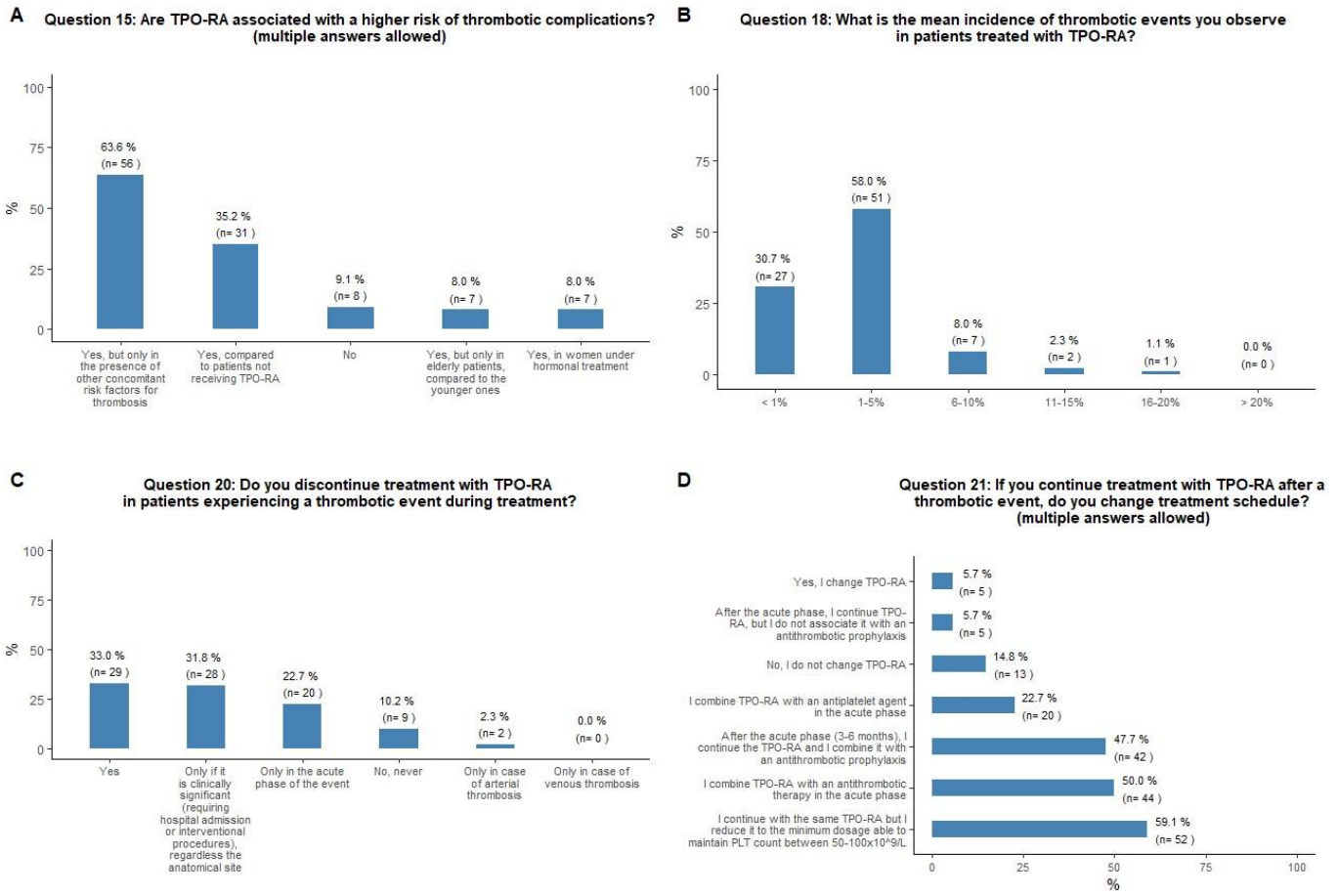

Figure 5. Frequency distribution of the different answers to questions 15, 18, 20 and 21.

of respondents consider the administration of TPO-RA in elderly patients to be overall sufficiently safe even in the presence of other concomitant thrombotic risk factors (in addition to advanced age); however, 68% of them consider appropriate to start primary antithrombotic prophylaxis as soon as a platelet count at least above $50x10^9$/L is obtained, aiming to reach a platelet count between 50-$100x10^9$/L. See questions 16, 25, and 17 in **Appendix 1**.

Perceived incidence of thrombosis during TPO-RA treatment and its management. This section investigated the participants' perception of the risk of early or late thrombotic events during treatment with TPO-RA and the treatment approach that would have been used in case of thrombosis during treatment.

Sixty-six percent of participants report that they have observed, in their common clinical practice, an incidence rate of 1-10% of thrombotic complications during treatment with TPO-RA; on the contrary, 31% reported thrombosis as a quite rare (with an incidence rate < 1%) complication in patients treated with TPO-RA (**Figure 5B**). Thrombosis involved the venous and arterial vascular districts indifferently according to 44% of the respondents; on the other hand, 44% and 12% of participants stated that thrombosis mainly involved veins and arteries respectively. See question 19 in **Appendix 1**.

About 57% of participants, according to their personal experience and knowledge of the literature, believe that the incidence of thrombotic complications within one year after starting TPO-RA treatment in ITP patients older than 60 years of age can be estimated at 1-5%, while 26% and 17% of participants stated that the incidence of thrombosis in these patients is <1% and 6-10% respectively. In the same context, the incidence of thrombotic complications beyond the first year of therapy with TPO-RA was considered <1% (43% of respondents), 1-5% (43%); 6-10% (12%) and 11-15% (2%). See questions 23 and 24 in **Appendix 1**.

Thirty-three percent of participants would withdraw TPO-RA in case of thrombosis, 32% would discontinue TPO-RA only if thrombosis is deemed as "clinically relevant", 23% would withdraw them temporarily in the acute phase of the event, and 10% would continue the treatment. Fifty-nine percent of participants that would continue TPO-RA treatment despite a thrombotic event would continue with the same agent and reduce it to the minimum dosage able to maintain platelet count between $50x10^9$/L and $100x10^9$/L. Most participants would associate an antiplatelet or anticoagulant agent in the absence of contraindication. Moreover, some participants agreed that, in case of thrombotic

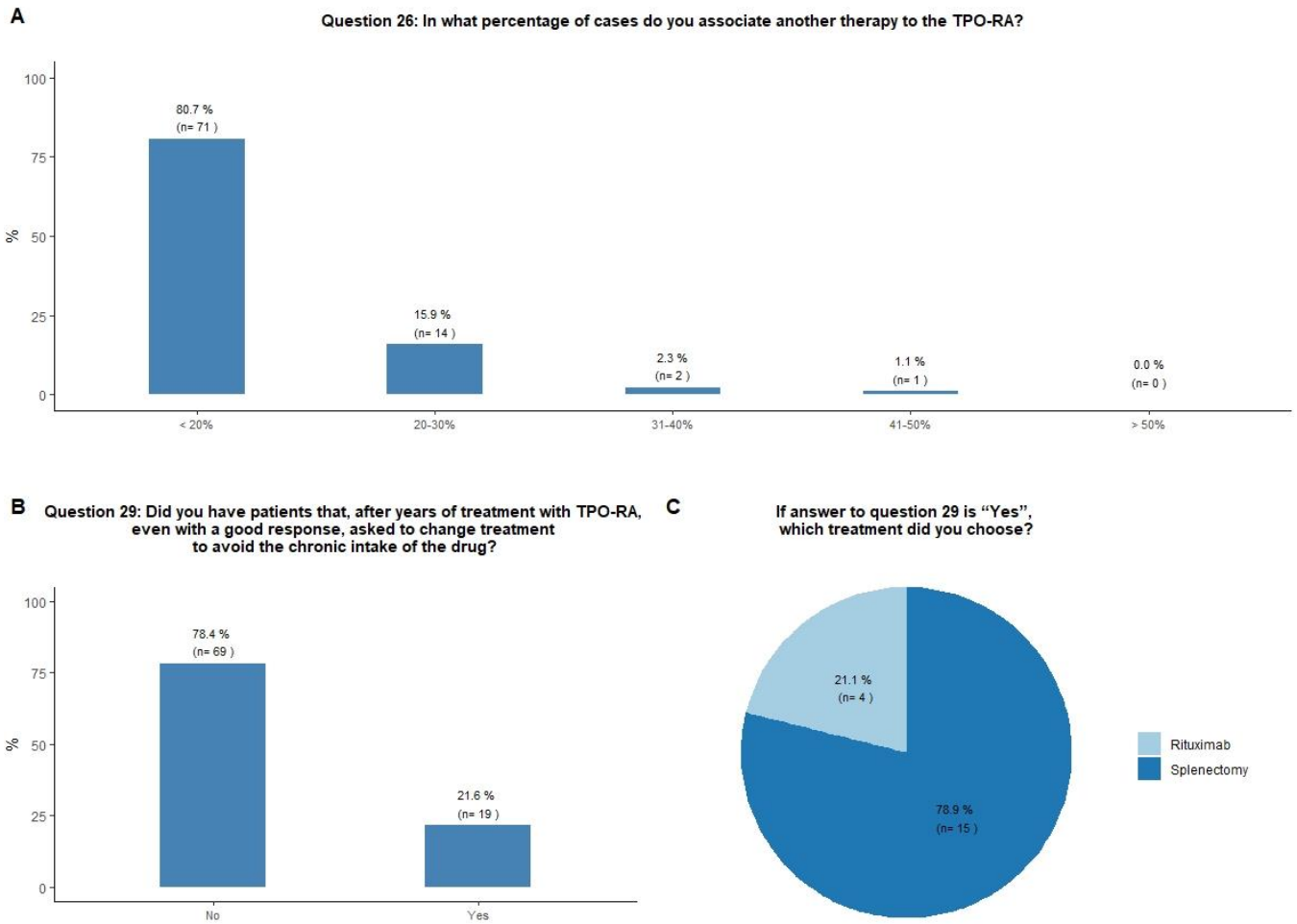

Figure 6. Frequency distribution of the different answers to questions 26, 29 and its sub-question.

complications, a multidisciplinary approach is desirable to define the most appropriate antiplatelet and anticoagulant agent (**Figures 5C** and **5D**).

TPO-RA during COVID-19 pandemic. The impact of the COVID-19 pandemic on TPO-RA use was also explored. Fifty-one percent of participants would not introduce any change in their current practice on TPO-RA administration, while 46% of them would prefer TPO-RA over a further, more immunosuppressive treatment, and 3% would use TPO-RA as second-line treatment. See question 22 in **Appendix 1**.

Administration of TPO-RA in combination or associated with other agents. Eighty-one percent of participants reported that they would associate another therapy to the TPO-RA in <20% of cases (**Figure 6A**). Preference for specific medications associated with TPO-RA was rarely indicated. Steroids and high-dose immunoglobulins (HDIg) are the most frequently proposed drugs in association with TPO-RA, followed by a far lower preference for azathioprine and cyclosporine. Ten percent of participants reported that they would occasionally combine the two available TPO-RA for selected refractory patients at a very high bleeding risk but with poor results expected, based on their experience. See questions 27 and 28 in **Appendix 1**.

Selected challenging scenarios. Seventy-eight percent of participants would indefinitely continue treatment with TPO-RA in their responding patients, while 22% reported that they received a request from the patient to change treatment to avoid the chronic intake of the drug, despite a good response. In this circumstance, participants would mostly suggest splenectomy, sometimes already proposed by their patients, in the hope of obtaining a treatment-free and long-term response (**Figures 6B** and **6C**).

Ten percent of participants reported using TPO-RA during pregnancy, regardless of its phase. Sixty-nine percent do not consider the presence of antiphospholipid antibodies as an absolute contraindication to the use of TPO-RA, while 31% do so. See questions 30 and 31 in **Appendix 1**. However, some participants suggest that it would be useful to have guidelines providing indications for managing patients at high risk of thrombosis.

Discussion. The availability of TPO-RA in the treatment

of ITP has significantly modified the therapeutic approach to this disease in the last ten years.[3-5] In 2014 the FDA decided to expand the indications for TPO-RA use in the light of the availability of further data concerning their efficacy and safety, allowing their administration even in the persistent phase of the disease by removing the limitation of refractoriness to splenectomy and, more recently, allowing their use in children. For adults, at the time of this survey, romiplostim was indicated after failure to first-line treatments[24] and eltrombopag after a minimum of 6 months.[25]

Recently, several authors described the efficacy and safety of romiplostim and eltrombopag immediately after an insufficient response to corticosteroids in the real-world context. The early use of TPO-RA aims to avoid inappropriate prolonged exposure to steroids with potentially severe side effects while reducing the risk of severe bleeding. There is also the emerging perspective that TPO-RA could modify the long-term outcome of ITP by allowing to reach a TFR in a sizable proportion of patients.[26-31]

TPO-RA are thus increasingly evaluated in clinical practice for use in different contexts with different modalities, not explored in the pivotal registration trials which enrolled patients unresponsive to several lines of therapy, including a significant proportion of those refractory to splenectomy.[32,33] In particular, TPO-RA were successfully used in elderly patients and as a bridge therapy to splenectomy.[34,35]

Gonzalez-Lopez et al.[36] performed a retrospective analysis on eltrombopag administration in adult patients affected by ITP, including 30 patients affected by newly diagnosed ITP, 30 patients with persistent ITP and 160 subjects with chronic ITP Results did not show any statistically significant difference in terms of efficacy and safety among the 3 groups; however, a trend towards a higher efficacy in newly diagnosed ITP was reported (93.3% of responses with 86.7% of CR).

Lozano et al.[37] revised available data on the early use of romiplostim reported in 9 clinical trials, 6 real-world studies and 10 case reports. Results of this integrated analysis showed that romiplostim was as effective in newly diagnosed/persistent ITP as in chronic ITP Therefore, the authors suggested that an early administration of romiplostim may reduce exposure duration to steroids.

Importantly, in recent years the possibility of obtaining sustained response off therapy in approximately 20-30% of responders has been reported in a phase 2 trial with romiplostim[26] and in several clinical series with both romiplostim and eltrombopag.[27-31] Tapering TPO-RA in search of a sustained response is part of current practice, even in the absence of standardized criteria to guide patient selection and tapering modalities.

Moreover, an effective cross-over use of romiplostim and eltrombopag was demonstrated in case of refractoriness or intolerance of one of the two.[38]

More recently, TPO-RA are becoming a valuable, well-tolerated treatment option for chronic and persistent ITP in children aged 1 year or older. In addition, TPO-RA are also attractive for the management of ITP during pregnancy in case of severe thrombocytopenia and lack of response or side effects to standard approach with low/intermediate doses of corticosteroids and/or IVIg.[39,40]

The publication of the several studies mentioned above, and many other similar reports worldwide, may have modified the clinicians' attitude toward TPO-RA. As for Italy, it is worth noting that some authors of the present paper contributed as co-authors in recent publications on the evolving use of TPO-RA in clinical practice.[16,17,20,41,42]

Hence, it is not surprising that the current survey has revealed that most Italian hematologists consider desirable an earlier and much more flexible administration of TPO-RA. Furthermore, most participants in the current survey did not consider age as a limiting factor in the use of this category of drugs, favorably taking into account the possibility of administering TPO-RA also in elderly and very elderly patients.

In about 30% of the interviewees, the risk of thrombosis secondary to using TPO-RA was perceived as quite inferior to what was reported in the available literature.[15] In any case, it was not considered a limit to TPO-RA prescription. However, it should be taken into account that thrombotic events represent a not negligible complication of the use of TPO-RA, reported to be 2-3 times higher than in untreated ITP patients, with an annual incidence of 4.1% and 2.5%, observed for romiplostim and eltrombopag, respectively.[9,15,43,44,45] Some uncertainty continues, as to the increased risk of thrombosis during TPO-RA administration. For example, a very recent meta-analysis concerning the risk of thrombosis during treatment with TPO-RA compared to placebo or standard of care shows that the number of thrombotic events, even if higher in the TPO-RA group than in the control group, does not translate into a statistically significant increment.[46] Moreover, in elderly and young ITP patients treated with TPO-RA, the annual incidence of thrombosis in a real-life context has recently been substantially similar.[41] However, further studies are required to dismiss the increased thrombotic risk caused by TPO-RA, definitely.

Italian hematologists consider important to administer primary antithrombotic prophylaxis in patients at high thrombotic risk. On the other hand, they would prefer, in most cases, to continue treatment with TPO-RA, even after thrombosis, if a safe platelet count will allow secondary prophylaxis. In the case of

thrombotic complications, a multidisciplinary approach with cardiologists and vascular medicine specialists emerged as a common clinical practice to define better the optimal anticoagulant and/or antiplatelet treatment.

Finally, the COVID-19 pandemic has led experts to use more and more TPO-RA instead of other treatments with immunosuppressive properties, aiming to reduce the risk of SARS-CoV-2 infection while ensuring therapeutic efficacy in keeping with current National and International guidelines.[18,47]

In this survey, some results, albeit obtained through a different methodology, were quite similar to those that emerged from some expert consensus reached by the Delphi method recently published[16,19,48] on the topic of TPO-RA treatment tapering and discontinuation. However, from all these data, there was not univocal and reliable guidance on this important issue, yet, and further studies on this specific topic were necessary. Moreover, specific issues afforded in the current survey, concerning, for example, the use of TPO-RA in patients of different ages, in context with a high risk of thrombosis or after a thrombotic event and during SARS-CoV-2 pandemic, have not been evaluated yet, thus leaving several questions still unanswered.

In conclusion, the current survey shows that most Italian hematologists assign a crucial role to TPO-RA, notwithstanding the many options for managing ITP In particular, a more flexible and extensive use of TPO-RA is suggested both in subjects who are refractory or poorly responsive to steroids and in other specific categories of patients, such as the elderly ones. However, the heterogeneous distribution of some answers to the proposed questionnaire confirms the need for more accurate information on several aspects concerning TPO-RA administration, including: the timing and the modality of TPO-RA tapering in responsive patients, the best management of relapsed patients after TPO-RA discontinuation and the optimal treatment approach to patients with concomitant cardiovascular risk factors or thromboembolic complications.

The current treatment scenario has been recently expanded by the approval of new drugs, either acting as TPO-RA (avatrombopag) or inhibitors of spleen tyrosine kinase (fostamatinib). Moreover, several other drugs are being currently evaluated in phase II-III studies exploring new mechanisms of action such as, to name the principal ones, FcRn (Fragment C Receptor Neonatal) inhibitors like efgartigimod; rilzabrutinib, a reversible inhibitor of Bruton Tyrosine Kinase; mezagitamab, an inhibitor of CD-38; and sutimlimab an inhibitor of C1s in the classical complement pathway.[49] Hence, in the next future, the present depicted real-world overview of the Italian management of ITP will change in relation to the new available drugs.

We trust that further real-life studies are needed to offer a substantial answer to the perceived critical clinical issues as those that emerged in this survey. These studies will also be useful in informing on old, recent, and upcoming drugs and help to better personalize ITP therapy by indicating each treatment's peculiar benefits and limitations in the common practice.

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