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A decade of changes in management of immune thrombocytopenia, with special focus on elderly patients

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ABSTRACT

Background: Ten years after their availability, thrombopoietin receptor agonists (TPO-RA) have heralded a paradigm shift in the treatment of immune thrombocytopenia (ITP). This study was aimed to analyze the implementation of current recommendations in the standard practice of adult ITP patients, and how age may influence those changes.

Methods: We included 121 adult patients (> 65 years, n = 54; younger individuals, n = 67) who initiated treatment with TPO-RA between January 2012 and December 2014.

Results: Patients older than 65 years treated with TPO-RA presented at diagnosis with significantly higher platelet counts, less bleeding, and a more prothrombotic profile than younger ones. The high efficacy rates of TPO-RA, preferentially used during the last decade in non-chronic phases, precluded from further therapies in the majority of ITP patients. Their administration was associated with a sharp decline in the last decade in the use of splenectomy and intravenous immunoglobulin, especially in younger ITP individuals.

Conclusion: These results confirm (1) that there is a preferential use of TPO-RAs in elderly ITP patients with fewer bleeding complications but more unfavorable prothrombotic conditions than in younger individuals, and

Abbreviations: ASH, American Society of Hematology; CBC, Complete blood count; ITP, Immune thrombocytopenia; IVIG, Intravenous immunoglobulins; TPO-RA, Thrombopoietin receptor agonists; VE, Vascular events

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(2) that early use of these agents has been established as an effective therapeutic alternative to other second line therapies.

1. Background

The management of patients with immune thrombocytopenia (ITP) is rapidly evolving. In the last 10 years much work and effort have been done to improve the care of adult patients with ITP. Based on a greater understanding of the disease pathophysiology and the availability of newer therapeutic options, mainly thrombopoietin receptor agonists (TPO-RA), in the last decade experts from different countries have elaborated national and international guidelines. The agreement or similarities in those consensus documents about the set of investigations to perform when suspecting the disease, and on who should be treated and how, were summarized in our previous study [1]. General diagnostic recommendations included, among others, peripheral blood smear to be tested in all patients while bone marrow aspirate was no longer considered a routine diagnostic test regardless of age. General therapeutic proposals recommended treatment with prednisone for a maximum of 3 weeks, followed by tapering and withdrawal for a period of another 2–4 weeks. Although there was a certain degree of heterogeneity in the choice of second-line treatment among different guidelines, TPO-RA were usually proposed as an option, and experts emphasized the risk of the considerable toxicity associated with continuous use of immunosuppressant therapy. In the above mentioned previous study including patients diagnosed after 2010 [1], we recognized important areas of inappropriateness in the management of adult ITP patients, encouraging better compliance with established guidelines in order to improve patient outcomes. Because guidelines are dynamic, they should be updated frequently; in that sense, recommendations from German/Swiss/Austrian experts were revised and renewed [2], and recent versions of the International Consensus guidelines [3] and those of the American Society of Hematology (ASH) have been elaborated [4]. Additionally, surveillance of clinical practice guidelines requires to consider data from real-world experiences to allow the evaluation of the applicability and effectiveness of their recommendations, and their gaps, as well as adherence by physicians when they are used in practice [5].

One important limitation of current guidelines is that in general, aging aspects are not integrated in their recommendations, so that the best practice for the management of seniors remains uncovered. In fact, in the most recent ASH guideline there is emphasis on the need to understand whether elderly patients should be treated differently [4]. Several large epidemiological studies indicate that the incidence of ITP increases with age, with a peak in adults ≥65 years of age, reaching 9/100.000 people/year in men > 75 years of age [6–8]. In clinical practice, in view of the considerable comorbidities of this population [9], physicians need to tailor their treatment approaches. Older patients are more likely to suffer from adverse effects of immunosuppression [10], and also present with more serious bleeding [9–11]. The high response rates and good safety profile of TPO-RA may make these agents especially attractive to be used in this population. A recent paper has analyzed the impact of older age in the management of this disease in real-life practice [12]. Considering the low numbers of therapies with TPO-RA in that study (n = 39), data are lacking to reflect whether the introduction of these drugs in the last decade has implied a paradigm shift in the treatment of ITP in elderly patients. Although meta-analysis of clinical trials of romiplostim and eltrombopag show that TPO-RA are effective and safe in this population, with the exception of increased thromboembolic risk [10,13], the impact of the use of these drugs in older patients raises several questions that have not been fully addressed.

We conducted this study to analyze variations on the diagnostic and therapeutic patterns in real-life practice before and after 2010. Additionally, to understand the influence of TPO-RA, regarded as the major therapeutic breakthrough in ITP the last ten years [14–16] on the management of elderly ITP patients, we explored if treatment approaches differed according to age.

2. Methods

We conducted an observational, retrospective, multicenter study from 19 hematology departments of secondary and tertiary Spanish hospitals with a wide geographic distribution. For that, the participant investigators had to recruit through the screening of the clinical records, all adult patients with a diagnosis of primary ITP according to previously established criteria [17] who were alive and had initiated TPO-RA treatment for ITP in their respective site between January 2012 and December 2014. The study was approved by the Clinical Research Ethics Committee of the Hospital General Universitario Morales Meseguer (Murcia, Spain) and the research project was carried out in accordance with the Declaration of Helsinki [18]. Written informed consent was obtained from every subject.

To evaluate the main differences in the laboratory diagnosis and the therapeutic management before and after TPO-RA were available, 2 cohorts of patients were considered, depending on whether the diagnosis was established before or after 2010. With that aim, we extracted the clinical data from 121 primary adult ITP patients who started TPO-RA as an indefinite treatment, including demographic information, complete blood count (CBC) and peripheral blood smear, bone marrow evaluation, and all platelet-increasing therapy given during the follow-up of the disease from diagnosis until inclusion.

To evaluate if physicians do take a different approach towards older ITP patients and whether age may have played a direct role in how these 121 patients were treated with TPO-RA, we analyzed the clinical management of elderly patients. Older patients were considered those that started TPO-RA at ages above 65 years (n = 54, median age 75 years; 66–96 years) and compared them with younger individuals (n = 67, median age 48 years; 19–65 years). The information collected from medical records incorporated demographics, diagnosis-related data (date of diagnosis, CBC, bleeding history, comorbidities), previous therapies and responses, TPO-RA administration (date, CBC, and bleeding symptoms), and treatment duration. Bleeding severity was evaluated at the time of diagnosis and also when TPO-RA was initiated, with an ITP bleeding score that includes the severity of bleeding at 11 specific sites, with scores ranging from 0 to 2 (0 = none, 1 = mild, 2 = severe bleeding) [19]. Need for unscheduled hospital care requirements (emergency treatment or hospital admission) 6 months before TPO-RA, and adverse events were also recorded.

Data were summarized using descriptive statistics including median, ranges, and percentages. Differences in dichotomous variables were analyzed by Pearson's χ^2 test, and differences in continuous variables by the Mann-Whitney non-parametric test. Statistical analysis was performed using SPSS software, version 22 (SPSS Inc., Chicago, IL).

3. Results

3.1. Diagnostic management and TPO-RA administration in the pre- and post-2010 periods

A total of 121 ITP patients (women 58.7%; median age of 63 years, range 19–96 years) who had been diagnosed before (n = 56) or after (n = 65) the year 2010 were included. Patients diagnosed before and

after 2010 had a median follow-up until data collection of 13.4 years (7.5–54.2 years) and 4.7 years (2.2–7.6 years), respectively. The minority of patients diagnosed in the pre-2010 period received TPO-RA as the first second line therapy, in contrast to almost three-fourth of those diagnosed after 2010, who received these agents immediately after first line therapy ($p < 0.001$). Notwithstanding the fact that when these patients initiated TPO-RA these agents were approved for chronic ITP (more than 1 year from diagnosis), those that had been diagnosed after 2010 started this therapy after a median of 6.7 months from diagnosis, that is 60% of cases receiving initial therapy with TPO-RA in non-chronic phases of the disease (Table 1).

The level of compliance of specific diagnostic tests (peripheral blood smear and bone marrow evaluation) were analyzed and compared. Peripheral blood smear, an examination of particular relevance for the diagnosis of ITP that is recommended by all guidelines, was to a large extent being overlooked and performed in only 67% of those diagnosed before 2010, and in 86% of patients diagnosed after that year ($P = 0.015$) (Table 1). Bone marrow assessment at the diagnosis of the disorder was ordinarily performed in around a half of the patients regardless of the time frame (57% and 46% in the pre- and post-2010 period, respectively; $P = 0.228$). Remarkably, age was a more important motivation to request bone marrow assessment in patients diagnosed after 2010, than in the previous time period ($p = 0.050$) (Table 1).

We have analyzed how TPO-RA have changed the management of adults with ITP. Although when interpreting changes in the management of patients, the number of second line therapies could be time-dependent (patients diagnosed before 2010 had longer follow-up), in general TPO-RA impact further treatment initiation. The high efficacy rates of TPO-RA (82.6% responders) precluded from further therapies in the majority of cases. A total of 24.8% of patients received short term steroids for a limited time following TPO-RA (median initial dose of prednisone 20 mg/day), and only 9.1% were treated with other second line therapies (5.8% intravenous immunoglobulins [IVIG], 1.6% cyclophosphamide, 0.8% splenectomy, 0.8% azathioprine). Considering splenectomy, our results indicate that 48% of patients in the pre-2010 period, compared to only 12% of those diagnosed after that year underwent the surgical procedure before receiving these agents ($P < 0.001$). Data also reflected a trend towards better initial response rate to splenectomy in the pre-2010 era (73.5% *vs.* 44.4% of responders, respectively; $P = 0.098$) (data not shown). Other therapies were also significantly more represented in the pre- compared to post-2010 periods, such as rituximab (28.2% *vs.* 14.7%, $P = 0.046$), other immunosuppressants (21.1% *vs.* 8.0%, $P = 0.024$), and danazol (18.3% *vs.* 4.0%, $P = 0.006$) (Fig. 1).

3.2. Impact of patient's age on TPO-RA administration

To analyze if age influences treatment with TPO-RA, we focused on the therapeutic management of patients having been prescribed these agents (romiplostim, $n = 54$; eltrombopag, $n = 67$). Although the initial intention to treat was indefinite therapy, TPO-RA were maintained for a median time of 35.2 months (1 to 67.3 months) and almost one half of the patients (46.3%, $n = 56$) tapered off these drugs [20]. The main reason for TPO-RA discontinuation was to test therapy free responses (TFR) (53.6%), followed by efficacy issues (23.2%), adverse events (12.5%), and patient decision (10.7%). There was a trend towards a preferential use of eltrombopag in older patients, and slightly higher platelet response rates to TPO-RA were seen among patients > 65 *versus* ≤ 65 years. However a more conservative management in terms of discontinuation of therapies was confirmed in elderly. Therefore, although the rate of tapering off TPO-RA was significantly lower in those > 65 years ($p = 0.028$), the proportion of patients that maintained therapy free response ($> 50 \times 10^9$/l platelets for at least 6 months) upon discontinuation was similar in both groups (Table 2).

As expected, older age was associated with comorbidities such as hypertension and diabetes ($P < 0.001$), and a decreased rate of splenectomy ($P = 0.002$). Additionally, elderly patients had a significantly higher number of prior vascular events (VE) ($P = 0.049$), with more patients receiving antithrombotic therapy ($P = 0.001$), and with a non-significant trend towards increased risk of current VE under TPO-RA therapy (Table 2). Among younger individuals that suffered from VE, the types of episodes were mostly arterial thrombosis (62.5% of VE both before and during TPO-RA, respectively). However, in elderly patients that had VE, there was a shift in the nature of events, from 100% of arterial thrombosis to 75% of venous thromboembolism before and during TPO-RA, respectively (Table 2). Patients that were offered TPO-RA at younger ages presented at diagnosis with significantly lower platelet counts (median 8 *vs.* 18 $\times 10^9$/l; $P = 0.003$), required more frequently hospital care due to bleeding complications in the six months previous to the start of TPO-RA (37.3% *vs.* 18.5%; $P = 0.023$), and also had significantly higher rates of non-mucocutaneous bleeding at the onset of TPO-RA therapy (14.5% *vs.* 2.1%; $P = 0.042$) than older patients (Table 2).

Table 1
Patient characteristics, blood smear, and bone marrow evaluation at diagnosis according to the time frame (diagnosis in the pre-, and post-2010 periods).

	All ($n = 121$)	Diagnosis before 2010 ($N = 56$)	Diagnosis after 2010 ($N = 65$)	P
Gender (% female)	58.7	64.3	53.8	0.245
Age (median, range)	63 (19–96)	59 (19–87)	66 (20–96)	0.249
Platelets at diagnosis (median, range)	11.5 (0–95)	11 (0–85)	13 (0–95)	0.959
Chronic phase (%)	67.8	100	40.0	< **0.001**
TPO-RA before another 2nd line therapy (%)	58.7	41.1	73.8	< **0.001**
Months from diagnosis to TPO-RA (median, range)	37.6 (0.3–603.4)	104.9 (39.6–603.4)	6.7 (0.3–46.3)	< **0.001**
Follow-up (months) since start of TPO-RA (median, range)	44.6 (23.8–67.5)	49.5 (27.2–62.7)	41.3 (23.8–67.5)	**0.002**
Diagnostic approach				
Peripheral blood smear (%)	77.3	67.3	85.9	0.015
Bone marrow examination (%)	51.2	57.1	46.1	0.228
Reasons for bone marrow evaluation[a]				
• Refractoriness to therapies	29.0	28.1	30.0	0.871
• Department policy	38.7	50.0	26.7	0.059
• Age	22.6	12.5	33.3	**0.050**
• Other (pre-splenectomy, suspicion or other disorders, additional cytopenia)	19.4	15.6	23.3	0.443
Bone marrow examination in the absence of blood smear evaluation (%)	15.0	21.9	7.1	0.111

Bold indicates significant differences (p equal or less than 0.05).

[a] Results are among those that underwent the evaluation; in some cases bone marrow examination was performed due to different reasons. Abbreviations: TPO-RA, thrombopoietin receptor agonist.

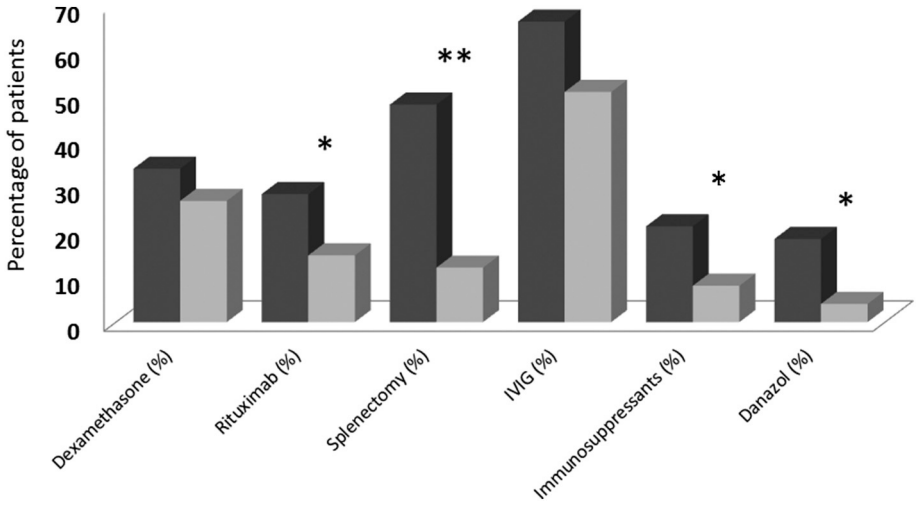

Fig. 1. Use of the various second line therapies according to the date of diagnosis. Dark grey bars indicate percentage of patients diagnosed in the pre-2010 exposed to the specific approach, and light grey bars those diagnosed in the post-2010 period. Immunosuppressive agents include azathioprine, cyclophosphamide, or cyclosporine. *Indicates $P < 0.05$; **indicates $P < 0.001$. Abbreviations: IVIG, intravenous immunoglobulin

3.3. Changes in the treatment pattern in the last decade according to age

The median follow-up of patients diagnosed before 2010 until TPO-RA were started was 104.9 months (39.6–603.4 months), a period that was similar in the two different age groups (> 65 and ≤ 65 years) ($p = 0.945$). When TPO-RA were initiated, the group of younger individuals had been significantly more exposed to splenectomy and to IVIG than elderly patients (61.1% *vs* 25.0%; $p = 0.010$, and 80.6% *vs* 40.0%; $p = 0.002$, respectively). If diagnosis was established after 2010, older ITP patients had delayed initiation of TPO-RA compared to younger patients (11.2 *vs* 3.4 months, $p = 0.040$). Notwithstanding this difference in more than 7 months until TPO-RA were prescribed in older patients, no significant differences were observed in the increased use of other types of therapies compared to the younger cohort (Table 3).

4. Discussion

The diagnosis and management of ITP patients have changed dramatically in the last decade. In these years, the continuous progress in the understanding of ITP pathophysiology and also the availability of novel therapies, have guided relevant changes in treatment strategies of the disease. These advances constituted a solid foundation for the elaboration and/or update of different ITP guidelines, which however rarely provided the tools needed in managing the particularly complicated elderly patients. Here, we have evaluated the translation of these recommendations (i) into the improvements of the diagnostic approach of the disease in the last decade, and (ii) into the clinical care of patients receiving TPO-RA, with an especial focus in the typically complicated older patients.

Overall, our study evidences that the post-2010 management of ITP patients shows certain relevant gaps in the diagnosis. These deviations include failure to perform universal peripheral blood film examination, and conducting ordinary bone marrow assessment in around half of the patients at diagnosis. Although the proportion of patients undergoing bone marrow examination has not significantly changed, the percentage of patients being diagnosed without a peripheral blood smear has experienced a considerable reduction compared to the pre-2010 period. Our study reflects that during the post-2010 period, in current clinical

Table 2
TPO-RA treatment, comorbidities, and bleeding and thrombotic history, according to age when TPO were initiated.

	> 65 yr ($n = 54$)	≤65 yr ($n = 67$)	*P*
Treatment with TPO-RA			
Time (months) from diagnosis to TPO-RA (median, range)	28.1 (0.7–233.2)	44.3 (0.3–603.4)	0.526
TPO-RA used (% romiplostim; % eltrombopag)	35.2;64.8	52.2; 47.8	0.061
Responses to first TPO-RA (%)	85.2	80.6	0.508
Time (years) on TPO-RA therapy (median, range)	3.1 (0.1–5.6)	2.5 (0.1–5.3)	0.144
Follow-up (years) since start of TPO-RA	3.6 (2.0–5.6)	3.9 (2.2–5.1)	0.612
% Discontinuation	35.2	55.2	**0.028**
% TFR in those that discontinue	57.9	54.0	0.784
TFR (%)	24.1	35.8	0.163
Comorbidities			
Hypertension (%)	55.6	6.0	< **0.001**
Diabetes (%)	27.8	3.0	< **0.001**
Bleeding risk/symptoms			
Platelet count at diagnosis x10^9/l (median, range)	18 (0–85)	8 (0–95)	**0.003**
Cumulative bleeding score at diagnosis	0 (0–7)	2 (0 − 10)	**0.034**
Non-mucocutaneous bleeding at start of TPO-RA (%)	2.1	14.5	**0.042**
Bleeding requiring unscheduled visits to hospital 6 months before TPO-RA (%)	18.5	37.3	**0.023**
Thrombotic risk			
Splenectomy (%)	14.8	40.3	**0.002**
Vascular events before TPO-RA (%)	14.8	4.5	**0.049**
Antithrombotic therapy before TPO-RA (%)	14.8	0	**0.001**
Vascular events during TPO-RA (%)	14.8	10.4	0.469
• Venous thromboembolism (%)	11.1	4.5	0.167
• Arterial thrombosis (%)	5.6	7.5	0.675

Abbreviations: TFR, therapy free responses; TPO-RA, thrombopoietin receptor agonist.
Bold indicates significant differences (p equal or less than 0.05).

Table 3
Variations in therapies according to the patient's age and period of diagnosis.

	Pre 2010			Post 2010		
	≤65 (*N* = 36)	> 65 (*N* = 20)	P	≤65 (*N* = 31)	> 65 (*N* = 34)	*P*
Months from diagnosis to TPO-RA (median, range)	99.4 (41.5–603.4)	118.2 (39.6–233.2)	0.945	3.4 (0.3–44.3)	11.2 (0.7–46.3)	**0.040**
Splenectomy (%)	61.1	25.0	**0.010**	16.1	8.8	0.371
Rituximab (%)	30.6	10.0	0.081	12.9	17.6	0.596
Immunosuppressants (%)	22.2	15.0	0.515	6.5	5.9	0.924
Danazol (%)	16.7	20.0	0.755	0	8.8	0.090
IVIG (%)	80.6	40.0	**0.002**	45.2	55.9	0.388
Dexamethasone (%)	38.9	35.0	0.773	25.8	20.6	0.618
First line prednisone (%)	83.3	95.0	0.206	90.3	79.4	0.223
Days under first line prednisone (median, range)	94 (11–5933)	155 (15–4989)	0.583	62 (14–851)	88 (14–2266)	0.223
Median cumulative days with prednisone since diagnosis	176 (11–6064)	317 (23–4989)	0.741	108 (14–851)	94.5 (14–2266)	0.925

Abbreviations: IVIG, intravenous immunoglobulin.
Bold indicates significant differences (p equal or less than 0.05).

practice, two-thirds of patients received TPO-RA immediately after first-line therapy, with an early use of romiplostim and eltrombopag (60% in non-chronic phases). The most recent guidelines now propose the use of TPO-RA in newly diagnosed or persistent ITP to help patients to avoid unnecessary adverse events associated with prolonged use of steroids, thereby improving quality of life [2–4]. While at the time when TPO-RA were initiated in these patients these recommendations did not apply, data from real-world already indicated that these agents are already being used in a significant number of patients in non-chronic phases with success [1]. The high efficacy rates of TPO-RA led to considerations regarding further therapies, and although the follow-up of patients was obviously longer in those diagnosed before 2010, the exposure to other non-TPO therapies was very scarce after the start of these agents. For that, the pre-2010 complex decision-making process affecting second line therapies was facilitated in the post-2010 period. TPO-RA therapy was associated with a sharp decline in other second line therapies. However, subgroup analysis has revealed age as a key factor influencing prescribing patterns. Before 2010, treatment was dominated by options such as splenectomy, or IVIG, with physicians usually opting for these treatments at younger ages. Since the majority of patients diagnosed after 2010 received TPO-RA as first second line therapies, the exposure to other second line agents was very limited. As a consequence, after 2010, splenectomy, rituximab, as well as other therapies such as immunosuppressive drugs and danazol, experienced a radical decrease in terms of use compared to the pre-2010 period.

Previous studies have highlighted that ITP presents as a more aggressive disease in older patients, who more frequently experience severe hemorrhages and need to start corticosteroid therapy with a higher platelet count [9,10,12,21]. Notwithstanding that, physicians should also be cautious when treating elderly patients with TPO-RA, since the annualized thrombosis rates in adults with these therapies appear to be 2–3 times higher than in an ITP population not treated with these agents [22]. A recent study indicates that elderly ITP patients treated with TPO-RA present a 4 times higher risk of venous –but not arterial-thrombosis, compared with age matched ITP individuals not receiving these agents [23]. Our data confirmed that elderly patients who were prescribed TPO-RA had significantly more unfavorable prothrombotic conditions before TPO-RA, and also a tendency towards increased risk for venous thromboembolism during TPO-RA compared to younger patients. Elderly patients initiated TPO-RA later, and had lower bleeding risk (in terms of higher platelet counts and fewer previous hemorrhagic events) than younger individuals treated with these drugs suggesting that caution about possible toxicities seems to predominate when adopting decisions concerning therapy in older patients. Also, the compromise towards effective therapies in these fragile patients avoiding potential complications of other second line therapies, associates with low discontinuation of TPO-RA to test for TFR, regardless of hematological responses being similar to the ones observed in younger patients.

The main limitation of our study is its observational retrospective design, the possibility that medical records were incomplete or missing data, and that errors might have occurred during medical record abstraction. The fact that patients that had not received TPO-RA were not included may limit the generalizability of the study to patients unexposed to these agents, and since only alive patients were evaluated, the impact of efficacy and adverse events among deceased patients is not contemplated. A strength of the approach is the use of a large nationally representative patient sample that includes heterogeneous patients managed by different doctors in distinct institutions.

Overall, this multicenter retrospective study shows that the diagnostic and therapeutic shortcomings have experienced a substantial reduction after 2010, likely from the translation into the physician's practice of the proposals of guidelines, and as a result of the availability of TPO-RA. Although there are no specific recommendations on how older ITP patients should be managed, in clinical practice the awareness of the increased burden of the disease in seniors has led to a widespread effort to avoid potential adverse effects, with a preferential use of TPO-RA in elderly individuals that present less bleeding complications than in younger patients. The compromise towards safe and effective therapies in these fragile patients, relates with a reduced percentage of patients discontinuing this therapy, regardless of the potential risk of increased thrombotic risk. Ultimately, with the aging of the ITP population, further studies are warranted to better understand the impact of current and future therapies on both the disease and patient outcomes.

5. Conclusion

First-line treatment with corticosteroids should be contemplated also in elderly patients with ITP, but if there is a loss of response while steroid tapering, a second line treatment should promptly be started. Effort should be made to avoid second line therapies with significant toxicities. TPO-RAs are attractive and effective, and are being used preferentially in elderly ITP patients with fewer bleeding complications than younger individuals. However, these drugs should be prescribed in this population after careful consideration of the potential increased risk of thrombosis.

Ethics approval and consent to participate

The study was approved by the Clinical Research Ethics Committee of the Hospital General Universitario Morales Meseguer (Murcia, Spain) and the research project was carried out in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants before inclusion.

CRediT authorship contribution statement

MLL designed the study, analyzed data, performed statistical analysis and wrote the manuscript. VV designed the study and edited the manuscript. All authors (MLL, MEM-C, MMP, IJ, RMC-A, TJG-L, GC-T, NB, MFL-F, AdA, DV, LFC-M, MTA-R, MIO, SN, JRG-P, EB, EL-A, EO-M, VV) contributed to data collection, provided critical review of the article, and approved the final version for publication.

Declaration of Competing interest

Dr. Lozano reports grants and personal fees from Amgen, personal fees from Novartis, grants and personal fees from Terumo S.A., personal fees from Macopharma, and personal fees from Grifols S.A., outside the submitted work. Dr. Mingot-Castellano reports grants and personal fees from Amgen, Novartis, Sobi, Novonordisk, Takeda, Bayer, Roche, CSL Behring outside the submitted work. Dr. Perera declares no competing interests. Dr. Jarque reports consulting honorarium from Amgen, Novartis, Shionogi. Dr. Campos-Alvarez reports speaker honorarium from Amgen, Novartis, outside the submitted work. Dr. Gonzalez-Lopez reports grants and personal fees from Amgenand Novartis outside the submitted work. Dr. Carreño-Tarragona declares no competing interests. Dr. Bermejo declares no competing interests. Dr. López-Fernández reports advisory honorarium & speaker honorarium from Amgen, outside the submitted work. Dr. de Andres declares advisory honorarium from Amgen outside the submitted work. Dr. Valcarcel reports Advisory board member for Amgen, Novartis, Celgene, Pfizer, JAZZ, Astellas, MSD; speaker honorarium from Amgen, Novartis, Celgene, Pfizer, JAZZ, Astellas, MSD; advisory honorarium from Amgen, Novartis, Celgene, Pfizer, JAZZ, Astellas, MSD; travel grants from Amgen, Novartis, Celgene, Pfizer, JAZZ, Astellas, MSD, outside the submitted work. Dr. Casado-Montero reports speaker honorarium from Amgen and Novartis; advisory honorarium from Amgen and Novartis; advisory board member for Novartis, outside the submitted work. Dr. Alvarez-Roman reports consultant and speaker for Sobi, CSL Behring, Roche, Pfizer, Bayer, Novartis, and Amgen; research grants from Takeda, outside the submitted work. Dr. Orts declares no competing interests. Dr. Novelli declares no competing interests. Dr. Gonzalez-Porras reports fees for consulting services by Amgen, Novartis, SOBI, Grifols and CSL Behring, and speaking honoraria for Novonordisk, Shire, SOBI, Daiichi Sankyo, Pfizer, Rovi, Amgen, and Novartis, outside the submitted work. Dr. Bolaños declares no competing interests. Dr. López-Ansoar reports personal fees from Amgen, outside the submitted work. Dr. Orna-Montero reports speaker honorarium from Amgen, Novartis, outside the submitted work. Dr. Vicente reports advisory & speaker honoraria from Amgen, Novartis, Boehringer-Ingelheim, Pfizer, Bayer, and Daiichi Sankyo, outside the submitted work.

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