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Title

Use of eltrombopag for patients 65 years old or older with immune thrombocytopenia

Running head

Eltrombopag in elderly ITP

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NOVELTY STATEMENT:

1. What is the NEW aspect of your work? To the best of our knowledge, here we present the first manuscript to report efficacy and safety clinical practice data of eltrombopag in elderly ITP patients.

2. What is the CENTRAL finding of your work? Efficacy and safety of eltrombopag in daily practice is high even in patients 65 years old or older with immune thrombocytopenia.

3. What is (or could be) the SPECIFIC clinical relevance of your work? Our paper shows eltrombopag has great effectiveness and a good safety profile in special populations such as elderly ITP patients.

AUTHOR CONTRIBUTIONS

Conception and design: TJGL

Data collection: All authors

Statistical analysis: TJGL

Analysis and interpretation of results: All authors

Writing article (text and tables): TJGL

Final approval of article: All authors

ABSTRACT

Background: Eltrombopag is useful for immune thrombocytopenia (ITP). However, results of clinical trials may not accurately mirror clinical practice reality. Here we evaluated eltrombopag for primary and secondary ITP in our ≥65-yr-old population. **Methods:** 106 primary ITP patients (16 with newly-diagnosed ITP, 16 with persistent ITP and 74 with chronic ITP) and 39 secondary ITP patients (20 with ITP secondary to immune disorders, 7 with ITP secondary to infectious diseases and 12 with ITP secondary to lymphoproliferative disorders [LPD]) were retrospectively evaluated. **Results:** Median age of our cohort was 76 (interquartile range, IQR, 70-81) years. 75.9% of patients yielded a platelet response including 66.2% complete responders. Median time to platelet response was 14 (IQR, 8-21) days. Median time on response was 320 (IQR, 147-526) days. 63 adverse events (AEs), mainly grade 1–2, occurred. The most common were hepatobiliary laboratory abnormalities (HBLAs) and headaches. One transient ischemic attack in a newly diagnosed ITP and two self-limited pulmonary embolisms in secondary ITP were the only thrombotic events observed. **Conclusion:** Eltrombopag showed efficacy and safety in ITP patients aged ≥65 years with primary and secondary ITP. However, efficacy results in LPD-ITP were poor. A relatively high number of deaths were observed.

Key Words

Immune thrombocytopenia, elderly, primary, secondary, eltrombopag.

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Introduction

Immune thrombocytopenia (ITP) is an acquired antibody-mediated immune disorder characterized by increased destruction and inadequate platelet production (1). Incidence of ITP increases with age (2) with no difference for sexes in over 60 year-old patients (3). ITP is clinically variable among patients (4) with those aged ≥60 years at enhanced risk for both major non-fatal and fatal hemorrhage (5).

ITP remains to be an exclusion diagnosis. Thus, primary ITP is defined as a platelet count < 100 x 10^9/L when other possible causes of thrombocytopenia are discarded (6, 7). On the other hand, secondary ITP represents close to 20% of ITP in adults (8) and is often due to other conditions such as immune, infectious or neoplastic disorders (9).

Primary ITP treatment tries to ameliorate hemorrhages and avoid new episodes if possible (7, 10). Standard first-line primary ITP treatment continues to be steroids. Intravenous immunoglobulins are usually reserved to treat bleeding cases. In refractory-to-first-line-treatment patients or relapsing situations, splenectomy is the traditional second line option. Although other therapies have relegated surgery use, splenectomy is still considered the only ITP curative treatment with the highest long-response rates reported to date (11, 12). Conversely, secondary ITP is often refractory to steroids and splenectomy (13) being the outcome of underlying disease usually parallel with improvement of thrombocytopenia (14).

Eltrombopag is an oral thrombopoietin receptor agonist drug (TPO-RA) which induces proliferation and differentiation of megakaryocytes and stimulates platelet production via JAK/STAT signaling pathway (15). Results of clinical trials show great efficacy of eltrombopag (around 80%) in achieving hemostatic platelet levels (≥50 x 10^9/L) with good tolerance (less than 5% of grade 3-4 side effects). This efficacy and safety data is reported to be very prolonged in time with a follow-up of up to 9 years (16). Although elderly and super-elderly patients were enrolled in clinical trials, (e.g. maximum age of 86 years in EXTEND trial), these studies may not reflect reality in over 65-yr-old ITP patients. Nevertheless, in last years good few studies regarding eltrombopag use in primary ITP beyond clinical trials were published (17-19) and increasing number of papers is available for elderly situations (20-27). Regarding secondary ITP, lack of clinical trials and shortage of publications outside of clinical trials avoid a clear demonstration of eltrombopag usefulness for this type of patients (28, 29).

The aim of our present study is to evaluate safety and efficacy of eltrombopag for primary and secondary ITP in patients aged ≥ 65 years in Spanish routine clinical practice.

Material and Methods

Patients and study design

Here we retrospectively evaluated 106 primary and 39 secondary ITP patients (aged 65 years or more) from 20 Spanish centers who had been treated with eltrombopag. Researchers reviewed clinical charts and collected biological and clinical patient data by means of a predetermined case report form. There were recorded patient and disease characteristics including age, gender, months since diagnosis, prior-to-eltrombopag ITP treatments, underlying disease treatments (in secondary ITP only), platelet levels (at diagnosis and before and during eltrombopag treatment), duration and dose of eltrombopag treatment, and adverse events (AEs) during treatment.

Eltrombopag for primary ITP was administered at standard doses approved by European Medicines Agency. The same standard doses (25-75mg/day) were used for secondary ITP when standard ITP treatment failed.

Primary ITP was defined as a platelet count of <100 x 10^9/L in the absence of other causes or diseases that might be associated with thrombocytopenia. The terms "newly diagnosed ITP, persistent and chronic ITP" were reserved for patients whose condition had lasted for less than 3 months, 3-12 months and more than 12 months respectively (6). The term "secondary ITP" included all forms of immune-mediated thrombocytopenia with a platelet count of <100 x 10^9/L except primary ITP. Given that the diagnosis of primary ITP remains one of exclusion with no robust clinical or laboratory parameters available, many authors suggest that no response to platelet transfusion and, on the contrary, rapid response (<1 week) to high dose immunoglobulins (IVIg) could be a necessary condition so as to diagnose ITP (either primary or secondary). So, our patients had to comply with this requirement to be adequate for enrollment. Obviously, other factors involved in non-immune thrombocytopenia had also to be discarded.

We studied in our work immune thrombocytopenia secondary to autoimmune diseases, lymphoproliferative disorders and viral infections (i.e. HCV, HIV). For the diagnosis of these three different subtypes of secondary ITP, we used two additional definitions. Thus, diagnosis of ITP secondary to autoimmune diseases or viruses required the following criteria: less than 100 x

10^9 platelets/L and half the initial platelet count without alterations in peripheral blood smear, in presence of an already stablished viral infection or autoimmune disorder related to an immune thrombocytopenia with no other possible explanation by means of medical conditions or treatments. Our diagnostic criteria also included the definition of ITP secondary to lymphoproliferative disorders (30), i.e. acute and severe thrombocytopenia (less than 2 weeks of duration), absence of splenomegaly, infection or cytotoxic treatments during last month with normal or augmented number of bone marrow megakaryocytes. Although there was no standard panel of testing to discard possible causes of secondary ITP, all physicians were advised to follow McMaster ITP diagnosis criteria (31).

Physician staff evaluated comorbidities at ITP diagnosis and soon afterwards classified them according with the age-adjusted Charlson Comorbidity Index (CCI). To point out, CCI is a list of 19 comorbid terms, each of them with a value ranking from 1 to 6 that predicts the ten-year mortality of our patients.

First we evaluated efficacy of eltrombopag. Thus, we followed international criteria to define complete response (CR) as a platelet count of $\geq$100 x 10^9/L and absence of hemorrhages. Response (R) was defined as a platelet count of 30–100 x 10^9/L, at least a twofold increase of the platelet baseline count with resolution of bleeding symptoms. No response (NR) was defined as a platelet count of < 30 x 10^9/L or less than twice the platelet baseline count (6). Response definition also needed a concurrent absence of any rescue intervention during 8 weeks previous to eltrombopag treatment.

Duration of eltrombopag response (or complete response) was measured as the proportion of cumulative time spent in R (or CR) during the period of examination (6). ITP treatment failure was defined as a platelet count of < 30 x 10^9/L for 4 consecutive weeks at the highest standard dose approved by European Medicines Agency in primary ITP or at 75 mg per day in secondary ITP, a major bleeding event, or the need to change therapy (including splenectomy and/or any other rescue treatment). Higher dose than baseline of a concomitant treatment to eltrombopag was considered as a rescue treatment. We evaluated and classified adverse events during eltrombopag treatment according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE).

Our study was performed in accordance with the guidelines of institutional boards of the 20 participating centers and the standards of the Helsinki Declaration. It was approved by Hospital Universitario de Burgos Ethics Committee (protocol code – REVOES-SCL-ET-2014-01) and was authorized afterwards as a post-authorization observational study by the Spanish Medicines and Health Products Agency. Informed consent of the patients was obtained prior to enrollment. Actual position of the protocol involves only spanish eltrombopag ITP treated patients.

Statistical analysis

A descriptive statistical analysis was performed in Excel (Microsoft Corp., Redmond, WA). Normally and non-normally distributed continuous variables were respectively summarized as the mean and standard deviation (SD), and as the median and interquartile range (IQR). Discrete variables were summarized as percentages. Quantitative and qualitative data were compared using the Mann–Whitney U and Fisher's exact tests, respectively. When analyzing three or more groups, Kruskal-Wallis test was used instead of Mann–Whitney U test. Statistical significance was concluded for values of $p < 0.05$. All statistical analyses were performed using SPSS version 19.0 for Windows (SPSS, Chicago, IL, USA).

Results

Patient characteristics

106 primary ITP and 39 secondary ITP patients aged ≥ 65 years who received eltrombopag treatment were recruited from 20 Spanish centers for this study. According to standard definition, we allocated our primary ITP cohort to three groups: 16 newly-diagnosed ITP, 16 persistent ITP and 74 chronic ITP patients. Meanwhile, in the secondary ITP cohort we collected 20 patients with ITP secondary to immune disorders, 7 with ITP secondary to infectious diseases (HCV and/or HIV) and 12 with ITP secondary to neoplastic (lymphoproliferative disorder-LPD) conditions. Underlying diseases causing secondary ITP were: chronic lymphocytic leukaemia (CLL) in 6 cases, 6 cases of hepatitis C virus (HCV), 5 patients with Sjögren syndrome, 4 anti-phospholipid (aPL) syndromes, 4 Waldenstrom macroglobulinemia (WM), systemic lupus erythematosus (SLE) in 3 cases, 3 cases of Evans syndrome, 2 rheumatoid arthritis, 2 patients with other lymphoma types (one marginal zone B-cell lymphoma and one peripheral T-cell lymphoma, not otherwise

specified [PTCL-NOS]), 1 patient with primary biliary cirrhosis, 1 Graves-Basedow patient (autoimmune thyroid disease), 1 antiphospholipid syndrome-SLE patient and 1 case with Evans Syndrome-HCV.

The main demographic and hematological features of our elderly population cohort are presented in Table 1. Median age of the whole cohort was 76 years [interquartile range (IQR), 70–81 years] with a majority of female patients (65%). 23% of patients had a Charlson comorbidity index greater than one at diagnosis. Months with ITP at the time eltrombopag was started were 30 months (IQR, 4–101 months). Median prior ITP treatments before eltrombopag was 2 (IQR, 2–4). Of these, 17% patients had previously received romiplostim and 22% rituximab. To note, only 17% of patients were splenectomized. Finally, median platelet count at eltrombopag initiation was 14 x 10^9 /l (IQR, 8–28 10^9/l).

Furthermore, we also observed primary and secondary elderly ITP cohorts characteristics. Here, both ITP diseases were homogeneous concerning most important parameters. Thus, median age of primary and secondary ITP cohorts was similar: 76 (IQR, 71–81) vs 74 (IQR, 68–78) years, respectively. Both thrombocytopenic conditions affected predominantly women (68, 64% in primary ITP vs 26, 66.6% in secondary ITP) with identical median number of therapies previous to eltrombopag initiation (2, IQR, 2–4) and low rates of prior splenectomy (17% vs 18%). However, significant statistical differences were found between both cohorts regarding Charlson comorbidity Index (24% of primary ITP had an index greater than one vs 19% in secondary ITP, p=0.004), ITP duration since diagnosis (35 [7;122] vs 15[2;55] months, p=0.021) and concomitant treatments (32, 30.2% vs 28, 69.2% patients receiving another ITP treatment simultaneously, p=0.000). To note, bleeding during the month before starting eltrombopag nearly reached statistical significance (31, 29% vs 16, 47%, p=0.056). Table 2 separately describes patient characteristics of the three subgroups of primary ITP. Nevertheless, no statistical differences were observed regarding clinical and epidemiological data of all three secondary ITP subtypes.

With the aim to look for differences regarding patient characteristics and following the scheme of previous publications (26,27), we divided our whole patient populations in two different cohorts: 65-74 year-old and 75-and-above year old ITP patients. Unfortunately, no statistical differences were found between groups (Table 3).

Eltrombopag efficacy

110 of 145 ITP patients (75.9%) of our whole elderly cohort yielded a platelet response (R) while 96 (66.2%) reached a complete response (CR). Subgroup analysis showed 83 (82%) primary ITP and 23 (59%) secondary ITP responders. This difference was statistically significant . Quite similar results were 80 (75%) primary ITP and 16 (41%) secondary ITP patients who achieved a CR. To note, platelet responses of whole, primary and secondary ITP cohorts are described in Table 4. Furthermore responses and complete responses were comparable in all primary ITP groups. On the contrary, secondary ITP efficacy results show high response rates achieved in immune (12, 60%) and infectious cohorts (6, 86%) but poor results in neoplastic cohort (5, 42%).

Response rate of whole cohort at 3 months was 66.9% with a CR rate of 49.6%. Statistically significant differences (p value = 0.043) where found when we compared responses in both primary (76, 72%) and secondary ITP (21, 54%). On the other hand, CR rates in primary ITP (62, 58%) were much higher than results obtained in secondary ITP patients (10, 26%). This CR rate difference was maintained at 6 months. Nevertheless, no significant differences in durable responses of the groups were observed (Figure 1). Median time to platelet response was 14 days (14 in primary ITP and 12 in secondary ITP). Similar results were also obtained in primary and secondary ITP subgroups. This term, nevertheless, was significantly longer in neoplastic cohort (27 days). Relapse rate was 24.8% (36 of 110 responders) being higher in secondary ITP (14, 35.9%) than observed in primary ITP (22, 20.7%). During the 15-month follow-up of our study, 26 patients (17.9%) needed rescue treatments. Interestingly, when compared with 65-74 year-old patients, the need for rescue therapy in patients aged ≥ 75 years was higher (20, 76.9%), with statistical differences observed between groups. However, all other efficacy data was similar in both cohorts. Median time to relapse was 5 months (IQR, 3-9 months).

Figure 2 and table 5 present response and complete response rates of elderly (65-74 year-old) and very elderly (75-and-above year-old) ITP populations.

Eltrombopag safety

Adverse events and number of deaths during eltrombopag treatment of 65-74 year-old and 75-and-above year-old ITP cohorts are presented in Table 6-and 7 respectively. Thus, 48 patients of our 145 elderly cohort experienced one or more AEs during eltrombopag treatment. Majority of AEs were grade 1-2 in severity. 40 affected primary ITP and 23 secondary ITP patients. The most common were hepatobiliary laboratory abnormalities (HBLA) and headaches who affected 9 and 7

patients respectively. Nevertheless, 24 AE were serious (grade 3-4). 3 SAEs occurred in newly diagnosed ITP: 1 brain haemorrhage in a non-responding ITP, 1 pneumonia in a chronic obstructive pulmonary disease patient and 1 transient ischemic attack. The first two patients died. The latter two were ITP in CR. Other two grade 3-4 events occurred in persistent ITP, both survived: one brain bleeding and one severe asthenia episode which forced eltrombopag discontinuation. Chronic ITP cohort registered 10 grade 3-4 AEs, 6 of them died. These deaths were 2 brain haemorrhages, 1 gastrointestinal bleeding, 2 sepsis of respiratory origin and 1 splenectomy septic complications. Other 4 SAEs were an episode of severe diarrhea and 3 cases of grade III HBLA that resolved despite continued treatment. In secondary ITP cohort, 9 SAEs were recorded: 5, 1 and 3 in immune, infectious and neoplastic (LPD) cohorts, respectively. 6 deaths occurred in this cohort: 1 brain haemorrhage in a patient with Evans syndrome in NR, 1 lupus patient who developed an acute myeloid leukemia, one multirefractory JAK2 positive myelofibrosis in an HCV patient, 1 brain bleeding with a platelet count of 53 x 10^9/L at the time of the event in a CLL patient, 1 episode of febrile neutropenia in a pancytopenic CLL patient and, finally, 1 episode of sepsis of unknown origin in a previously responder WM-ITP. The other 3 SAEs were an HBLA episode who required treatment discontinuation in a Sjögren-ITP, another Sjögren related ITP experienced a mild increase of bone marrow reticulin (grade II) but after eltrombopag cessation fibrosis decreased to grade I and, finally, a disseminated intravascular coagulation (DIC) episode in a non-responder pancytopenic CLL-ITP. 2 patients, 1 APS and 1 CLL, both with cardiovascular risk factors, experienced both grade 2 episodes of venous thromboembolism 12 and 8 months after starting eltrombopag with platelet counts of 263 and 158 x10^9/L respectively, which resolved with medical intervention.

Number of AEs was quite similar in elderly and very elderly populations (30 and 33 respectively). 8 HBLAs and 4 arthralgias in 65-74 yr-old ITP with 4 diarrheas and 4 upper respiratory tract infections in 75-and-above yr-old ITP were the most common adverse events observed. SAEs and deaths were higher in very elderly ITP (14, 18.7% and 9,12% respectively). Infections and hemorrhages were the most frequent causes of death of the whole cohort. Despite its low frequency, brain hemorrhages are clearly more commonly observed in very elderly patients (4, 66.7%).

Discussion

Pivotal trials demonstrate an excellent efficacy and safety profile of eltrombopag in primary ITP (16, 32). Besides, our real-life studies have also shown this drug is useful for this type of patients (18, 19). On the other hand, the role of eltrombopag in secondary ITP needs to be elucidated. Our group was the first to publish a large clinical practice study of 87 secondary ITP patients treated with eltrombopag. We reported great evidence in favor of eltrombopag use in ITP secondary to both infectious and immune diseases (29). Nevertheless we consider additional trials in this context are mandatory. Something similar happens with ITP and aged patients. A classic analysis focused on eltrombopag usefulness in elderly patients (i.e. results from 5 eltrombopag clinical trials) as reported in abstract form by Olney *et al* in 2011 (33). Nevertheless, recently a very interesting manuscript has been published reporting treatment decision strategies in the elderly ITP. Authors studied TPO-RA use in patients aged >75 years versus <65 years showing a higher use of TPO-RAs in the elderly, probably because of comparable response rates of these drugs in older and younger patients (26). However, no clear data is achieved about eltrombopag effectiveness in daily clinical practice in ITP patients aged ≥65 years. This Spanish elderly ITP population study is, to the best of our knowledge, the biggest clinical practice investigation of eltrombopag treatment for primary and secondary ITP in 65 years old or older patients.

Here we describe safety and efficacy results of eltrombopag in a cohort of 145 patients 65 years old or older. 106 of them were treated for primary ITP and 39 for secondary ITP during a follow-up of 15 months. Efficacy results in our whole cohort report 75.9% of responders. As expected, this efficacy outcome was higher in primary ITP (82%) than in secondary ITP setting (59%). Median age of our whole, primary and secondary ITP cohorts was high and quite similar among groups. Actually, median age of our primary ITP cohort (76 years) is older than median enrollment age of primary ITP clinical trials (e.g. median age of EXTEND trial is 50 years). Given that EXTEND clinical trial obtained 91% of responses, we can conclude that regardless of a higher age, efficacy results of our primary ITP elderly population are consistent with results of clinical trials. We previously reported high response rates in primary ITP regardless of the phase of disease studied (18, 19). Outcome results obtained here were akin when we focused on our elderly population with 94%, 75% and 81% of responses in newly diagnosed, persistent and chronic ITP respectively. Comparable outcome is observed when romiplostim, another TPO agonist, is analyzed. Efficacy results obtained from 3 clinical trials reported effectiveness of the drug in 39

older primary ITP patients with even slightly greater platelet responses in the population aged ≥65 years (23).

In our case series, 4 primary ITP patients suffered from serious brain hemorrhages. All of them were shown to be refractory to eltrombopag. 2 patients were very elderly patients (aged >75 years). 3 patients (one newly diagnosed and two chronic ITP) died, all of them with a platelet count lower than 30 x 10^9/L when bleeding occurred. This finding agrees with the correlation between severe bleeding and a very low platelet count observed in previous studies (21). Similarly, romiplostim has also demonstrated a low risk of grade ≥3 bleeding in adults aged ≥65 years (23). Given that elderly patients with low platelet counts have an increased risk of bleeding (8, 22, 25, 26), great efficacy and low bleeding rates of eltrombopag in our elderly ITP cohort confirm usefulness of the drug, as previously reported by other groups (27).

Frequency of ITP is close to 30% in some diseases (e.g. lymphoid tumors or SLE) (34). However, few publications have been issued to date regarding usefulness of TPO analogs in secondary ITP of the elderly (17). Thus, limited communications point out their success when treating ITP secondary to autoimmune diseases (35) or lymphoproliferative disorders (LPDs) (36) in patients aged ≥65 years. Our efficacy results in secondary ITP show high response rates in immune and infectious ITP with poor results in LPD-ITP. So, quite similar results to those previously reported by our group (29). 6 deaths occurred in this cohort but only 2 were directly related to treatment failure (2 brain haemorrhages in an Evans syndrome and in a CLL patient respectively, both very elderly patients). Therefore, here we demonstrate eltrombopag can also be effective in secondary ITP in elderly situations. This conclusion gets special relevance if we consider secondary ITP is often multirefractory to treatments (37).

48 patients of our whole cohort suffered from AEs during treatment. Similar rates of SAEs (grade 3-4 adverse events) were reported both in primary (15, 37.5%) and secondary (9, 39.1%) ITP groups but 14 (58.3%) of them were observed in very elderly ITP. If we focus on our chronic ITP group we observe 10 (32.2%) SAEs. To note, in EXTEND trial 97 patients (32%) experienced SAEs being headache (86, 28%) and nasopharyngitis (74, 25%) the most frequent (16). By contrast, previous communications communicated fatigue, constipation and cataracts as the more frequent AEs in older patients (33). Here we found 63 AEs (40 in primary ITP cohort and 23 in secondary ITP cohort), with 9 HBLAs and 7 headaches as the main toxicities observed.

Nevertheless, given that it is expected to yield a twofold increase of treatment-related adverse event rate in elderly ITP (21), our study reflects consistent results with prior publications and an acceptable safety profile of eltrombopag, especially if we take into account the high comorbidity rate of any elderly ITP population. Even more when we report here a similar rate of AEs regardless of elderly or very elderly condition.

Thrombotic risk in immune thrombocytopenia is controversial. Some authors find a trend towards elevated thromboembolic rates in ITP (38) specially in patients with comorbidities (39), while others do not (40). Thus, Italian group reports higher thrombosis incidence in the elderly (26). Furthermore, some studies suggest TPO-RA use predisposes to thrombosis (22), while other publications do not find that association (40) even in elderly populations (27). Recently, Wong *et al* (2017) reported EXTEND study results with 19 chronic primary ITP patients (6%) who experienced thrombotic events (16). Likewise, one transient ischemic attack in a CR newly diagnosed ITP is the only thrombotic event we observed in our primary ITP cohort. Michel *et al* (2011) yielded similar results, only 2 suspected pulmonary embolisms, when analyzing their single-center experience with 55 patients aged ≥70 years (21). Unlike this, Olney *et al*, 2011 reported an elevated incidence of thromboembolic events (9%) in patients ≥65 years treated with eltrombopag (33). Risk of venous thrombosis is high in many autoimmune disorders (41). However, low evidence exists about thromboembolic risk in secondary ITP and TPO-RA. In our case series, only 2 secondary ITP patients (one APS male and one CLL-ITP female) experienced a self-limited pulmonary embolism as a side effect of eltrombopag. In fact, risk of thrombosis when receiving TPO analogs still remains on discussion, especially in older patients with high risk for thromboembolic events (32). Our study supports a low thrombotic risk for eltrombopag in elderly ITP.

We noticed that more severe side effects usually affected to our very elderly adult patients. Moreover, majority of deaths of our whole ITP cohort were in aged >75 years ITP. 8 deaths occurred in primary ITP and 6 in secondary ITP. Probably, number of deaths of our case series is relatively high. However, given the elevated age of our population and its high number of comorbidities, we consider safety profile of eltrombopag in this scenario is good and comparable to our previous observations with younger cohorts (18,19,29). Similarly, prior publications confirm low overall survival in the elderly compared to younger patients (26).

The possibility of major selection bias and the retrospective data analysis are the principal limitations of our study. Despite these restrictions, our study demonstrates efficacy and good tolerance of eltrombopag in elderly setting.

In summary, in our daily clinical practice, eltrombopag is effective and safe in unselected patients 65 years old or older with primary ITP. However, efficacy results–of eltrombopag in secondary ITP are quite good for immune and infectious secondary ITP cohorts, but unfortunately its efficacy is low for the neoplastic cohort. On the other hand, many safety corcerns with our secondary ITP population were observed in the neoplastic cohort of the study.

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Table 1. Patient characteristics: whole, primary and secondary ITP cohorts

Table 1. Patient characteristics	**Whole cohort**	**Primary ITP**	**Secondary ITP**	***p* value**
Variable	**Total**	**Total**	**Total**	
	(n = 145)	**(n = 106)**	**(n = 39)**	
Age, years, median [Q_1;Q_3]	76 [70;81]	76 [71;81]	74 [68;78]	0.090
Women (n)	51/94	38 / 68	13/26	0.778
Charlson comorbidity Index > 1, %	23	24	19	0.004
Months with ITP, median [Q_1;Q_3]	30 [4;101]	35 [7;122]	15 [2;55]	0.021
Past ITP treatments, median [Q_1;Q_3]	2 [2;4]	2 [2;4]	2 [2;4]	0.354
Splenectomy, n (%)	25 (17)	18 (17)	7 (18)	0.986
Rituximab, n (%)	32 (22)	20 (19)	12 (31)	0.166
Romiplostim, n (%)	25 (17)	19 (18)	6 (15)	0.635
Platelet count at start of eltrombopag treatment ($x10^9$/L), median [Q_1;Q_3]	14 [8;28]	14 [8;28]	14 [7;28]	0.451
Bleeding at start of eltrombopag treatment, n **(%)**	47 (32)	31 (29)	16(47)	0.056
Concomitant treatment, n (%)	60 (41.4)	32 (30.2)	28 (69.2)	0.000
Corticoids	34 (23.4)	16 (15.1)	18 (46.1)	0.949
Immunoglobulins	10 (6.9)	7 (6.7)	3 (7.7)	0.169
Corticoids plus immunoglobulins	10 (6.9)	6 (5.7)	4 (10.2)	0.336
Chemotherapy	4 (2.75)	1 (1)	3 (5.1)	0.336
Rituximab	1 (0.6)	1 (1)	0 (0)	1.000
Splenic radiotherapy	1 (0.6)	1 (1)	0 (0)	1.000

Table 2. Patient characteristics of primary ITP cohorts: newly diagnosed ITP (A), persistent ITP (B) and chronic ITP (C)

Table 2. Patient characteristics	**Newly diagnosed ITP**	**Persistent ITP**	**Chronic ITP**	***p* value**
Variable	**Total**	**Total**	**Total**	
	(n = 16)	**(n = 16)**	**(n = 74)**	
Age, years, median [Q_1;Q_3]	79 [71;81]	76 [73;85]	76 [71;81]	0,280
Women (n)	6/10	9/7	23/51	0,162
Charlson comorbidity Index > 1, %	43	19	22	0,324
Months with ITP, median [Q_1;Q_3]	1 [0;2]	5 [4;9]	70 [31;184]	0.000
Past ITP treatments, median [Q_1;Q_3]	2 [1;3]	2 [1;2]	3 [2;4]	0.000
Splenectomy, n (%)	1 (6)	0 (0)	17 (23)	0.652
Rituximab, n (%)	2 (12)	1 (6)	17 (23)	0.329
Romiplostim, n (%)	2 (12)	2 (12)	15 (20)	0.415
Platelet count at start of eltrombopag treatment ($x10^9$/L), median [Q_1;Q_3]	11 [6;32]	14 [4;20]	16 [8;32]	0.447
Bleeding at start of eltrombopag treatment, n **(%)**	6 (38)	8 (50)	17 (23)	0.358
Concomitant treatment, n (%)	5 (31.2)	6 (37.5)	21 (28.4)	0.185
Corticoids	2 (12.5)	5 (31.2)	9 (12.2)	0.220
Immunoglobulins	0 (0)	0 (0)	7 (9.4)	0.350
Corticoids plus immunoglobulins	1 (6.25)	1 (6.2)	4 (5.4)	0.159
Rituximab	0 (0)	0 (0)	1 (1.3)	0.305
Chemotherapy	1 (6.25)	0 (0)	0 (0)	0.430
Splenic radiotherapy	1 (6.25)	0 (0)	0 (0)	0.847

Table 3. Patient characteristics: 65-74 yr-old and ≥75 yr-old ITP cohorts

Table 3. Patient characteristics	**65-74 yr-old ITP**	**≥75 yr-old ITP**	***p* value**
Variable	**Total**	**Total**	
	(n =70)	**(n =75)**	
Age, years, median [Q_1;Q_3]	70 [67;73]	81 [78;84]	0.000
Women (n)	29/41	22/53	0.127
Charlson comorbidity Index > 1, %	23	24	0.431
Months with ITP, median [Q_1;Q_3]	40 [6;108]	21 [4;66]	0.108
Past ITP treatments, median [Q_1;Q_3]	2 [2;4]	3 [2;4]	0.976
Splenectomy, n (%)	16 (22.8)	9 (12.0)	0.089
Rituximab, n (%)	18 (25.7)	14 (18.7)	0.322
Romiplostim, n (%)	12 (17.1)	13 (17.3)	0.950
Platelet count at start of eltrombopag treatment ($x10^9$/L), median [Q_1;Q_3]	17 [9;30]	13 [7;24]	0.095
Bleeding at start of eltrombopag treatment, n **(%)**	19 (27.1)	28 (37.3)	0.258
Concomitant treatment, n (%)	23 (32.8)	34 (45.3)	0.141
Corticoids	15 (21.4)	19 (25.3)	0.481
Immunoglobulins	3 (4.3)	7 (9.3)	0.724
Corticoids plus immunoglobulins	4 (5.7)	6 (8.0)	1.000
Chemotherapy	1 (1.4)	3 (4.0)	0.641
Rituximab	1 (1.4)	0 (0)	0.404
Splenic radiotherapy	0 (0)	1 (1.3)	1.000

Table 4. Platelet response: whole, primary and secondary ITP cohorts

Table 4. Platelet Response	**Whole cohort**	**Primary ITP**	**Secondary ITP**	***p* value**
Variable	**Total**	**Total**	**Total**	
	(n = 145)	**(n = 106)**	**(n = 39)**	
Quality of response				
Patients with a platelet response (R), n (%)	110 (75.9)	87 (82)	23 (59)	0.004
Patients with a complete platelet response (CR), n (%)	96 (66.2)	80 (75)	16 (41)	0.052
Number of days to platelet response, median [Q1;Q3]	14 [8;21]	14 [8-21]	12 [9-13]	0.741
Number of days to complete platelet response, median [Q1;Q3]	20 [12;47]	17 [11-45]	25 [14-58]	0.083
Duration of response				
Months with eltrombopag, median [Q1;Q3]	11 [5-18]	12 [5-19]	9 [3-18]	0.648
Platelet response (R) at 3 months, n (%)	97 (66.9)	76 (72)	21 (54)	0.043
Platelet complete response (CR) at 3 months, n (%)	72 (49.6)	62 (58)	10 (26)	0.000
Platelet response (R) at 6 months, n (%)	83 (57.2)	65 (61)	18 (46)	0.102
Platelet complete response (CR) at 6 months, n (%)	57 (39.3)	53 (50)	4 (10.2)	0.074
Days on response, median [Q1;Q3]	320 [147;526]	334 [165;529]	227 [111;648]	0.786
Days on platelet complete response (CR), median [Q1;Q3]	213 [84;398]	247 [104;413]	139 [75;297]	0.197
Treatment failure or relapse				
Rescue treatment, n (%)	26 (17.9)	21 (20)	5 (13)	0.331
Number of patients with treatment failure or relapse	36 (24.8)	22 (20.7)	14 (35.9)	0.205
Treatments after eltrombopag	26 (17.9)	21 (19.8)	5 (12.8)	0.365

Immunoglobulins	16 (11.0)	14 (13.2)	2 (5.1)	0.159
Steroids	4 (2.7)	4 (3.8)	0 (0)	0.252
Romiplostim	1 (0.7)	1 (0.94)	0 (0)	0.353
Rituximab	3 (2.1)	1 (0.94)	2 (5.1)	0.684
Chemotherapy	1 (0.7)	1 (0.94)	0 (0)	0.735
Splenectomy	1 (0.7)	0 (0)	1(2.5)	0.359

Table 5. Platelet response: 65-74 yr-old and ≥75 yr-old ITP cohorts

Table 5. Platelet Response	**65-74 yr-old ITP**	**≥75 yr-old ITP**	***p value***
Variable	**Total**	**Total**	
	(n = 70)	**(n = 75)**	
Quality of response			
Patients with a platelet response (R), n (%)	52 (74.3)	58 (77.3)	0.668
Patients with a complete platelet response (CR), n (%)	51 (72.9)	52 (69.3)	0.640
Number of days to platelet response, median [Q1;Q3]	14 [8-21]	14 [9-21]	0.928
Number of days to complete platelet response, median [Q1;Q3]	19 [13-43]	20 [11-48]	0.719
Duration of response			
Months with eltrombopag, median [Q1;Q3]	9 [6-19]	12 [4-18]	0.909
Platelet response (R) at 3 months, n (%)	46 (65.7)	51 (68.0)	0.770
Platelet complete response (CR) at 3 months, n (%)	35 (50.0)	37 (49.3)	0.936
Platelet response (R) at 6 months, n (%)	41 (58.5)	42 (56.0)	0.754
Platelet complete response (CR) at 6 months, n (%)	34 (48.5)	32 (42.7)	0.476
Days on response, median [Q1;Q3]	274 [175;517]	340 [126;529]	0.870
Days on platelet complete response (CR), median [Q1;Q3]	202 [113;366]	267 [79;416]	0.715
Treatment failure or relapse			
Rescue treatment, n (%)	6 (8.5)	20 (26.7)	0.005

Number of patients with treatment failure or relapse	18 (25.7)	18 (24.0)	0.668
Treatments after eltrombopag			
Immunoglobulins	3 (4.3)	13 (17.3)	0.315
Steroids	0 (0)	4 (5.3)	0.211
Romiplostim	1 (1.4)	0 (0)	0.231
Rituximab	1 (1.4)	2 (2.7)	1.000
Azathiprine	0 (0)	1 (1.3)	0.311
Splenectomy	1 (1.4)	0(0)	0.403

Table 6. Adverse events during eltrombopag treatment: 65-74 yr-old and ≥75 yr-old ITP cohorts

Table 6. Adverse events during eltrombopag treatment	65-74 yr-old ITP	≥75 yr-old ITP
Variable	**n (%)**	**n (%)**
Any adverse event	30 (42.8)	33 (44.0)
Number of grade 3-4 events†	10 (14.3)	14 (18.7)
Brain hemorrhage	2	4
Gastrointestinal bleeding	0	1
Upper respiratory tract infection	1	4
Rash	1	0
Cataract	0	1
Urinary tract infection	0	1
Transient ischemic attack (TIA)	0	1
Hepatobiliary laboratory abnormalities (HBLA)	8	1
Diarrhea	2	4
Headaches	4	3
Sepsis	3	3
Asthenia	1	2
Arthralgia	4	0
Myalgia	2	0
Anorexia	0	1

Abdominal pain	1	1
Neoplasms	1	1
Venous thromboembolism	0	2
Increase of reticulin in bone marrow	0	1
Cardiac insufficiency	0	1
Pancreatitis	0	1

Table 7. Deaths of whole elderly ITP cohort

Table 7. Deaths during eltrombopag treatment	ITP type	ITP subtype	Platelet count	Age	Underlying disease
Cause of death					
Pneumonia	Primary ITP	Newly diagnosed ITP	104	84	Chronic obstructive pulmonary disease
Brain hemorrhage	Primary ITP	Newly diagnosed ITP	7	79	-
Brain hemorrhage	Primary ITP	Chronic ITP	1	73	-
Brain hemorrhage	Primary ITP	Chronic ITP	12	84	-
Gastrointestinal bleeding	Primary ITP	Chronic ITP	42	77	-
Sepsis of respiratory origin	Primary ITP	Chronic ITP	140	78	-
Sepsis of respiratory origin	Primary ITP	Chronic ITP	107	66	-
Splenectomy septic complications	Primary ITP	Chronic ITP	211	68	-
Brain hemorrhage	Secondary ITP	Immune disorders	4	80	Evans syndrome
Acute myeloid leukemia	Secondary ITP	Immune disorders	75	71	SLE
JAK2+ Myelofibrosis	Secondary ITP	Immune disorders	22	78	HCV
Febrile neutropenia	Secondary ITP	Neoplastic condition	24	83	CLL
Sepsis of unknown origin	Secondary ITP	Neoplastic condition	84	74	Waldenstrom macroglobulinemia
Brain hemorrhage	Secondary ITP	Neoplastic condition	53	82	CLL

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Figure 1. Platelet count over time in whole cohort (A), whole primary cohort (B) and whole secondary cohort (C)

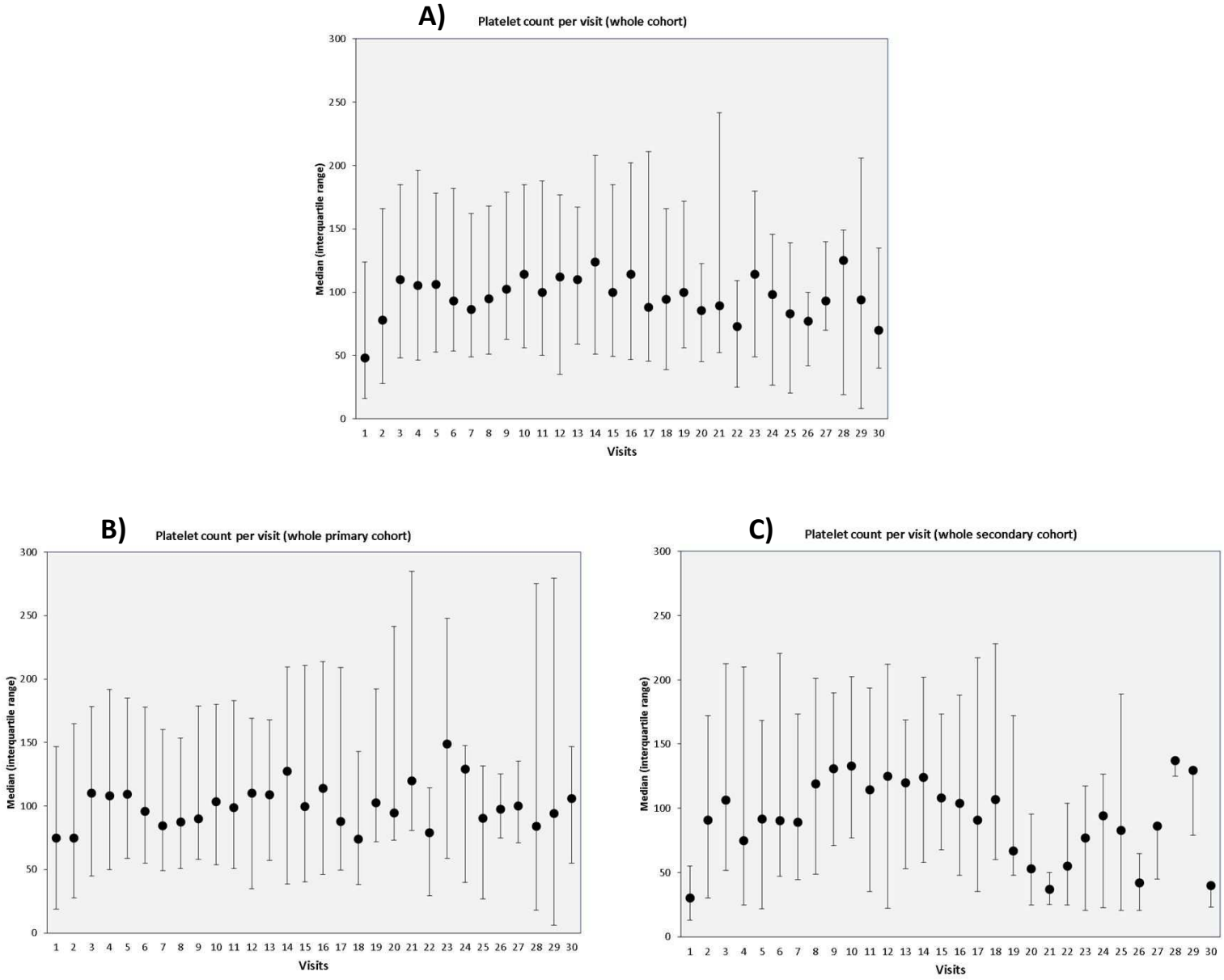

Figure 2. Response (R) and Complete response (CR) rates of 65-74 yr-old ITP and ≥75 yr-old ITP populations.