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Thrombopoietin Receptor Agonists for Severe Thrombocytopenia after Allogeneic Stem Cell Transplantation: Experience of the Spanish Group of Hematopoietic Stem Cell Transplant

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A B S T R A C T

Persistent thrombocytopenia is a common complication after allogeneic hematopoietic stem cell transplantation (allo-SCT). Romiplostim and eltrombopag are the currently available thrombopoietin receptor agonists (TPO-RAs), and some studies with very small numbers of cases have reported their potential efficacy in the allo-SCT setting. The present retrospective study evaluated the safety and efficacy of TPO-RAs in 86 patients with persistent thrombocytopenia after allo-HSCT. Sixteen patients (19%) had isolated thrombocytopenia (PT), and 71 (82%) had secondary failure of platelet recovery (SFPR). TPO-RA therapy was started at a median of 127 days (range, 27 to 1177 days) after allo-SCT. The median initial and maximum administered doses were 50 mg/day (range, 25 to 150 mg/day) and 75 mg/day (range, 25 to 150 mg/day), respectively, for eltrombopag and 1 μg/kg (range, 1 to 7 μg/kg) and 5 μg/kg (range, 1 to 10 μg/kg), respectively, for romiplostin. The median platelet count before initiation of TPO-RA therapy was 14,000/μL (range, 1000 to 57,000/μL). Platelet recovery to $\geq$50,000/μL without transfusion support was achieved in 72% of patients at a median time of 66 days (range, 2 to 247 days). Eighty-one percent of the patients had a decreased number of megakaryocytes before treatment, showing a slower response to therapy (P = .011). The median duration of treatment was 62 days (range, 7 to 700 days). Grade 3-4 adverse events (hepatic and asthenia) were observed in only 2% of the patients. At last follow-up, 81% of patients had discontinued TPO-RAs and maintained response, and 71% were alive. To our knowledge, this is the largest series analyzing the use of TPO-RAs after allo-SCT reported to date. Our results support the efficacy and safety in this new setting. Further prospective trials are needed to increase the level of evidence and to identify predictors of response.

INTRODUCTION

Persistent thrombocytopenia is a common complication after allogeneic hematopoietic stem cell transplantation (allo-SCT) and can lead to increased morbidity and mortality [1]. Underlying

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mechanisms are usually multifactorial but are poorly known [2]. Prolonged isolated thrombocytopenia (PT), defined as persistent thrombocytopenia (<20,000/μL) with normal cell count in the other hematopoietic lines or requirement of platelet transfusion within the first 60 days after allo-SCT, has been described in 5% to 20% of cases [3,4]. It may be caused by antibody-mediated platelet destruction, splenic sequestration, or delayed production due to impaired megakaryocytic differentiation.

The phenomenon of secondary failure of platelet recovery (SFPR) has been defined by the Seattle group as a decline in platelet counts to <20,000/μL for 7 consecutive days or requirement for transfusion after achieving a platelet count ≥50,000/μL without transfusion for 7 days post-SCT. It occurs in an estimated ~20% of allo-SCT recipients [5]. Risk factors for the development of SFPR include hematopoietic stem cell (HSC) dose, donor-recipient HLA disparity, conditioning regimen intensity, immunosuppression, infections, myelotoxic drugs, graft-versus-host disease (GVHD), and other immunologic processes. Treatment options are not well defined and based mostly on platelet transfusion. However, transfusion support is associated with several adverse events, including infusion reactions, platelet refractoriness, acute lung injury, cardiac failure due to volume overload, and viral transmission, which can impose a heavy financial burden. A boost of CD34 cells has also been proposed for patients with poor grant function, many of whom present with severe thrombocytopenia, but this strategy is not always available and carries potential risks. Thus, it is important to identify new strategies to manage this important post-SCT complication.

Romiplostim and eltrombopag are currently available thrombopoietin receptor agonists (TPO-RAs) that stimulate platelet production. Eltrombopag is approved for the treatment of refractory immune thrombocytopenia [6,7] and thrombocytopenia secondary to hepatitis C infection [8]. Recently, it has been associated with multilineage responses in some patients with refractory severe aplastic anemia [9], supporting the idea that it may directly stimulate the few surviving HSCs [10]. Romiplostim is also approved for treating refractory chronic immune thrombocytopenic purpura [11]. Both TPO-RAs have shown promising activity in the treatment of myelodysplastic syndrome-related thrombocytopenia [12,13].

Given the success of TPO-RAs in several scenarios, the use of these agents in the post-transplantation setting for persistent thrombocytopenia has emerged. Some studies with small numbers of cases have reported encouraging results in allo-SCT recipients. For this reason, the present study aimed to analyze the efficacy and safety of TPO-RAs in the largest series of patients with severe and persistent thrombocytopenia after allo-SCT reported to date.

METHODS

Thirteen allo-SCT units from across Spain participated in this study. The median number of patients included from each center was 5 (range, 1 to 19). Pediatric (age <18 years) and adult patients who underwent an allo-SCT between 2009 and 2017 and received TPO-RA therapy (eltrombopag or romiplostim) as compassionate use for severe thrombocytopenia were included. These patients were retrospectively identified using both the transplantation database of each center and information from the Pharmacy Department, to avoid selection bias. Their clinical data were entered into a centralized database.

TPO-RA therapy was initiated according to the clinical criteria at each center. Platelets were transfused in accordance with institutional protocols; clinically stable and afebrile patients received a transfusion when their platelet count dropped to ≤10,000/μL, whereas patients with fever or hemorrhage and unstable patients received a transfusion when their platelet count reached <20,000/μL.

PT was defined as the engraftment of all peripheral blood cell lines but with a platelet count <20,000/μL for 7 consecutive days or the need for transfusion within the first 60 days after allo-SCT [4]. SFPR was defined as a decline in platelet count to <20,000/μL for 7 consecutive days or the need for transfusion after achievement of a platelet count ≥50,000/μL without transfusion for 7 days post-SCT [5]. Patients with severe hemorrhagic complications were included as well.

Some patients had a platelet count >20 000/μL before the initiation of TPO-RA therapy as a result of platelet transfusion. Patients with thrombocytopenia related to primary disease recurrence, detected by immunophenotyping and/or monitoring of chimerism, and those with thrombotic microangiopathy were excluded. This retrospective study was approved by the Ethics Committee of Son Espases University Hospital.

For this study, efficacy of treatment was defined as platelet recovery to ≥50,000/μL without transfusion for 7 consecutive days after initiation of TPO-RA treatment. Time to response, freedom from platelet transfusion, predictors of response, and rate of successful taper of TPO-RAs without recurrence of thrombocytopenia after successful platelet recovery were analyzed. Adverse events were graded using the National Cancer Institute's Common Toxicity Criteria, version 4.0. Clot sections stained with hematoxylin and eosin were used to assess the number of bone marrow megakaryocytes. The number of megakaryocytes was considered normal at 1 per 1 to 3 low-power fields and decreased at 1 per 5 to 10 low-power fields.

Statistical Analysis

Descriptive statistics are used to present the patients' general characteristics. Variables following a binomial distribution (ie, response rate, RR) are expressed as frequency and percentage. Comparisons between qualitative variables were done using Fisher's exact test or the chi-square test. Comparisons between quantitative and qualitative variables were performed using the nonparametric Mann-Whitney *U*or Kruskal-Wallis test. Time-to-event variables were measured from the date of therapy onset and estimated

Table 1
Patient and Allo-SCT Characteristics

Characteristic	Value
Number of patients	86
Age, yr, median (range)	53 (8-74)
Sex, male/female, n (%)	50 (58)/36 (42)
Disease, n (%)	
Myelodysplastic syndrome	6 (7)
Acute myelogenous leukemia	33 (38)
Acute lymphoblastic leukemia	12 (14)
Non-Hodgkin lymphoma	16 (19)
Hodgkin lymphoma	4 (5)
Aplastic anemia	5 (5)
Others	11 (13)
Donor type, n (%)	
HLA-identical sibling	21 (24)
Unrelated	28 (33)
Haploidentical	32 (37)
Cord blood/haploidentical cord	5 (6)
Pre-SCT status, n (%)	
Complete remission	55 (64)
Partial remission	9 (10)
Active disease	22 (26)
$CD34^+$ cell dose, cells × 10^6/kg, median (range)	5 (0.6-11.8)
Stem cell source, n (%)	
Peripheral blood	74 (86)
Bone marrow	6 (7)
Cord blood	6 (7)
Conditioning regimen, n (%)	
Myeloablative	34 (39)
Reduced intensity	52 (60)
GVHD prophylaxis, n (%)	
Methotrexate + cyclosporine or tacrolimus	13 (15)
Mycophenolate mofetil + cyclosporine or tacrolimus	10 (12)
Tacrolimus + sirolimus	9 (10)
Post-SCT cyclophosphamide	35 (41)
Antithymocyte globulin/alemtuzumab-based prophylaxis	19 (22)

according to the Kaplan-Meier method. Comparisons between the variables of interest were performed using the log-rank test. All reported *P*values are 2-sided, and statistical significance was defined at $P < .05$.

RESULTS

Patient Characteristics

Baseline patient and transplantation characteristics of the 86 cases included in this study are presented in Table 1. The median patient age was 53 years (range, 8 to 74 years). Indications for allo-SCT were acute myelogenous leukemia in 33 patients (38%), myelodysplastic syndrome (n = 7; 7%), acute lymphoblastic leukemia in 12 patients (14%), non-Hodgkin lymphoma in 16 patients (19%), Hodgkin lymphoma in 4 patients (5%), aplastic anemia in 5 patients (5%), and other hematologic malignancies in 11 patients (13%). The median $CD34^+$ cell dose was 5×10^6/kg (range, .6 to 11.8×10^6/kg). Allo-SCT was performed using a related donor in 21 patients (24%), an unrelated donor in 28 patients (33%), a haploidentical donor in 32 patients (37%), and cord blood or a haplo-cord donor in 5 patients (6%). Fifty-five patients (64%) were in complete remission before allo-SCT, 9 (10%) were in partial remission, and 22 (26%) had active disease. Stem cells were collected from peripheral blood in 74 patients (86%), from bone marrow in 6 patients (7%) and from cord blood in 6 patients (7%). Sixteen patients (19%) had PT and 71 (82%) had SFPR. Before starting TPO-RA therapy, 7% of the patients had acute GVHD, 18% had cytomegalovirus infection, 25% had other infections, and 25% of the patients had received myelotoxic drugs at therapeutic doses (19% with valganciclovir or ganciclovir, 50% with valganciclovir or ganciclovir and sulfamethoxazole-trimethoprim, and 31% with other drugs). The median duration of follow-up after initiation of TPO-RA therapy was 10 months (range, 1 to 59 months).

Treatment Characteristics

The median platelet count before initiation of TPO-RAs was 14,000/μL (range, 1000 to 57,000 /μL), median neutrophil count was 1740/μL (range, 0 to 13,900/μL), and median hemoglobin concentration was 9.7 g/dL (range, 6.4 to 13.5 g/dL). Eltrombopag was used in 51 patients (59%), and romiplostim was used in 35 patients (41%). The median starting and maximum doses for eltrombopag were 50 mg/day (range, 25 to 150 mg/day) and 75 mg/day (range, 25 to 150 mg/day), respectively and the median starting and maximum doses for romiplostim were 1 μg/kg/week (range, 1 to 7 μg/kg/week) and 5 μg/kg/week (range, 1 to 10 μg/kg/week). TPO-RAs were started at a median of 127 days (range, 27 to 1177 days) after allo-SCT. There were no differences between the 2 TPO-RAs at the time of initiation ($P = .41$), and no differences by type of thrombocytopenia at the time of initiation, 78 days for PT and 155 days for SFPR ($P = .37$). The median time from a platelet count of $<$20,000/μ/L to the start of TPO-RAs was 32 days (range, 0 to 1016 days). Eighteen patients (21%) were previously treated with cell infusion (67% with mesenchymal cells and 33% with $CD34^+$cell boost). In addition, 78% of the patients with

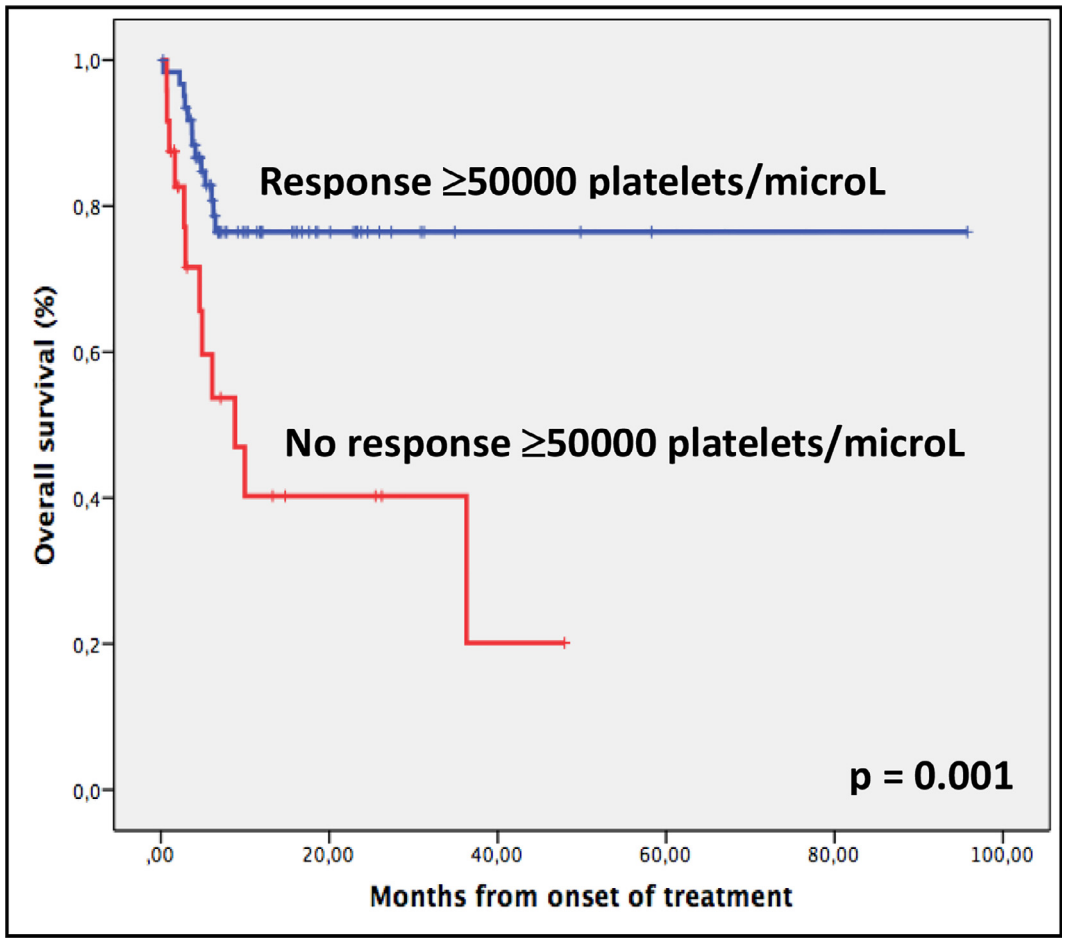

Figure 1. Overall survival of all series depending on TPO-RAs response.

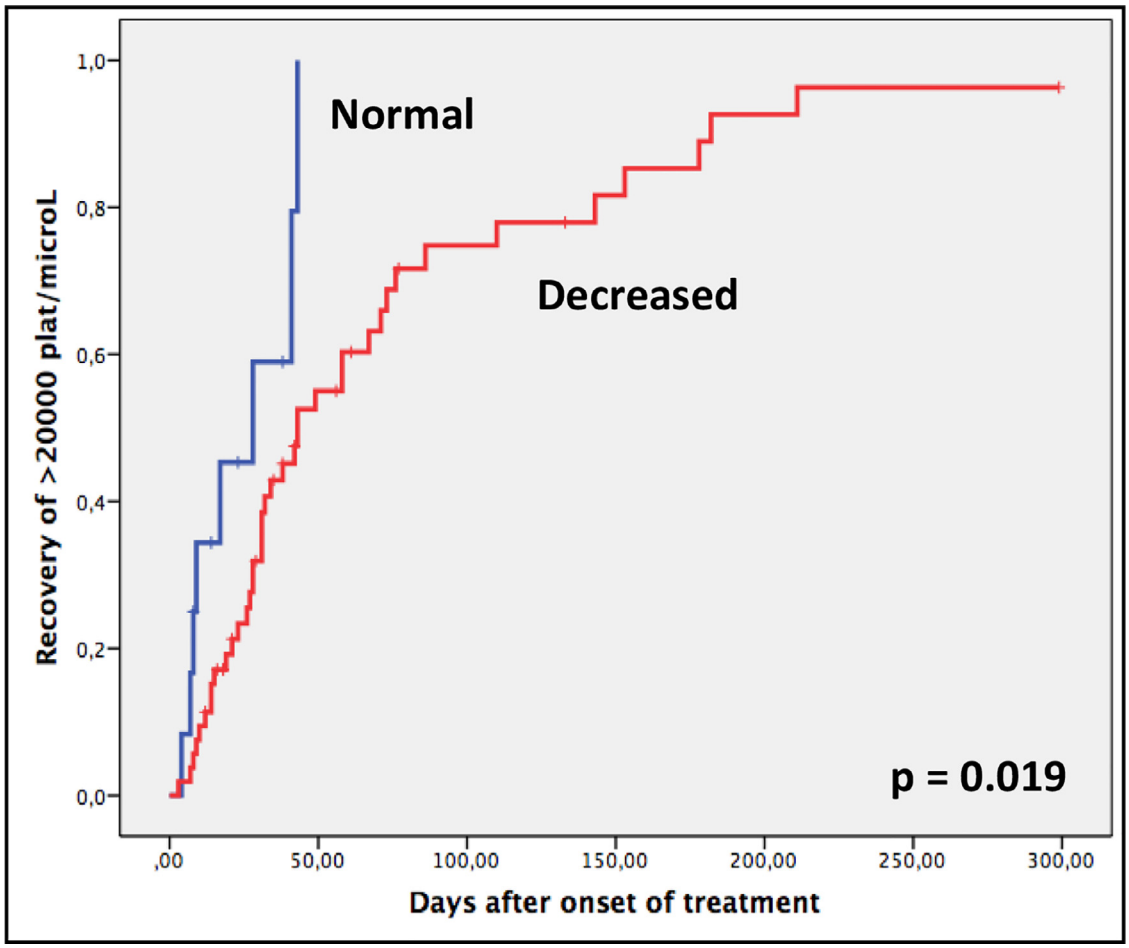

Figure 2. Time to response with ≥20,000/μL platelet recovery depending on number of megacaryocytes before starting TPO-RAs.

concomitant neutropenia had received granulocyte colony-stimulating factor before starting TPO-RA treatment, with 74% showing neutrophil responses, and 52% of the patients with anemia had received erythropoietin (EPO) before starting TPO-Ras, with 62% showing hemoglobin responses.

Efficay of TPO-RAs

The overall response rate (ORR) for platelet recovery ≥50,000/μL was 72%, including 73% in the SFPR group and 67% in the PT group (*P* not significant). The response was achieved at a median time of 66 days (range, 2 to 247 days) after TPO-RA initiation. The patients with PT required more time to response compared with those with SFPR (median, 93 days [range, 8 to 217 days] versus 60 days [range, 2 to 247 days]). Also, the median time from initiation of TPO-RAs to the last transfusion was 37 days (range, 0 to 298 days), including 33 days (range, 0 to 298 days) for the SFPR group and 69 days (range, 14 to 188 days) for the PT group. On the other hand, 22 patients (25%) had a neutrophil count <1000/μL before initiation of TPO-RAs, and 17 (77%) achieved a count ≥1000/μL after therapy. Regarding erythroid lineage, 10 patients (12%) had a hemoglobin concentration <8 g/dL before TPO-RA therapy, and 5 (50%) achieved ≥8 g/dL after therapy.

The median duration of TPO-RA therapy was 62 days (range, 7 to 700 days). No differences in duration of treatment by type of thrombocytopenia were observed. However, the median duration was shorter in nonresponders than in responder-patients: 32 days (range, 7 to 299 days) versus 97 days (range, 7 to 700 days) (*P* = .001). At the last follow-up, 63% of the patients had a neutrophil count ≥50,000/μL, and 81% discontinued TPO-RAs, maintaining response. Sixty-one patients (71%) were alive. Mortality was significantly lower in responders to TPO-RAs compared with nonresponders (15% versus 53%; *P* < .001) (Figure 1). Causes of death were disease progression in 28%, infections in 48%, GVHD in 16%, and other causes in 8%.

Predictors of Response

No differences in response rate were observed based on type of thrombocytopenia (*P* not significant). Donor type and GVHD prophylaxis did not influence in response (*P* not significant). Likewise, age and previous response to other growth factors, such as EPO or granulocyte colony-stimulating factor, did not affect response. Seventy patients (81%) had a decreased number of megakaryocytes before treatment and showed a slower response to therapy, with a median time to achieving a platelet count >20,000/μL of 43 days (range, 25 to 61 days) versus 28 days (range, 3 to 53 days) in patients with a normal number of megakaryocytes (*P* = .019) (Figure 2). No difference in the median time to platelet recovery of ≥50,000/μL was observed between patients with a normal number of megakaryocytes and those with decreased megakaryocytes in the total series (*P* not significant); however, in the SFPR group, faster responses were observed in patients with a normal number of megakaryocytes (*P* = .016) (Figure 3).

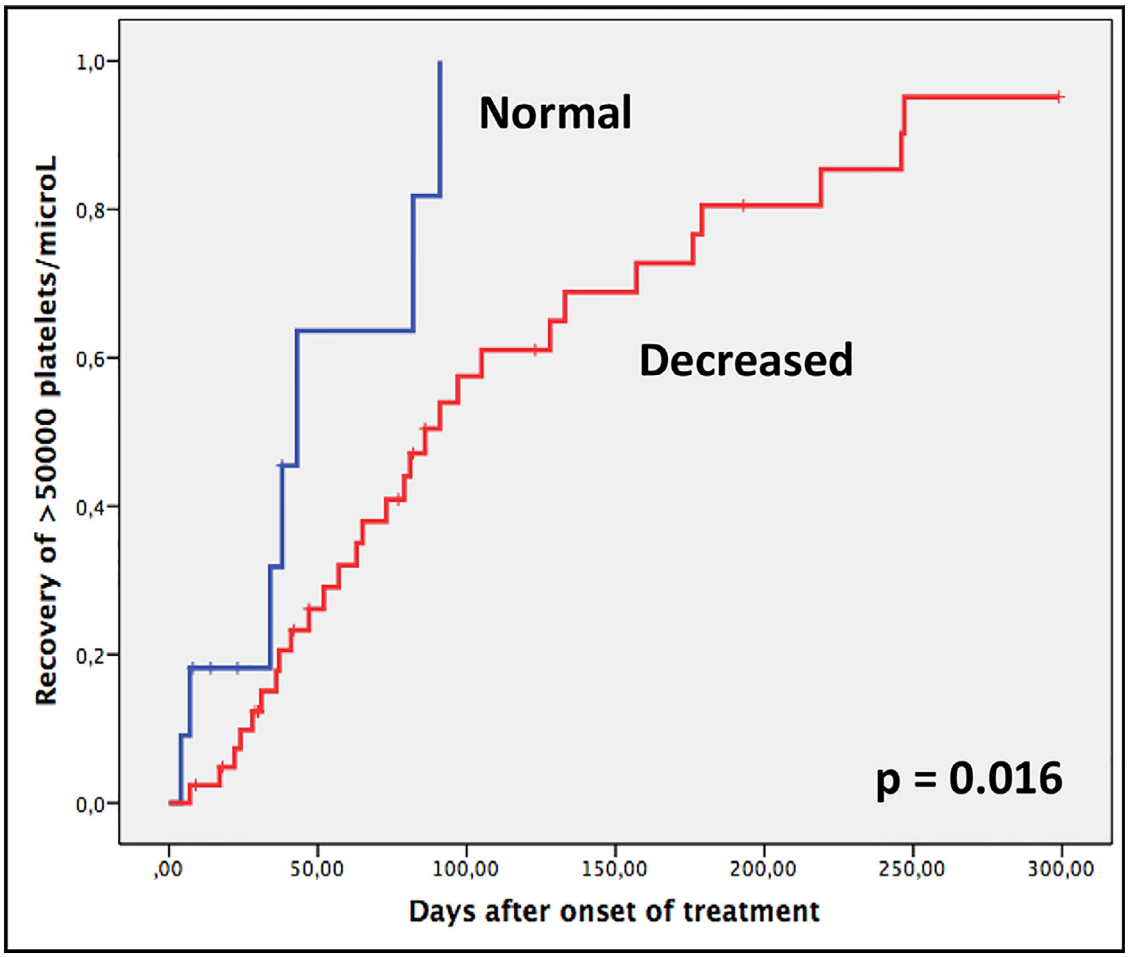

Figure 3. Time to response with ≥50,000/μL platelet recovery depending on number of megacaryocytes in the SFPR group.

Adverse Effects after TPO-RA Treatment

The TPO-RAs were well tolerated, and no patients discontinued treatment because of adverse events. Grade 3-4 liver abnormalities and fatigue were observed in only 2% of patients. No patients developed thrombosis or other grade 3-4 toxicities, and no patients relapsed while receiving TPO-RA treatment.

DISCUSSION

In this study, the largest series analyzing the use of TPO-RAs after allo-SCT reported to date, our results support the efficacy and safety in this setting with an overall response rate (ORR) of 72% and few side effects. In addition, 81% of patients managed to discontinue TPO-RA treatment.

To date, 17 retrospective studies analyzed the potential benefits of TPO-RAs in this setting, most of them with a small number of cases (Table 2) [14–30]. In addition, there are currently 7 registered ongoing clinical trials with similar scenarios (www.clinicaltrials.gov). Data from clinical trials are not available, with the exception of a preliminary report from a phase II placebo-controlled randomized trial [31]. In that study, which enrolled 53 allo-SCT recipients and 7 autologous SCT recipients with persistent thrombocytopenia or neutropenia treated with eltrombopag, the response rate in the experimental arm was 36%, but results were statistically inconclusive in terms of superiority compared with the 28% response rate in the control arm. That randomized study differs from ours in several areas. First, it included 7 patients who received an autograft, whereas ours included only allografts. In addition, 38% of their patients received bone marrow instead of peripheral blood, whereas in our study, only 7% of the patients received bone marrow. These differences might have had some effect on the differing response rate in the 2 studies. Although retrospective data are at risk of bias, and we agree that the best design is a prospective study, we included all consecutive patients from each center who had received TPO-RAs after allo-SCT in an attempt to avoid any kind of selection bias.

Fu et al [22] recently reported the experience of eltrombopag in 38 patients after haploidentical SCT. Eight patients had delayed platelet engraftment, 15 patients had SFPR, and 15 patients had poor graft function. Twenty-four patients responded to eltrombopag treatment, and the cumulative incidence of overall response was 63.2%, similar to our results. Similar results with a low number of cases (n = 13) were recently published by Yuan et al [21], with an ORR of 62%. However, Fu et al reported a shorter median time to response of 17 days (range, 2 to 89 days), compared with 66 days (range, 2 to 247 days) in our cohort. Our data also confirm that PT required more time to response compared with SFPR, 93 days (range, 8 to 217 days) versus 60 days (range, 2 to 247 days). During treatment, 5 patients (13.2%) developed liver injury, with elevated transaminases >2.5 times normal values or bilirubin twice the normal level, but no patient discontinued eltrombopag because of adverse events or intolerability, the same as in our case series.

Hartranft et al [16] published the largest study on the use of romiplostim, comprising 13 patients with SFPR and PT, until

Table 2
Experience with TPO-RAs for Persistent Thrombocytopenia in the Allo-SCT Setting

Thrombocytopenia Type	N	TPO-RAs	Transfusion Independence	Response Rate, Platelets $\geq 50 \times 10^9$/L, n/N (%)	Reference
SFPR	1	Romiplostim	Yes	1/1 (100)	Beck et al, 2010 [14]
SFPR	7	Romiplostim	Yes	7/7 (100)	Calmettes et al, 2011 [15]
PT	1	Eltrombopag	Yes	NR	Reid et al, 2012 [23]
SFPR	1	Romiplostim	Yes	1/1 (100)	Bollag et al, 2012 [24]
PT, SFPR	3	Romiplostim	Yes	3/3 (100)	Poon et a, 2013 [25]
SFPR	1	Romiplostim	No	NR	DeRemer et al, 2013 [26]
SFPR	1	Romiplostim	Yes	1/1 (100)	Buchbinder et al, 2015 [27]
PT	1	Eltrombopag	Yes	1/1 (100)	Fujimi et al, 2015 [28]
SFPR	7	Romiplostim	Yes (n = 6)	6/7 (86)	Maximova et al, 2015 [29]
SFPR	3	Romiplostim	Yes	3/3 (100)	Battipaglia et al, 2015 [30]
PT, SFPR	13	Romiplostim	Yes (n = 7)	7/13 (54)	Hartranft et al, 2015 [16]
PT, SFPR	12	Eltrombopag	Yes (n = 9)	9/12 (75)	Tanaka et al, 2016 [17]
PT, SFPR	20	Eltrombopag Romiplostim	Yes (n = 12)	12/20 (60)	Bosch-Vilaseca et al, 2018 [18]
PT, SFPR	14	Eltrombopag	Yes	8/14 (57)	Rivera et al, 2108 [19]
PT, SFPR	13	Eltrombopag	Yes	7/13 (54)	Marotta et al, 2018 [20]
PT, SFPR	13	Eltrombopag	Yes (n = 8)	8/13 (62)	Yuan et al, 2019 [21]
PT, SFPR	38	Eltrombopag	Yes (n = 24)	24/38 (63)	Fu et al, 2019 [22]

now. In that case series, 54% of patients achieved the primary endpoint of a platelet count $\geq$50,000/μL at a median of 35 days (range, 14 to 56 days) after initiation of TPO-RAs. The time to response was shorter than in our series, although the response rate was lower.

In our study, 81% of the patients had a decreased number of megakaryocytes before treatment and showed a slower response to therapy (median time to $\geq$20,000/μL platelets, 43 days versus 28 days; P= .019). Tanaka et al [17] reported a series of 12 patients treated with eltrombopag, with a faster and higher rate of platelet recovery in patients with a normal number of megakaryocytes before starting treatment compared with patients with decreased megakaryocytes. These results suggest that the number of megakaryocytes in bone marrow may better predict the response to TPO-RAs than type of thrombocytopenia after allo-SCT.

Eltrombopag induces differentiation of $CD34^+$ hematopoietic precursor cells into committed $CD41^+$ megakaryocyte progenitor cells and stimulates the proliferation of megakaryocyte progenitor cells [32]. On the other hand, this synthetic small-molecule thrombopoietin agonist stimulates c-MPL receptors and can improve hematopoiesis at the level of primitive cells (platelet, erythroid and neutrophil lineages) [9,33,34]. In contrast to eltrombopag, the use of which has been shown to induce a multilineage response in refractory aplastic anemia [9,35], there are little published data on the effect of romiplostim in multilineage responses [36]. Scant data are available to explain such differences, since both agonists activate the same molecular pathways. In our study, 22 of 86 patients (25%) had <1000/μL neutrophils before TPO-RA therapy, and 17 of 22 (77%) achieved $\geq$1000/μL after therapy. Regarding erythroid lineage, 10 patients (12%) had hemoglobin <8 g/dL before TPO-RA therapy and 5 (50%) achieved $\geq$8 g/dL after therapy. However, in all these patients, we could not rule out the possibility that the hematologic response was due at least in part to some improvement or resolution of the possible causes underlying the development of cytopenia as infections or GVHD.

Death rate was significantly lower in responders to TPO-RAs, 15% versus 53% in nonresponders ($P < .001$). This confirms that refractory thrombocytopenia is an adverse prognostic factor for survival in allo-SCT setting and likely a surrogate marker of defective hematopoiesis or an altered immune system.

Nonetheless, the present study has several limitations. First, this was a retrospective study, which may have influenced the uncertainty about effect size—response rate in this case. Second, although this study had the largest number of patients of any study reported to date, the cohort size is still small. Ultimately, there was no untreated control population against which to better measure the impact of TPO-RAs.

In conclusion, to our knowledge this is the largest series analyzing the use of TPO-RAs after allo-SCT reported to date. Our results support the efficacy and safety in this new setting with an ORR of 72% and few side effects. Further prospective trials are needed to increase the level of evidence and to identify predictors of response.

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