A 2-Year, Longitudinal, Prospective Study of the Effects of Eltrombopag on Bone Marrow in Patients with Chronic Immune Thrombocytopenia

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Keywords

Bone marrow · Chronic immune thrombocytopenia ·
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Abstract

Background: The long-term effects of eltrombopag on bone marrow (BM) reticulin and/or collagen deposition in previously treated adults with chronic immune thrombocytopenia (ITP) were assessed. **Methods:** Three BM biopsies were collected at baseline and after 1 and 2 years of eltrombopag treatment. Specimens were centrally processed, stained for reticulin and collagen, independently reviewed by 2 hematopathologists, and rated according to the European Consensus 0–3 scale of marrow fibrosis (MF). **Results:** Of 162 patients enrolled, 93 completed all 3 protocol-specified BM biopsies. All patients with a baseline assessment were negative for collagen. Of 159 patients assessed at baseline, 150 (94%) had normal reticulin (MF-0) and 9 (6%) had minimally increased reticulin (MF-1). After 2 years, 83/93 patients (89%) with BM biopsies had MF-0, 10 (11%) had MF-1, and none had MF-2 or MF-3. Five out of 127 patients (4%) at 1 year and 1 out of 93 (1%) at 2 years had collagen deposition. None of the patients had clinical symptoms typical of BM dysfunction

or abnormalities of clinical concern based on white blood cell count or peripheral blood smear. **Conclusion:** For most patients with chronic ITP, eltrombopag is not associated with clinically relevant increases in BM reticulin or collagen formation.

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Introduction

The acquired disorder immune thrombocytopenia (ITP) results in low platelet counts due to an increase in platelet clearance [1], as well as an inhibition of megakaryocyte platelet release [2]. Mild reticulin has been shown to be present in the bone marrow (BM) of approximately 27–31% of hematologically normal patients [3, 4] and 28–52% of patients diagnosed with primary ITP [5, 6].

Eltrombopag, an oral nonpeptide thrombopoietin receptor agonist (TPO-RA), increases platelet counts in patients with chronic ITP [7–10]. However, TPO-RAs have

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been associated with increases in reticulin fibers in the BM [11–13]. Whether the risk of BM fibrosis is due to the TPO-RAs themselves or to the underlying disease remains unclear. While BM biopsies can detect an increase in reticulin deposition in the BM, they are not routinely performed in the management of patients with chronic ITP. Although some studies have retrospectively reviewed biopsy specimens, prospectively collected data in patients with chronic ITP are limited. Additionally, inconsistencies in specimen preparation, staining, and pathologic analysis across institutions in previous studies have further confounded conclusions.

The purpose of this study was to prospectively investigate the potential effects of eltrombopag on the BM. Specifically, the study was designed to characterize any change in BM fibrosis in patients with previously treated persistent/chronic ITP from baseline to 1 and 2 years after initiating treatment with eltrombopag.

Methods

Study Design

This phase IV, open-label safety study was conducted at 28 centers in 11 countries from May 6, 2010, to May 6, 2014. The study was conducted according to the principles set forth in the 2008 Declaration of Helsinki. Written informed consent was obtained from each patient prior to the performance of any study-specific procedures. The study protocol was reviewed and approved by national, regional, or investigational center ethics committees or institutional review boards as appropriate. The primary objective was to assess the levels of BM reticulin and/or collagen fibers at baseline and to detect any changes after 1 and 2 years of treatment with eltrombopag in adult patients with persistent/chronic ITP. The secondary objective was the long-term safety and tolerability of oral eltrombopag treatment in patients with persistent/chronic ITP.

Eligibility

Adult patients with a diagnosis of persistent ITP (for ≥ 6 months) or chronic ITP (for ≥ 12 months) based on the American Society of Hematology/British Committee for Standards in Haematology guidelines [14–16], with no evidence of other disease that could cause thrombocytopenia, were eligible for study inclusion. Patients who had previously received eltrombopag or romiplostim must have completed treatment with these agents ≥ 6 months before the screening BM biopsy. Patients treated with any other TPO-RA were not eligible. Patients were not eligible if their baseline BM biopsy had a marrow fibrosis (MF) reticulin grade of MF-3 (the highest grade according to the European Consensus scale) [17].

Enrollment and Treatment

The enrollment of patients previously exposed to a TPO-RA was limited to no more than 20% of the total study population. The duration of the screening period was up to 8 weeks. Eltrombopag

Table 1. AEs leading to discontinuation ($n = 162$)

Event	<i>n</i> (%)
Increased ALT level	3 (2)
Toxic hepatitis	2 (1)
Cerebral hemorrhage	2 (1)
Increased blood bilirubin	2 (1)
Hepatitis	1 (1)
Acute hepatitis	1 (1)
Hepatosplenomegaly	1 (1)
Cerebral venous thrombosis	1 (1)
Transient ischemic attack	1 (1)
Increased AST level	1 (1)
Acute respiratory distress syndrome	1 (1)
Cough	1 (1)
Pulmonary embolism	1 (1)
Gastrointestinal hemorrhage	1 (1)
Gingival bleeding	1 (1)
Nausea	1 (1)
Vomiting	1 (1)
Cardiovascular disorder	1 (1)
Vertigo	1 (1)
Chest pain	1 (1)
Myalgia	1 (1)
T cell lymphoma	1 (1)
Deep vein thrombosis	1 (1)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

was administered for 2 years (± 8 weeks) followed by a 4-week follow-up period. The total study duration was up to 116 weeks. The starting dose of eltrombopag was 50 mg/day, or 25 mg/day for patients of East Asian ancestry. The dosing regimen of eltrombopag was then adjusted to a lower dose or a maximum dose of 75 mg for each patient to maintain platelet counts within the clinically indicated range.

Specimen Collection and Analysis

Biopsy specimens were collected at baseline (before treatment) and after 1 and 2 years of treatment with eltrombopag, or at early withdrawal of treatment if the patient withdrew > 3 months after the last BM biopsy. Fresh trephine biopsy was used for all assessments with the exception of the screening biopsy, which used paraffin block, if available. An independent central laboratory processed and stained the BM biopsies with hematoxylin and eosin, and for reticulin (Gordon and Sweet method) and collagen (Masson trichrome) to reduce preanalytical variation. Two hematopathologists (R.K.B. and A.O.) independently conducted the morphology review and assessed specimens for cellularity, megakaryocyte, erythroid, and myeloid quantity and appearance, trabecular bone quality, reticulin grade (MF-0 through MF-3) [17], and the presence of collagen. Differences in scoring were reconciled by review and discussion.

Table 2. Patients with BM biopsies graded $\geq$ MF-2 during the study

Patient No.	Sex and race	Age, years	Study day: MF grade	Presence of collagen	Eltrombopag modal dose, mg	Discontinued study (yes/no) and reason
1	Female; South/Central Asian	48	Day -35: MF-1 Day 310: MF-2	Negative Negative	75	Yes; lack of efficacy
2	Female; South/Central Asian	25	Day -80: MF-0 Day 399: MF-2 Day 568: MF-0	Negative Negative Negative	75	Yes; increased ALT
3	Female; East Asian	29	Day -21: MF-0 Day 334: MF-3 Day 516: MF-0	Negative Positive Negative	75	Yes; patient decision
4	Female; East Asian	18	Day -23: MF-0 Day 365: MF-3 Day 396: MF-0 Day 732: MF-0	Negative Positive Negative Negative	50	No
5	Female; South/Central Asian	48	Day -33: MF-0 Day 393: MF-2 Day 720: MF-2 ^a Day 1,016: MF-0 ^b	Negative Positive Positive Negative	75	No

BM, bone marrow; ALT, alanine aminotransferase; MF, marrow fibrosis.

^a Biopsy performed 22 days posttreatment. ^b Biopsy performed 288 days posttreatment.

Results

Patient Disposition

Of 186 patients screened, 167 were enrolled and received at least 1 dose of the study drug. Five patients from one center were excluded due to protocol/Good Clinical Practices violations. Of the 162 remaining patients, 118 (73%) completed the study and 113 (70%) completed >22 months of treatment with eltrombopag. Of the 48/162 (30%) patients who discontinued eltrombopag, 22 (14%) discontinued due to adverse events (AEs), 11 (7%) due to lack of efficacy, 7 (4%) due to investigator discretion, and 8 (5%) due to patient decision.

Of the AEs leading to discontinuation, only increased alanine aminotransferase (ALT) levels ($n = 3$), toxic hepatitis ($n = 2$), cerebral hemorrhage ($n = 2$), and increased blood bilirubin ($n = 2$) occurred in more than 1 patient each (Table 1). Information on the completion status was not available for 1 ($<1\%$) patient.

Three patients who discontinued eltrombopag had increased reticulon formation at the time of discontinuation (Table 2). A biopsy from patient 1, who discontinued due to lack of efficacy, was graded MF-2 with no collagen. She had no AEs related to BM function, although there was no subsequent biopsy performed. Patient 2, who discontinued on day 525 because of an ALT level that was more than 5 times the upper limit of normal, had a biopsy grad-

ed MF-2; a biopsy on day 568 showed MF-1. Finally, a biopsy was graded MF-3 with the presence of collagen for patient 3, who discontinued treatment because she wanted to become pregnant. The follow-up biopsy 182 days later, on day 516, was graded MF-0 and negative for collagen. Biopsies from the remaining 2 patients with findings of MF-2/MF-3 and collagen who were not withdrawn from the study are also shown in Table 2.

Demographics and Baseline Characteristics

Demographic and baseline characteristics of the 162 patients are summarized in Table 3. The majority of patients (63%) were between 18 and 49 years old, and the median age was 42 years (range 18–80). The overall study population comprised 50% Caucasian and 49% Asian patients (20% East Asian, 29% Central/South Asian), and 1% had missing ethnicity data. A total of 155 patients (96%) had an ITP diagnosis for ≥ 6 months, and 124 (77%) had an ITP diagnosis for ≥ 12 months at baseline. A total of 114 patients (70%) had received prior therapy for ITP, and 93 (57%) were receiving ITP medication at baseline. Thirteen patients (8%) had prior exposure to a TPO-RA, of whom 7 received eltrombopag and 4 received romiplostim ≥ 6 months before enrollment. Approximately three quarters (76%) of the patients had a baseline platelet count of $\leq 50 \times 10^9/L$, and 23% of patients were splenectomized.

Table 3. Patient demographics and baseline characteristics (*n* = 162)

Median age, years (range)	42.0 (18–80)
Female, <i>n</i> (%)	104 (64)
Ethnicity, <i>n</i> (%)	
Caucasian	81 (50)
East Asian	33 (20)
Central/South Asian	47 (29)
Splenectomized, <i>n</i> (%)	37 (23)
≥12 months since ITP diagnosis, <i>n</i> (%)	124 (77)
Platelet counts, <i>n</i> (%)	
<15 × 10 ⁹ /L	59 (36)
15 to <30 × 10 ⁹ /L	34 (21)
30 to 50 × 10 ⁹ /L	31 (19)
>50 × 10 ⁹ /L	38 (23)

ITP, immune thrombocytopenia.

Table 4. Baseline and 2-year comparison of BM fibrosis grade in patients who all had 3 protocol-defined biopsies (*n* = 93)

Baseline grade	2-year grade, <i>n</i> (%)				total
	MF-0	MF-1	MF-2	MF-3	
MF-0	79 (85)	9 (10)	0	0	88 (95)
MF-1	2 (2)	1 (1)	0	0	3 (3)
MF-2	0	0	0	0	0
MF-3	0	0	0	0	0
Missing	2 (2)	0	0	0	2 (2)
Total	83 (89)	10 (11)	0	0	93 (100)

BM, bone marrow; MF, marrow fibrosis.

Treatment

The median daily dose of eltrombopag was 49.7 mg (range 5–75 mg), and the median time on treatment was 104 weeks (range 2.4–113 weeks). The majority of patients (61%) completed at least 24 months of eltrombopag treatment, and 73% completed more than 18 months of treatment.

Analysis of BM Biopsies

Baseline BM biopsies for 3 patients were not assessable, 2 because the sample was inadequate and 1 because of a procedural error. These patients were not included in the BM analysis. Of the 159 patients assessed at baseline, 150 (94%) had MF-0 and 9 (6%) had MF-1 (Fig. 1). No baseline biopsies were positive for collagen. Most patients' (96%) on-treatment biopsies were normal or had

Fig. 1. Reticulin level at baseline and the 1- and 2-year assessments. MF grades at baseline and each on-treatment time interval were recorded using the European Consensus scale. On-treatment biopsies, performed within 14 days of the last dose of study medication, were categorized as 1 year if assessed between 10 and 22 months, and 2 years if assessed at ≥22 months after treatment initiation.

minimally increased reticulin (graded as either MF-0 or MF-1, respectively).

Overall, 127 patients completed the baseline and 1-year BM biopsies, and 93 patients completed all 3 BM biopsies (i.e., baseline and 1 and 2 years). At 1 year (*n* = 127), biopsies of 87 patients (69%) had a grade of MF-0, 35 (28%) had MF-1, 3 (2%) had MF-2, and 2 (2%) had MF-3 (Fig. 1). At 2 years (*n* = 93), 83 patients (89%) had a grade of MF-0, 10 (11%) had MF-1, and no patients had MF-2 or MF-3. Biopsies of 5 patients (4%) at 1 year and 1 patient (1%) at 2 years were positive for collagen.

Eight patients had either ≥MF-2 only (*n* = 2), the presence of collagen only (*n* = 3), or both (*n* = 3; Table 2). None of these patients had clinical symptoms typical of BM dysfunction or abnormalities of clinical concern reported in the white blood cell count or peripheral blood smear.

During the first year, 2 patients (2%) had shifts from MF-0 to MF-2, and 2 patients (2%) had shifts from MF-0 to MF-3. There was also 1 patient (<1%) with a shift from MF-1 to MF-2. One patient was graded as MF-2 at 1 year and remained at MF-2 at the posttreatment day 22 assessment. One patient was graded as MF-3 at 1 year, but an on-treatment biopsy 1 month later was graded as MF-0, as was a biopsy at 2 years.

Table 5. Lineage-specific BM biopsy analysis at baseline and the 1- and 2-year assessments

	Megakaryocytic			Myeloid			Erythroid		
	BL	1 year	2 years	BL	1 year	2 years	BL	1 year	2 years
Quantity, <i>n</i> (%)	157	126	92	157	126	93	157	126	93
Normal	12 (8)	2 (2)	2 (2)	140 (89)	98 (78)	75 (81)	140 (89)	112 (89)	82 (88)
Increased	143 (91)	124 (98)	90 (98)	15 (10)	27 (21)	17 (18)	15 (10)	13 (10)	11 (12)
Decreased	2 (1)	0	0	2 (1)	1 (<1)	1 (1)	2 (1)	1 (<1)	0
Quality, <i>n</i> (%)	157	121	92	157	126	93	157	126	93
Normal maturation	153 (97)	120 (99)	88 (96)	156 (>99)	124 (98)	87 (94)	156 (>99)	125 (>99)	93 (100)
Left shift	4 (3)	1 (<1)	4 (4)	1 (<1)	2 (2)	6 (6)	1 (<1)	1 (<1)	0

BM, bone marrow; BL, baseline; *n*, number of patients with data available.

Table 6. Comparison of cellularity, trabecular bone quality, and collagen at baseline and the 1- and 2-year assessments

	Baseline	1 year	2 years
Cellularity, <i>n</i> (%)	141	127	94
Markedly hypocellular ($\leq 20\%$)	1 (<1)	1 (<1)	0
Moderately hypocellular (30%)	4 (3)	2 (2)	7 (7)
Normal (40–60%)	127 (90)	101 (80)	71 (76)
Moderately hypercellular (70%)	1 (<1)	11 (9)	10 (11)
Markedly hypercellular ($\geq 80\%$)	8 (6)	12 (9)	6 (6)
Trabecular bone quality, <i>n</i> (%)	145	122	88
Normal	72 (50)	61 (50)	55 (63)
Thinning	73 (50)	61 (50)	33 (38)
Collagen, <i>n</i> (%)	3	127	93
Negative	3 (100)	122 (96)	92 (99)
Positive ¹	0	5 (4)	1 (1)

n, number of patients with data available.

¹ Includes patients with any MF grade.

Compared with baseline, 79 out of 93 patients (85%) had MF-0 at 2 years, 9 (10%) had a 1-grade increase, 2 (2%) had a 1-grade decrease, 1 (1%) remained MF-1, and none had 2- or 3-grade increases (Table 4). Data were missing for 2 (2%) patients. None of the on-treatment biopsies was prompted by an abnormal peripheral blood smear or performed at the investigator's discretion for clinical symptoms suggestive of BM dysfunction.

In addition to grading for reticulin and collagen, BM specimens were assessed for cellularity, quantity, appearance of megakaryocytes, erythroid, and myeloid cells, and trabecular bone quality (Table 5). Megakaryocyte hyper-

plasia was observed in the majority of patients (91% at baseline and 98% at both years 1 and 2). Erythroid hyperplasia was observed in 10–12% of patients, and myeloid hyperplasia was found in 10–21%. Megakaryocyte, myeloid, and erythroid morphology was normal in most patients.

Cellularity was normal in 80, 80, and 76% of patients at baseline and the 1- and 2-year assessments, respectively (Table 6). Trabecular bone thinning was found in 50% of patients at baseline, 50% at year 1, and 38% at year 2. No pathologic patterns of changes or clinically relevant changes in lineage features were identified in the on-treatment biopsies compared with baseline.

Safety

There were no BM fibrosis-related AEs reported. The most common AEs occurring in >10% of patients were headache, cough, arthralgia, diarrhea, nausea, upper respiratory tract infection, and pyrexia (Table 7).

Discussion

This open-label safety study was designed to prospectively determine baseline levels of BM fibrosis in previously treated adults with persistent/chronic ITP and to evaluate the long-term effect of eltrombopag treatment on the formation of BM reticulin and/or collagen fibers. Six percent of patients had a BM fibrosis score of MF-1 at baseline. After 2 years of treatment, 86% of patients had no increase in grade of reticulin, and 10% had an increase of 1 grade in reticulin. No patient with an increase to MF-2 or the presence of collagen had clinical signs or symptoms indicative of BM dysfunction.

Table 7. AEs occurring in >10% of patients (safety population) (*n* = 162)

AE	<i>n</i> (%)
Any common event	118 (73)
Headache	31 (19)
Cough	23 (14)
Arthralgia	22 (14)
Diarrhea	22 (14)
Nausea	21 (13)
Upper respiratory tract infection	21 (13)
Pyrexia	18 (11)
Back pain	17 (10)
Fatigue	17 (10)
Gingival bleeding	17 (10)
Nasopharyngitis	17 (10)
Dyspepsia	16 (10)
Vomiting	16 (10)

AEs, adverse events.

BM biopsies are not routinely performed in the diagnosis or management of chronic ITP. Although some studies have retrospectively reviewed biopsy specimens, prospectively collected data in patients with chronic ITP are limited. A Danish study of 187 patients with chronic ITP never treated with TPO-RAs showed that 60% had MF-0, 39% had MF-1, and approximately 2% had MF-2 or MF-3 [18]. Whether the risk of BM fibrosis is due to the TPO-RAs themselves or the underlying disease remains unclear. Even in the absence of TPO-RAs, the results of several studies have revealed the presence of background BM reticulin fibrosis in patients with a diagnosis of ITP [6, 11, 18–20]. Furthermore, increased BM reticulin formation has been described in patients with refractory ITP, as well as in those with other autoimmune diseases [21, 22].

TPO-RAs have been associated with increases in the formation of reticulin fibers [11, 13, 19], but the lack of prospectively collected and consistently stained and analyzed pretreatment BM specimens has limited the robustness of the conclusions. An open-label study was conducted to assess the incidence of fibrosis after 3 years of treatment with romiplostim using the Bauermeister scale, and it also included a central review by 2 hematopathologists [23]. Patients were required to have normal BM at baseline and were assigned to 1 of 3 cohorts, with BM biopsies scheduled after 1, 2, or 3 years of treatment rather than annual assessments in the same patients, as in the current study. After 2 and 3 years of treatment, 7 patients had increases in reticulin of ≥ 2 grades, and specimens

from 2 patients showed the presence of fibrosis. After discontinuing romiplostim, 3 out of 9 patients with BM changes had follow-up biopsies that showed normal BM.

In this prospective, longitudinal study, we found that most patients with chronic ITP had MF-0 at baseline, and most patients experienced no change or a mild increase in reticulin over 2 years of treatment with eltrombopag. Furthermore, our findings indicate that collagen fibrosis was reversible.

In conclusion, these data suggest that treatment with eltrombopag is generally not associated with clinically relevant increases in BM reticulin or collagen.

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Author Contributions

R.K.B. contributed to the conception and design of the study, acquisition of the data, and data analysis and interpretation; R.S.M.W. and A.O. contributed to the acquisition of the data and data analysis and interpretation; M.M.T. contributed to the acquisition of the data; K.K.B. contributed to the conception and design of the study and data analysis and interpretation; and P.B. and D.T. contributed to the data analysis and interpretation. All authors provided critical review of the manuscript and approval of the final version of the manuscript. All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

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