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ORIGINAL ARTICLE

Hemostatic challenges in patients with chronic immune thrombocytopenia treated with eltrombopag

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Abstract

Chronic immune thrombocytopenia (ITP) is an autoimmune disease that results in chronically low platelet counts. Treatment guidelines recommend a platelet count of at least 50 000/μl before minor surgery and at least 80 000/μl before major surgery. This retrospective analysis explored invasive non-dental procedures associated with the risk of bleeding (hemostatic challenges) among patients with chronic ITP in five phase 2/phase 3 studies of the thrombopoietin-receptor agonist, eltrombopag. Data collection for patients who underwent hemostatic challenges included demographics, study medication, timing of the procedure, platelet counts at last assessment before and first assessment after the procedure, supplemental ITP treatment, and bleeding events. Among 494 patients who participated in the studies, 87 hemostatic challenges were recorded. Median platelet counts before 44 major procedures in 32 patients were 100 000/μl and 18 500/μl among patients who received eltrombopag and placebo, respectively; before 43 minor procedures in 38 patients, median platelet counts were 82 000/μl and 20 000/μl among patients who received eltrombopag and placebo, respectively. A minority of patients required supplemental ITP treatment. Only 2 of 87 hemostatic challenges were associated with bleeding events; both patients received eltrombopag and pre-procedural platelet counts were 83 000/μl and 2000/μl. Although the number of patients who did not undergo procedures due to thrombocytopenia was not captured, these data suggest a majority of patients with chronic ITP who receive eltrombopag and experience increases in platelet counts meet current pre-procedural platelet count recommendations. The potential role of eltrombopag in supporting preparation of chronic ITP patients for surgical procedures still needs to be clinically established.

Keywords: Immune thrombocytopenia, platelets, bleeding, surgery, thrombopoietin

Introduction

Chronic immune thrombocytopenia (ITP) is an autoimmune disease in which antiplatelet antibodies induce accelerated platelet destruction and impair platelet production resulting in chronically low platelet counts [1, 2]. Although traditionally the immunologic abnormality in ITP has been ascribed to B-cells and antibody-mediated injury, recent research suggests that a direct toxic effect of T-cells and imbalances in T-cell and cytokine profiles have been observed in some patients with chronic ITP [3, 4].

Standard care for chronic ITP in adults with a platelet count of at least 30 000/μl involves monitoring without intervention [5]. When platelet counts drop below 30 000/μl, corticosteroids can be administered, plus intravenous immunoglobulin (IVIg) if a more rapid rise in platelet count is needed [5]. Recently published guidelines suggest using treatment algorithms when patients do not respond to the aforementioned first line therapies, including anti-D immunoglobulin, mycophenolate mofetil and thrombopoietin receptor agonists, among others [2].

The increased bleeding risk due to low platelet counts in chronic ITP poses a potentially serious concern during medical and surgical procedures typically associated with bleeding (i.e. hemostatic challenges), whether they are major or minor invasive procedures. However, the use of immunosuppressive medications to increase platelet counts prior to invasive procedures is not ideal, because it may increase the risk of perioperative infection [6–9]. In adults with ITP, treatment guidelines recommend a pre-operative platelet count of at least 50 000/μl before minor surgery and at least 80 000/μl before major surgery [2]. Increasing the platelet count can minimize the risk of bleeding, which is the primary goal of treatment in patients with chronic ITP. This also facilitates the undertaking of invasive procedures that would otherwise carry an increased risk of bleeding.

Eltrombopag is an oral, nonpeptide, thrombopoietin-receptor agonist that binds to the transmembrane domain of the thrombopoietin receptor without competing with endogenous thrombopoietin [10]. This results in increased proliferation and differentiation of bone marrow progenitor cells into megakaryocytes and increased production of normally functioning platelets [10]. Efficacy and safety data from the phase 2 and phase 3 clinical program of eltrombopag in chronic ITP are available from completed and ongoing studies [11–14]. In these studies, eltrombopag increased and maintained platelet counts and reduced bleeding [11, 12, 14], and was shown to reduce the need for concomitant and rescue medications [13, 15].

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This retrospective analysis of data from patients across the eltrombopag clinical program in chronic ITP who underwent hemostatic challenges was conducted to explore platelet counts, use of supplemental ITP treatment, and bleeding events.

Methods

Data were included from five clinical studies of eltrombopag in 494 patients with previously treated chronic ITP. In addition to study treatment (double-blind eltrombopag or placebo, or open-label eltrombopag), all patients received standard care for chronic ITP, in accordance with the investigator's usual practice and discretion.

The studies included three randomized, placebo-controlled studies of patients with a baseline platelet count of less than 30 000/μl: Study 773A ($n = 117$) was a 6-week, phase 2, dose-finding study [11]; Study 773B ($n = 114$) was a 6-week, phase 3 study [12]; and RAISE ($n = 197$) was a 6-month, phase 3 study [13]. The other two studies were open-label, single-arm eltrombopag studies: REPEAT ($n = 66$) was a phase 2 study of intermittent treatment (three treatment cycles of up to 6 weeks on therapy and up to 4 weeks off therapy) in patients with baseline platelet counts between 20 000/μl and 50 000/μl [14]; and EXTEND is an ongoing extension study for patients who participated in one of the other four studies [15]. The cutoff date for this analysis of data from EXTEND was December 2008. Each study was conducted in accordance with the principles contained in the Declaration of Helsinki, each study site received approval from an Institutional Review Board to conduct the study, and each patient provided written informed consent to participate in the study.

Invasive non-dental procedures associated with risk of bleeding were denominated ''hemostatic challenges''; minor procedures (e.g. endoscopy, colonoscopy, biopsy) were distinguished from major procedures (e.g. hip arthroplasty, splenectomy, abdominal aneurism repair). Patients were included in this analysis if a non-dental hemostatic challenge was undertaken while the patient was taking study medication (eltrombopag or placebo). Patients were excluded from the analysis if the procedure was more than 10 days after the last dose of study medication, when study treatment was not necessarily expected to influence platelet count or the risk of bleeding events. Information about hemostatic challenges was collected retrospectively in Study 773A and prospectively in the other studies. Investigators were asked to record information about any surgical or medical procedure. Data collection included basic demographic information, platelet counts before and after procedures, type of procedure, need for supplemental ITP treatment to increase platelet counts (from 1 week before through 1 week after the procedure), use of blood products, and information about bleeding events. Supplemental ITP treatments were defined as receiving a new ITP medication, an increase in dose from baseline of a concomitant ITP medication, a platelet or other blood product transfusion, or a splenectomy.

Results

Hemostatic challenges

Data were available from 494 patients, including 365 who received eltrombopag and 129 who received placebo in the parent study (773A, 773B, RAISE, or REPEAT). Of these patients, 299 subsequently enrolled in EXTEND and received open-label eltrombopag. A total of 87 hemostatic challenges were recorded (Figure 1), including 44 major procedures in 32 patients and 43 minor procedures in 38 patients; 7 patients had both major and minor procedures. Major procedures are listed by study and patient in Table I. Minor procedures are listed by study and patient in Table II. Four patients had major procedures during both a parent study (773A, 773B, RAISE, or REPEAT) and in EXTEND, including 3 patients from the eltrombopag group and 1 patient from the placebo group of the parent study (Table I).

Platelet counts

Platelet counts at the last assessment before hemostatic challenge are summarized in Table III. Before major hemostatic challenges, median platelet counts were 100 000/μl (range, 0–491 000/μl) in the eltrombopag group and 18 500/μl (range, 6000–36 000/μl) in the placebo group. Before minor hemostatic challenges, median platelet counts were 82 000/μl (range, 0–528 000/μl) in the eltrombopag group and 20 000/μl (only one procedure) in the placebo group. One patient had platelet counts of 0 reported before three hemostatic challenges, including bone marrow biopsy on day 386 (Table II), lumbar puncture on day 448 (Table II), and splenectomy on day 474 (Table I).

Supplemental ITP treatment

Among the patients who underwent a major hemostatic challenge, supplemental ITP treatment was administered to 4 of 29 patients in the eltrombopag group (including 1 in RAISE, 2 in EXTEND, and 1 in both RAISE and EXTEND) and 2 of 4 patients in the placebo group. Among the patients with minor hemostatic challenges, supplemental ITP treatment was administered to 9 of 37 patients in the eltrombopag group (including 3 in RAISE and 6 in EXTEND) and was not administered to the 1 patient in the placebo group.

Bleeding events

No patient had a bleeding event after a minor procedure. No bleeding events were reported among the 5 placebo-treated patients. Two patients who received eltrombopag had bleeding events reported up to 2 days after major procedures, as follows.

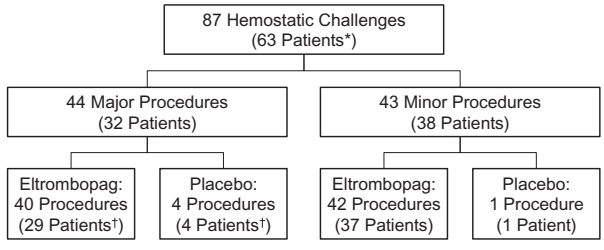

Figure 1. Hemostatic challenges and bleeding events across the eltrombopag ITP clinical program.
*The total of 63 patients includes 7 patients who had both major and minor procedures.
†One patient with a hemostatic challenge received placebo in Study 773B and subsequently received open-label eltrombopag in the EXTEND study; this patient underwent a major procedure in each study.

Table I. Major hemostatic challenges during (or within 10 days after) study treatment.

Study Sex/Age	Treatment	Major hemostatic challenge		Platelet count (/μl)				Supplemental ITP treatment		Bleeding event[a]
				Before		After				
		Day	Procedure	Day	Count	Day	Count	Day	Treatment	
773A										
F/53	50 mg	24	Cholecystectomy	15	428 000	29	114 000			
F/53	50 mg	29	Laparoscopic cholecystectomy	22	369 000	36	319 000			
F/57[e1]	75 mg	9	Motor vehicle accident	8	491 000	57	4000			
F/36	Placebo	19[b]	Trabeculectomy	12	12 000	36	26 000	12,13	IVIg	
773B										
M/69	Placebo	29	Hip arthroplasty	22	25 000	71	86 000	22,23	IVIg	
								29	Transfusion	
F/27[e2,f1]	Placebo	37	Excision papilloma	36	36 000	43	32 000			
RAISE										
M/62[f2]	50 mg	93	Aortic aneurysm repair	71	123 000	98	292 000	93	Transfusion	
F/67[f3]	50 mg	119	Tendon sheath incision	112	117 000	140	109 000			
F/51[f4]	50 mg	107	Hysterectomy	105	175 000	132	280 000			
F/59[e3]	50 mg	95[c]	Colectomy	85	2000	211	1000	92	IVIg	Yes
		97[c]	Laparotomy	85	2000	211	1000			
F/18	Placebo	91	Limb operation	85	6000	101	9000			
REPEAT										
F/56[e4]	50 mg	48	Sinus operation	43	83 000	50	359 000			Yes
M/63	50 mg	84	Transurethral prostatectomy	83	126 000	92	261 000			
M/71	50 mg	162[d]	Biopsy pancreas	157	128 000	164	77 000			
M/48	50 mg	64	Colon polypectomy	61	130 000	68	123 000			
EXTEND										
F/28[f1]	50 mg	258	Biopsy cervix	228	27 000	263	39 000			
M/63[f2]	50 mg	93	Hip arthroplasty	90	75 000	118	357 000	93	Platelet transfusion	
F/68[f3]	50 mg	141M	Cystocele repair	135	412 000	148	54 000			
		141	Cystopexy							
		141	Enterocele							
		141	Vaginal vault prolapse repair							
F/75[f4]	50 mg	351	Carpal tunnel decompression	337	92 000	365	63 000			
		351	Tendon sheath incision							
F/59	50 mg	205	Hip arthroplasty	190	62 000	239	116 000	141[g]	Mycophenolic acid	
								198, 199	IVIg	
M/30[e5]	50 mg	474	Splenectomy	448	0	484	43 000	465–473	Prednisolone	
M/71	50 mg	511	Hip arthroplasty	508	79 000	536	265 000			
		518	Catheterisation cardiac	508	79 000	536	265 000			
M/55	50 mg	449	Incisional drainage	442	85 000	467	106 000			
F/49	50 mg	204	Cataract operation right[h]	184	152 000	215	96 000			
		425	Cataract operation left[h]	418	140 000	448	165 000			
F/50[e6]	50 mg	353	Micrographic skin surgery	349	88 000	358	94 000			
F/54	50 mg	312	Splenectomy	308	90 000	332	44 000			
F/52[e7]	50 mg	150	Medical device implantation	87	19 000	–	–			

(*continued*)

Table 1. Continued.

Study Sex/Age	Treatment	Major hemostatic challenge		Platelet count (/μl)				Supplemental ITP treatment		Bleeding event[a]
				Before		After				
		Day	Procedure	Day	Count	Day	Count	Day	Treatment	
F/65	50 mg	293	Ovarian operation	286	108 000	309	208 000			
F/68	50 mg	176	Cataract operation[i]	175	88 000	182	48 000			
		204	Cataract operation[i]	189	74 000	210	54 000			
F/65	50 mg	71	Cataract operation[h]	56	16 000	78	158 000			
F/38	50 mg	172	Uterine polypectomy	155	117 000	183	174 000			
F/76	50 mg	548	Femur fracture	540	89 000	575	76 000			
F/75	50 mg	216	Carpal tunnel decompression	210	205 000	224	76 000			
M/42	50 mg	123	Arthroscopy	122	42 000	150	35 000			
F/57	50 mg	98	Splenectomy	98	256 000	99	328 000			
F/46	50 mg	468	Hemorrhoid operation	460	264 000	467	38 000			

[a]See text for details of reported bleeding adverse events.

Patients were still on study at the time of the hemostatic challenge, except as follows: [b]study medication had stopped on day 12 to switch patient to IVIg prior to operation; [c]study medication had stopped on day 91 due to adverse event; [d]study medication had stopped on day 157 for unspecified reason.

[e]Seven patients (labeled e1 to e7 in this table and in Table II) underwent a major procedure and a minor procedure.

[f]Four patients (labeled f1 to f4) underwent a major procedure in both a parent study and in the EXTEND study.

[g]Supplemental ITP treatment was ongoing at the time of study completion on day 253.

[h]Cataracts were present at baseline in this patient and were not considered related to eltrombopag treatment.

[i]Cataracts were present at baseline in this patient and worsening of cataracts was considered related to eltrombopag treatment.

Table II. Minor hemostatic challenges during (or within 10 days after) study treatment.

Study Sex/Age	Treatment	Minor hemostatic challenge Day	Procedure	Platelet count (/μl) After Day	After Count	Before Day	Before Count	Supplemental ITP treatment Day	Treatment
RAISE									
F/59[e1]	50 mg	87	Colonoscopy	85	2000	211	1000		
F/80	50 mg	10	Skin lesion	8	49 000	17	163 000	1–11	Prednisone
F/47	50 mg	16[a]	Lumbar puncture	16	339 000	21	375 000	83–91	Methylprednisolone
F/48	50 mg	82	Lumbar puncture	78	79 000	96	17 000	86	Anti-D Ig
								87	Transfusion
M/52	50 mg	54[b]	Endoscopy (GI)	50	34 000	105	31 000		
		93[b]	Endoscopy (GI)	50	34 000	105	31 000		
F/47	50 mg	166	Biopsy	160	342 000	168	365 000		
		166	Skin operation						
F/72	50 mg	114	Skin biopsy	111	180 000	118	190 000		
F/33	Placebo	141	Bone marrow biopsy	141	20 000	155	21 000		
REPEAT									
F/56	50 mg	41	Colonoscopy	36	101 000	43	112 000		
F/59	50 mg	111	Endoscopy (upper GI)	106	528 000	113	280 000		
F/53	50 mg	113	Colonoscopy	106	107 000	114	85 000		
EXTEND									
F/58[e2]	50 mg	210	Bronchoscopy	209	227 000	215	44 000	250–251	IVIg
		252	Bone marrow biopsy	252	29 000	256	20 000		
F/49[e3]	50 mg	396	Bone marrow biopsy	396	46 000	425	56 000		
F/57[e4]	50 mg	334	Colonoscopy	329	139 000	369	168 000		
M/30[e5]	50 mg	386	Bone marrow biopsy	386	0	420	0	463	IVIg
		462	Lumbar puncture	448	0	484	43 000		
F/50[e6]	50 mg	211	Skin biopsy	202	80 000	230	87 000		
F/52[e7]	50 mg	130	Dialysis	87	19 000	—	—		
F/56	50 mg	102	Endoscopy	101	3000	113	975 000	96, 101–105	IVIg
								101–104	Dexamethasone
M/54	50 mg	56	Colonoscopy	56	87 000	62	102 000		
F/70	50 mg	353	Endoscopy (upper GI)	337	209 000	365	189 000		
F/82	50 mg	471	Colonoscopy	461	36 000	489	140 000		
F/61	50 mg	15	Colonoscopy	8	204 000	17	510 000		
F/80	50 mg	29	Skin neoplasm excision	29	268 000	34	208 000		
M/78	50 mg	389[c]	Endoscopy	387	248 000	400	185 000		
F/49	50 mg	42	Bone marrow biopsy	42	28 000	48	26 000		
F/65	50 mg	131	Colonoscopy	127	96 000	134	265 000		
M/68	50 mg	313	Acrochordon excision	288	56 000	316	68 000		
F/22	50 mg	348	Endoscopy (upper GI)	344	156 000	351	76 000		
F/45	50 mg	83[d]	Stem cell transplant	82	41 000	89	29 000	74–79	Transfusion
								75–97	Prednisolone
								80	Anti-D Ig
F/45	50 mg	656	Tissue sealing	649	54 000	670	164 000		
F/55	50 mg	100	Endoscopy (upper GI)	100	100 000	108	29 000		
F/51	50 mg	414	Bone marrow biopsy	414	88 000	443	77 000		
F/68	50 mg	406	Bone marrow biopsy	406	5000	416	2000		
F/47	50 mg	31	Bone marrow biopsy	31	77 000	37	61 000	32–60	Prednisolone
F/53	50 mg	19	Suture insertion	19	450 000	31	6000		
F/57	50 mg	227	Tumor excision	225	64 000	232	73 000	221–224	Methylprednisolone
F/60	50 mg	402	Bone marrow biopsy	388	159 000	409	123 000		
F/43	50 mg	85	Colonoscopy	82	82 000	92	74 000		
		85	Endoscopy (upper GI)						

No bleeding adverse events were reported after minor hemostatic challenges.

Patients were still on study at the time of the hemostatic challenge, except as follows: [a]study medication was stopped on day 15 due to adverse event; [b]study medication was stopped on day 53 due to adverse event; [c]study medication was stopped on day 387 due to adverse event; [d]study medication was stopped on day 75 due to lack of efficacy.

[e]Seven patients (labeled e1 to e7 in this table and in Table I) underwent a major procedure and a minor procedure.

One patient in the REPEAT study underwent sinus surgery (endoscopic sinus surgery with balloon sinuplasty and balloon dilation) on day 13 of the on-therapy period of the second treatment cycle. The platelet count at the start of the second treatment cycle was 28 000/μl and 5 days before the surgery it was 83 000/μl. The patient experienced a post-procedural bleeding event beginning on the day of surgery, described by the investigator as ''bloody nasal discharge post surgery'' and considered it to be mild and not related to study treatment. No rescue treatment was reported and the patient continued to take

Table III. Median platelet count (range) at the last assessment before the procedure.

Type of procedure	Study treatment	No. of subjects	Platelet count, μl median (range)
Major	Eltrombopag	29	100 (0–491)
	Placebo	4	18.5 (6–36)
Minor	Eltrombopag	37	82 (0–528)
	Placebo	1	20 (NA)

NA, not applicable.

eltrombopag once daily. The platelet count 2 days after the surgery was 359 000/μl without supplemental ITP treatment; because the platelet count was >200 000/μl, eltrombopag treatment was interrupted and the off-therapy period of the cycle began.

One patient in RAISE, who did not respond to treatment with eltrombopag (platelet count range, 2000/μl to 29 000/μl), presented with rectal bleeding and a platelet count of 2000/μl after 87 days on study. A colonoscopy with biopsy demonstrated a colorectal adenocarcinoma. Eltrombopag was interrupted, IVIg was initiated, and a colectomy was performed on study day 95, with no prophylactic anticoagulation. On day 96, the patient experienced a bilateral pulmonary embolism, which required anticoagulation with heparin. On day 97, the patient experienced intra-abdominal bleeding, which required red blood cell transfusion and a laparotomy for hemostasis. Platelet counts were not available at the time of these events. The post operative course was subsequently unremarkable. After completing her participation in RAISE the patient entered EXTEND, where she responded to open-label eltrombopag. On day 334 of EXTEND, the patient underwent a colonoscopy with a pre-procedural platelet count of 139 000/μl without supplemental ITP treatment and no bleeding event was reported after this procedure.

Discussion

In this analysis of data from five studies of eltrombopag in patients with chronic ITP, patients treated with eltrombopag had median platelet counts of 100 000/μl before major invasive procedures and 82 000/μl before minor procedures. These findings are in line with recent clinical guidelines for the identification and management of ITP [2], which recommend a target platelet count of at least 80 000/μl before a major procedure and at least 50 000/μl before a minor procedure. None of the patients who had received placebo and underwent a hemostatic challenge had platelet levels above these targets prior to the procedures. Although none of the 4 patients in the placebo group who underwent a major procedure had a bleeding event recorded, 2 of them required supplemental ITP treatment. Because of the retrospective nature of this analysis, it was not possible to determine how many patients in either treatment group required a minor or major procedure but were not eligible due to low platelet counts.

The primary goal of increasing platelet counts in patients with chronic ITP is to reduce bleeding events. Few bleeding events were reported in this analysis, which adequately correlates to the acceptable pre-procedural platelet counts. No difference in the use of peri-procedural blood products between groups was apparent, which can possibly be correlated to the acceptable platelet counts and low frequency of bleeding events reported. However, given that the studies were not specifically designed to investigate these endpoints, the number of patients who were not able to undergo procedures due to thrombocytopenia was not captured, which limits the conclusions that can be drawn from this analysis.

Conclusion

In five phase 2 and phase 3 studies of eltrombopag in patients with previously treated chronic ITP, eltrombopag was associated with sustained increases in platelet counts and reductions in bleeding events [11, 12, 14] and reduced the need for concomitant and rescue medications [13, 15]. Data from the 87 hemostatic challenges that were reported in these studies suggest that the majority of patients with chronic ITP who are treated with eltrombopag and experience increases in platelet counts will achieve the platelet count recommendations to undertake invasive procedures, potentially reducing the risk of bleeding complications and the need for additional ITP treatment. The potential role of eltrombopag in supporting the preparation of chronic ITP patients for surgical procedures still needs to be clinically established.

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