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. Among 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.](image-url)

*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.
| Study Sex/Age | Treatment | Day | Major hemostatic challenge | Day | Count | Day | Count | Supplemental ITP treatment | Bleeding eventa |
|--------------|-----------|-----|---------------------------|-----|-------|-----|-------|---------------------------|---------------|
| 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/57e1      | 75 mg     | 9   | Motor vehicle accident    | 8   | 491 000 | 57  | 4000   |                          |               |
| F/36 Placebo |          | 19a | 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               |               |
| F/27e2,n    | Placebo   | 37  | Excision papilloma        | 36  | 36 000  | 43  | 32 000  |                          |               |
| RAISE M/62f2| 50 mg     | 93  | Aortic aneurysm repair    | 71  | 123 000 | 98  | 292 000 | 93 Transfusion            |               |
| F/57f3      | 50 mg     | 119 | Tendon sheath incision    | 112 | 117 000 | 140 | 109 000 |                          |               |
| F/59e3      | 50 mg     | 107 | Hysterectomy              | 105 | 175 000 | 132 | 280 000 | 92 IVIg Yes              |               |
| F/59         | 50 mg     | 97a | Laparotomy                | 85  | 2000    | 211 | 1000   |                          |               |
| F/18         | Placebo   | 91  | Limb operation            | 85  | 6000    | 101 | 9000   |                          |               |
| REPEAT F/56e4| 50 mg     | 48  | Sinus operation           | 43  | 83 000  | 50  | 359 000 | 359 000                   |               |
| M/63        | 50 mg     | 84  | Transurethral prostatectomy| 83  | 126 000 | 92  | 261 000 |                          |               |
| M/71        | 50 mg     | 162d | Biopsy pancreas           | 157 | 128 000 | 164 | 77 000  |                          |               |
| M/48        | 50 mg     | 64  | Colon polypectomy         | 61  | 130 000 | 68  | 123 000 |                          |               |
| EXTEND F/28f1| 50 mg     | 28  | Biopsy cervix             | 228 | 27 000  | 263 | 39 000  | 93 Platelet transfusion   |               |
| M/63f2      | 50 mg     | 93  | Hip arthroplasty          | 90  | 75 000  | 118 | 357 000 | 93 Platelet transfusion   |               |
| F/68f3      | 50 mg     | 141 | Cystocele repair          | 135 | 412 000 | 148 | 54 000  |                          |               |
|             |           | 141 | Cystocele                 |     |         |     |        |                          |               |
|             |           | 141 | Enterocele                |     |         |     |        |                          |               |
|             |           | 141 | Vaginal vault prolapse repair | 337 | 92 000  | 365 | 63 000  |                          |               |
| F/75f4      | 50 mg     | 351 | Carpal tunnel decompression| 337 | 92 000  | 365 | 63 000  |                          |               |
| F/50         | 50 mg     | 205 | Hip arthroplasty          | 190 | 62 000  | 239 | 116 000 |                          |               |
| M/30f5      | 50 mg     | 474 | Splenectomy               | 448 | 0       | 484 | 43 000  |                          |               |
| M/71        | 50 mg     | 511 | Hip arthroplasty          | 508 | 79 000  | 536 | 265 000 |                          |               |
| M/55        | 50 mg     | 518 | Catheterisation cardiac   | 508 | 79 000  | 536 | 265 000 |                          |               |
| F/40        | 50 mg     | 449 | Incisional drainage       | 442 | 85 000  | 467 | 106 000 |                          |               |
| F/40        | 50 mg     | 425 | Cataract operation rightb | 184 | 152 000 | 215 | 96 000  |                          |               |
| F/50e6      | 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/52e7      | 50 mg     | 150 | Medical device implantation| 87  | 19 000  | –   | –      |                          |               |

(continued)
Table 1. Continued.

| Study Sex/Age | Treatment | Day | Procedure | Before Day | Count | After Day | Count | Supplemental ITP Treatment Day | Treatment |
|---------------|-----------|-----|-----------|------------|--------|-----------|--------|-------------------------------|-----------|
| F/65          | 50 mg     | 293 | Ovarian operation | 286        | 108 000 | 309       | 208 000 |                               |           |
| F/68          | 50 mg     | 176 | Cataract operation | 175        | 88 000  | 182       | 48 000  |                               |           |
| F/68          | 50 mg     | 204 | Cataract operation | 189        | 74 000  | 210       | 54 000  |                               |           |
| F/68          | 50 mg     | 71  | Cataract operation | 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  |                               |           |

Platelet count (/μl)

- **Before**
- **After**
- **Supplemental ITP treatment**

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*See text for details of reported bleeding adverse events.*

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

aSeven patients (labeled e1 to e7 in this table and in Table II) underwent a major procedure and a minor procedure.

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

cSupplemental ITP treatment was ongoing at the time of study completion on day 253.

cCataracts were present at baseline in this patient and were not considered related to eltrombopag treatment.

cCataracts were present at baseline in this patient and worsening of cataracts was considered related to eltrombopag treatment.
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
etrombopag once daily. The platelet count 2 days after the surgery was 359,000/\mu l without supplemental ITP treatment; because the platelet count was >200,000/\mu l, etrombopag treatment was interrupted and the off-therapy period of the cycle began.

One patient in RAISE, who did not respond to treatment with etrombopag (platelet count range, 2000/\mu l to 29,000/\mu l), presented with rectal bleeding and a platelet count of 2000/\mu l after 87 days on study. A colonoscopy with biopsy demonstrated a colorectal adenocarcinoma. Eltrombopag was interrupted, IVlg 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 etrombopag. On day 334 of EXTEND, the patient underwent a colonoscopy with a pre-procedural platelet count of 139,000/\mu l without supplemental ITP treatment and no bleeding event was reported after this procedure.

Discussion
In this analysis of data from five studies of etrombopag in patients with chronic ITP, patients treated with etrombopag had median platelet counts of 100,000/\mu l before major invasive procedures and 82,000/\mu l 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/\mu l before a major procedure and at least 50,000/\mu l 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 etrombopag in patients with previously treated chronic ITP, etrombopag 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 etrombopag 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 etrombopag in supporting the preparation of chronic ITP patients for surgical procedures still needs to be clinically established.

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