PLATON: use of romiplostim to treat chronic primary immune thrombocytopenia

An observational, nonintervention study of real-life practice

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Summary Chronic primary immune thrombocytopenia (ITP) is an autoimmune disease involving the formation of antibodies to thrombocytes, leading to increased platelet destruction and chronic thrombocytopenia. Additionally, impaired platelet production is due to relative thrombopoietin deficiency. Romiplostim, a thrombopoietin receptor agonist, normalized platelet counts in affected patients in randomized controlled trials and real-world observational studies. The present study collected real-world practice data from Central and Eastern Europe, i.e. Slovakia, Slovenia, Bulgaria, Russia, and Czech Republic, between December 2010 and July 2017. This was an ambidirectional observational, noninterventional cohort study within the approved romiplostim indication. One-hundred patients were analyzed. Prior to romiplostim start, 98% had received other ITP medications and, in the prior 6 months, 40% had experienced bleeding events. Romiplostim was started 1.92 years (median) after ITP diagnosis. The median mean on-study dose was 2.62 µg/kg/week. During romiplostim treatment, platelet counts rapidly normalized to >50 × 10^9/L, 20%
of patients experienced bleeding events (none grade 3/4), and 13% required splenectomy. At the end of study, 25% of patients were in remission. One patient experienced serious adverse drug reactions (thrombosis, dysphagia), none were fatal. In conclusion, romiplostim dosing, effectiveness and safety in these unsolicited ITP patients seemed comparable with observations in clinical trials and similarly designed observational studies.

Keywords Thrombopoietin receptor agonist · Blood platelets · Splenectomy · Bleeding · Remission

Introduction

Chronic primary immune thrombocytopenia (ITP) is an autoimmune disease characterized by premature degradation and impaired production of platelets [1]. The clinical symptoms include petechiae, hematomas, and mucosal bleeding. The cause of the disease remains unknown. The ITP incidence ranges between 1.6 and 3.9 cases per 100,000 person–years for adults, with an age-specific increase from 60 years onwards [2].

Romiplostim specifically binds to the thrombopoietin receptor and increases and subsequently maintains platelet counts in splenectomized and non-splenectomized patients, allowing patients to reduce or discontinue concomitant ITP medications [3–5]. The present observational study collected data from Central and Eastern Europe to further evaluate the benefits and risks of the drug in real-life clinical practice.

Materials and methods

Study design

This was a single-arm, ambidirectional, observational, noninterventional cohort study conducted between December 2010 and July 2017 as part of an international study program [4, 5].

The data were collected from medical files and documented the physicians’ own routine practice. No study-specific diagnostic or therapeutic protocol was to be followed. Bleeding was graded according to the World Health Organization scale and documented in a standardized manner [6, 7]. Treatment response was documented as per the physicians’ assessment and local hospital definition.

Patient and disease history were collected upon study inclusion. The last available data prior to romiplostim initiation were documented as baseline. Documentation of prior bleeding events covered a period of 6 months prior to romiplostim start. Further data were collected from the first dose of romiplostim onwards over a period of two years, independent of the duration of romiplostim treatment. For further definitions consult the online supplement.

Study objectives

The main objectives were to describe the study population, the application and dosage of romiplostim and other ITP therapies, romiplostim safety, clinically relevant bleeding events, health care resource usage, and reasons for romiplostim discontinuation.

Eligibility criteria

Adult (≥18 years) ITP patients were included. Patients must have received ≥1 romiplostim administration as per approved indication, i.e. as second-line therapy after splenectomy or failure of other therapies, or before splenectomy when surgery was contraindicated. Patients were excluded, if they previously or concurrently received any thrombopoiesis-stimulating drugs, participated in clinical trials, had been treated with romiplostim before its market introduction, or if they showed hypersensitivity to romiplostim, any excipient, or E. coli-derived proteins.

Ethical considerations

This study was conducted in accordance with regulations in the participating countries and was approved by local ethical committees (see online supplement). Written informed consent was provided.

Statistical methods

The statistical analysis was descriptive, and no formal hypothesis was tested. Categorical variables were summarized as number, percentage, and exact 2-sided 95% confidence intervals (CIs). CIs were based on Poisson distribution. Continuous variables were summarized as mean, 95% CI, standard deviation, median, interquartile range (IQR), and range. Data were analyzed as documented with no imputation for missing data. Prespecified time windows were allowed for platelet counts and dose information.

Results

Of the 100 patients analyzed, 27 (27%) discontinued observation; 52 (52%) discontinued romiplostim, mainly within the first 9 months (Table S1). Fifty-six patients (56%) were female. Prior splenectomy had been performed in 23 patients (23%). The median (IQR) age at diagnosis was 45.0 (26.5; 57.5) years. Forty-nine patients (49%) had received ≥3 prior ITP therapies, most frequently corticosteroids or intravenous immunoglobulin (IVIg); patients were initiated on romiplostim after a median (IQR) of 1.92 (0.28; 6.73) years after ITP diagnosis at a median (IQR) platelet count of 19.0 (7.5; 42.0) × 10⁹/L (Table 1). The median (IQR) time of observation was 24.0 months (23.0; 24.1).
Table 1  Patient demographics and characteristics

| All patients (N=100) |
|-----------------------|
| Female, n (%)         | 56 (56.0) |
| Age at ITP diagnosis, years – median (IQR) | 45.0 (26.5; 57.5) |
| Age at initiation of romiplostim, years – median (IQR) | 49.5 (34.0; 61.0) |
| Splenectomized before baseline, n (%) | 23 (23.0) |
| ITP duration at initiation of romiplostim, years – median (IQR) | 1.92 (0.28; 6.73) |
| Baseline platelet count, 10^9 cells/L – median (IQR) | 19.0 (7.5; 42.0) |
| Number of prior ITP therapiesa | 2 (2.0) |
| Most common (≥10% frequency) prior ITP therapiesa, n (%) |
| Corticosteroids | 91 (91.0) |
| IVIg | 29 (29.0) |
| Azathioprine | 14 (14.0) |
| Platelet transfusion | 10 (10.0) |
| Ongoing medications for ITP at initiation of romiplostim, n (%) |
| Corticosteroids | 3 (3.0) |
| IQRinterquartile range; SD standard deviation |

*Prior medications include those that have ended prior to initiation of romiplostim

Patient demographics and characteristics by country are available in Table S2 in the supplement.

Bleeding prior to romiplostim treatment

During the 6 months prior to romiplostim initiation, 40 patients (40%) experienced bleeding events (35.9% of nonsplenectomized, 47.2% of splenectomized patients), with a median (IQR) of 1.0 (1.0; 1.0) event, mostly petechiae, mucocutaneous hemorrhage, epistaxis, and purpura. The study observation-adjusted prior bleeding event incidence per 100 patient–years (95% CI) was 130.7 (97.6; 171.4; Table 2).

Hospitalizations prior to romiplostim treatment

Sixty-two patients (62%) had a total of 133 prior ITP-related hospitalizations, mainly due to ITP treatment administration (n=78 hospitalizations; 58.6%), bleeding events (n=21; 15.8%) or other, nonspecified reasons (n=24; 18.0%). The study observation-adjusted incidence (95% CI) of prior hospitalizations per 100 patient–years was 103.8 (86.9; 123.0; Table S2).

Romiplostim exposure

The initial median weekly dose was 1µg/kg body weight and the median (IQR) mean weekly dose across the entire observation period was 2.62µg/kg (1.09; 4.50). Overall, 166 episodes of treatment gaps of ≥3 weeks were counted, mainly due to high platelets

Table 2  Summary of bleeding events

| All patients (N=100) |
|-----------------------|
| Entire study perioda | 100 (100.0%) |
| Patient experienced any bleeding event | 20 (20.0%) |
| Abnormal vaginal bleeding | 1 (1.0%) |
| Bleeding from invasive sites, soft tissue or musculoskeletal bleeding | 0 |
| CNS bleeding with neurologic symptoms | 0 |
| Conjunctival bleeding | 1 (1.0%) |
| Ecchymosis | 3 (3.0%) |
| Epistaxis | 3 (3.0%) |
| Hematemesis | 0 |
| Hematochezia | 1 (1.0%) |
| Hematoma | 5 (5.0%) |
| Hematuria | 0 |
| Hemoptysis | 1 (1.0%) |
| Melena | 1 (1.0%) |
| Mucocutaneous hemorrhage (oral blood blisters) | 5 (5.0%) |
| Oropharyngeal bleeding | 0 |
| Petechiae | 6 (6.0%) |
| Purpura | 5 (5.0%) |
| Retinal hemorrhage with visual impairment | 0 |
| Otherb | 4 (4.0%) |

*Percentages are based on the number of patients remained at study at the specified timepoint

Multiple bleeding event occurrence is counted only once per timepoint per event type. Patients may be counted in different categories and percentages may add up to more than 100%.

*Percentages are based on the number of patients in Full Analysis Set

Bleeding events grouped in the ‘other’ category are treated as one bleeding event.
Table 3  Exposure to romiplostim

|                          | All patients (N= 100) |
|--------------------------|------------------------|
| Number of patients exposed to romiplostim, n (%) | 100 (100.0) |
| Duration of exposure to romiplostim, months       |  |
| Mean (SD)                | 16.80 (9.112) |
| Median (IQR)             | 23.10 (6.70; 24.21) |
| Range                    | 0.5–24.4            |
| Continuous treatment with romiplostim for ≥6 months, n (%) | 65 (65.0) |
| Initial dose, µg/kg Mean (SD) | 1.2 (0.62) |
| Median (IQR)             | 1.0 (1.0; 1.0) |
| Range                    | 1–5                  |
| Number of patients who received initial dose of 1 µg/kg, n (%) | 91 (91.0) |
| Mean weekly dose, µg/kg | 2.97 (2.111)         |
| Median (IQR)             | 2.62 (1.0; 4.50)    |
| Range                    | 0.1–8.4             |
| Number of injections     | 53.6 (36.38)        |
| Median (IQR)             | 60.0 (14.5; 88.5)   |
| Range                    | 2–106               |
| IQR interquartile range; SD standard deviation |          |

(n = 101; 60.8%), adverse drug reactions (ADRs; n = 1; 0.6%), or other reasons (n = 64; 38.6%). Forty-five patients (45%) had no such gaps (Table 3). The median (IQR) time on romiplostim treatment was 23.1 months (6.7; 24.1). Reasons for discontinuation of romiplostim are listed in supplemental Table S1.

Bleeding events and platelet counts after romiplostim initiation

Twenty patients (20%, Table 2) experienced any bleeding event after romiplostim initiation (18.8% of non-splenectomized, 22.2% of splenectomized patients). None were grade 3/4 or fatal. Of these 20 patients, 15 (75%) already had experienced prior bleeding events. The study observation-adjusted incidence (95% CI) of bleeding events per 100 patient-years was 42.0 (32.9; 52.8). The median (IQR) platelet count had increased from 19.0 × 10⁹/L (7.5; 42.0) prior to romiplostim initiation to >50.0 × 10⁹/L one week thereafter, a threshold commonly defined as platelet response [3]. Within the first 6 months the median platelet counts steadily increased before reaching a plateau (Fig. 1).

Concurrent ITP medications after romiplostim initiation

Ninety-eight patients (98%) received other ITP medications prior to romiplostim, including corticosteroids (n = 91; 91%) and IVIg (n = 29; 29%); 49 patients (49%) had ≥3 prior ITP treatments. The number of patients and of individual treatments decreased over time (Fig. 2). Ninety-six patients (96%) discontinued concurrent ITP therapies and 29 (29%) started such drugs after romiplostim initiation. Seven patients (7%) required further ITP treatment after romiplostim discontinuation.

Splenectomies

Thirteen patients (13%) required splenectomy because of persistent ITP symptoms (n = 8; 61.5% of splenectomized patients), intolerable side effects (n = 2, 15.4%), patient request (n = 1; 7.7%), or other reasons (n = 2; 15.4%). Of these 13 patients, 6 (46.2%) already had bleeding events prior to romiplostim, 3 (23.1%) during observation, and 2 (15.4%) during both periods. Their median (IQR) prior platelet count was 6.0 (3.0; 19.0) × 10⁹/L, increasing to 45.0 (8.0; 163.5) × 10⁹/L one week after romiplostim initiation and remaining >50 × 10⁹/L at all but two analyzed timepoints (weeks 2 [47.0 × 10⁹/L] and 12 [48.0 × 10⁹/L]).

Treatment outcomes

At the end of study, 25 patients (25%) had a durable response/remission of whom 23 patients were able to discontinue romiplostim therapy; 45 (45%) had active disease and continued to receive treatment, 18 (18%) had active, untreated disease, and 3 (3%) had died; for 9 (9%) ITP status was unknown.

Safety

Four patients experienced 10 different ADRs; 16 ADR events were documented (Table 4), none fatal. One patient (1%) experienced two serious ADRs (thrombosis, dysphagia). The exposure-adjusted incidence (95% CI) per 100 patient-years was 11.4 (6.5; 18.6) for ADRs and 1.4 (0.2, 5.2) for serious ADRs.

Discussion

The PLATON study showed similar efficacy in real-world clinical practice in Central and Eastern Europe as two similar studies in Western Europe, an international phase IV study [4] and the German PLATEAU study [5].

All three studies showed that a substantial proportion of patients received romiplostim prior to splenectomy. Despite the indication approved at the time of study, i.e. in the post-splenectomy setting or in patients with contraindications to splenectomy, 77% had not undergone splenectomy before initiating romiplostim (range between countries: 67–92%). In the international phase IV study this proportion was 66%, with a wide range between countries [4], and 83% in the German PLATEAU study [5]. From the
recorded medical histories, it was unclear whether patients were contraindicated or objected to splenectomy.

All three studies also showed that romiplostim was used prior to the chronic stage of ITP, as indicated. Chronic ITP is defined as lasting for more than 12 months [8]. In PLATON, the median duration of ITP at romiplostim initiation was 1.92 years with a lower quartile of 0.28 years, showing that numerous patients received romiplostim already at the persistent stage of ITP of 3 to 12 months. In the large international study, romiplostim was also used in newly diagnosed or persistent ITP (34%) [4]. In the German PLATEAU study, the median duration of ITP at baseline was 25 months [5].

The romiplostim starting dose was generally in line with the label with a median of 1.0 µg/kg/week. However, the range of 1–5 µg/kg/week shows that at least some patients received higher than recommended starting doses. In the international phase IV study, 31% received higher-than-recommended starting doses [4].

In PLATON, 49% of patients had ≥3 prior ITP treatments, including corticosteroids (91%) and IVIg (29%). As adverse effects of corticosteroids rapidly outweigh their benefits, they should be tapered and stopped after response or after 4 weeks in nonresponders [9]. In PLATON, 96% discontinued and 29% started concurrent ITP therapies. The number of patients and treatments, specifically corticosteroids, decreased continuously. In the international phase IV study [4], 55% had ≥3 prior ITP treatments, including 39% with off-label rituximab. The proportion of patients previously receiving corticosteroids was comparable in both studies (91% each) [4], but more patients had previously received IVIg (72%) in the international phase IV study [4] compared to PLATON (29%).

During romiplostim treatment platelet counts normalized to an average median of >50 x 10⁹/L. Both, splenectomized and nonsplenectomized patients, experienced a comparable incidence of bleeding and both groups reported fewer bleeding events during treatment with romiplostim. This observation is in line with the other studies, although those studies reported grade 3 or 4 bleeding events despite romiplostim treatment, whereas PLATON did not [4, 5]. Of 32 patients requiring hospitalizations after initiation of romiplostim, 20 had also required prior hospitalizations. Of 20 patients experiencing any bleeding event after initiation of romiplostim, 15 had also experienced prior bleeding events.

At study end, 25% of patients were in remission, as assessed by the physicians. In the international phase IV study, 10% were able to discontinue romiplostim due to a hemostatic platelet count [4]. In both studies, splenectomized and nonsplenectomized patients were able to achieve a remission. Their duration of remission is unknown.

The number of ADRs was substantially lower in PLATON than in the international phase IV study (4% versus 22% with ADRs, 2% versus 4% with serious ADRs) and the German PLATEAU study (no cumulative ADR rate reported, but ≥5% for fatigue, dizziness, nausea, vomiting and diarrhea) at a comparable administered dose [4, 5].

This study has limitations inherent to the observational design, especially selection and reporting bias, lack of blinding and no control group. As romiplostim was relatively new on the market, more severe patients may have been selected creating a bias against the general ITP population. In addition, data collected in observational studies may be less complete compared to clinical trials. The reduction in bleeding events may thus be a conservative estimate of the true reduction.
Fig. 2 Summary of concurrent ITP cedations. Red bars show overall proportions of patients receiving concomitant ITP therapies in the given time period. Percentages are based on the number of patients in Full Analysis Set. Patients may be counted in different categories and percentages may add up to more than 100%. 

ITP immune thrombocytopenia, IVig intravenous immunoglobulin
PLATON: use of romiplostim to treat chronic primary immune thrombocytopenia

Conclusions

Romiplostim dosing, effectiveness and safety in these unselected ITP patients seemed comparable with observations from similarly designed observational studies. After initiation of romiplostim, platelet counts rapidly increased to hemostatic levels and the observation-adjusted incidence rate of bleeding declined to approximately one-third. Of patients who experienced bleeding three quarters had already had prior bleeding events. Remissions were achieved in one quarter of patients.

Take home message

- The results of this study show that clinical efficacy of romiplostim in the routine practice setting was comparable to its clinical efficacy in other studies of real-world practice.
- The median platelet count increased to >50 x 10^9/L within one week of romiplostim initiation.
- The exposure-adjusted incidence of bleeding was reduced from 131 to 42 events per 100 patient-years after the initiation of romiplostim.
- At the end of study, 25% of patients achieved remission from ITP.

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Author Contribution

Daniela Niepel was responsible for the conception and design of the study. Georgi Mihaylov, Zusana Sninska, Nikolai Tzvetkov, Barbara Skopec, and Peter Cernelc were responsible for patient data collection and acquisition of data. Katja Björklöf was responsible for data cleaning and site queries. Vladlen Ivanushkin conducted statistical programming and analysis. All authors were responsible in the interpretation of the data, and review and critical appraisal of the manuscript.

Conflict of interest

G. Mihaylov, Z. Sninska, N. Tzvetkov, O. Cerna, V. Ivanushkin, and P. Cernelc declare that they have no competing interests. B. Skopec has received consulting fees from Amgen and Novartis. K. Björklöf and D. Niepel are employees of Amgen and hold Amgen stock.

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