Effectiveness and safety of romiplostim among patients with newly diagnosed, persistent and chronic ITP in routine clinical practice in central and Eastern Europe: an analysis of the PLATON study

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**ABSTRACT**

**Objectives:** The objective of this analysis was to assess the effectiveness and safety of romiplostim in the real-world by duration of primary immune thrombocytopenia (ITP): <3 (‘newly diagnosed’), 3–12 (‘persistent’), and >12 (‘chronic’) months.

**Methods:** This was a post-hoc analysis of the PLATON single-arm, observational cohort study of adults from five Central and Eastern European countries receiving \(\geq 1\) romiplostim dose as second-line therapy, or where surgery was contraindicated. Durable (\(\geq 75\%\) of measurements with \(\geq 50 \times 10^9\) platelets/L during weeks 14–24) and overall platelet response (\(\geq 30\) or \(\geq 50 \times 10^9\) platelets/L at least once), rescue therapy, bleeding, discontinuation of other ITP medications, and adverse drug reactions (ADRs) were assessed.

**Results:** Of 100 participants, 22.0% had newly diagnosed, 17.0% had persistent, and 61.0% had chronic ITP. Prior splenectomy was most frequently reported in chronic ITP (32.8%), prior bleeding was predominant in newly diagnosed patients (68.2%). Durable platelet response was achieved in 50.0% (95% confidence interval [CI]: 28.2–71.8%) of newly diagnosed, 35.3% (95% CI: 14.2–61.7%) of persistent, and 31.1% (95% CI: 19.9–44.3%) of chronic ITP patients. Overall platelet response was achieved in >80% across all strata. Safety was comparable across groups, with a low incidence of thrombotic ADRs and no bone marrow ADRs.

**Discussion:** In this real-world study, platelet response to romiplostim was consistent across all strata of ITP duration. ADRs were infrequent and similar across ITP settings.

**Conclusion:** These findings support the utilization of romiplostim in patients with newly diagnosed and persistent ITP in accordance with recent guidelines and the recent romiplostim label extension.

**KEYWORDS**

Immune thrombocytopenia (ITP); thrombocytopenia; TPO; bleeding; bleeding disorder; romiplostim; real-world evidence; thrombopoietin receptor agonist; Central and Eastern Europe

**Introduction**

Immune thrombocytopenia (ITP) is defined as an immune-related condition with repeatedly low platelet counts of <100 \(\times 10^9\)/L \([1, 2]\), where no trigger can be identified. It occurs relatively rarely with an annual incidence of 0.2–0.4 new cases per 10,000 in adults and 0.2–0.7 per 10,000 in children \([3, 4]\). An increased haemorrhagic tendency is the cardinal symptom of ITP \([5]\). Bleeding severity can range from cutaneous purpura to more severe mucosal bleeding and, more rarely, to intracranial haemorrhage \([6]\). Patients with ITP also have a slightly increased risk of thrombosis and venous thromboembolism \([7, 8]\) and may experience impaired physical and psychological health-related quality of life \([9]\), as well as fatigue \([10]\) or depression \([11]\).

As proposed by the American Society of Haematology (ASH) \([12]\) and other international working groups \([1, 2, 13, 14]\), three phases of ITP have been defined based on the duration of ITP: newly diagnosed (<3 months after diagnosis), persistent (3–12 months after diagnosis), and chronic (>12 months after diagnosis). Romiplostim, a thrombopoietin receptor agonist (TPO-RA), has been commercially available since 2009. Recently, the indication for romiplostim in adults has been expanded in the United States of America (USA) and Europe, whereby it is now licensed upon insufficient response to corticosteroids, immunoglobulins, or splenectomy, irrespective of ITP duration (i.e. across all phases of ITP) \([15, 16]\). This extended indication is aligned with treatment guidelines that
have been published in the past two years, including those from ASH [12], the International Consensus Report [13], the European Joint Working Group of the German Society for Haematology and Medical Oncology (DGHO), the Austrian Society for Haematology and Medical Oncology (ÖGHO), the Swiss Society for Haematology (SGH), the Society for Paediatric Oncology and Haematology (DGHO), and the German Society for Transfusion Medicine and Immunohematology (DGTI) [1], as well as the Japanese reference guide for management of primary ITP [14], which all recommend the use of TPO-RAs, including romiplostim, in patients with ITP <1 year from diagnosis (i.e. prior to chronic ITP).

In clinical studies, romiplostim treatment led to sustained platelet responses in adults with newly diagnosed or persistent ITP [17]. While evidence from real-world studies and case reports indicates that romiplostim is already being used in the newly diagnosed and persistent settings [18–21], efficacy and safety data are based on studies with relatively small numbers of patients. The aim of the present research was to analyse previously published data from the PLATON (Prospective Analysis of Management of ITP Patients) study [19] according to duration of primary ITP to extend the knowledge base on the effectiveness and safety of romiplostim in adults with newly diagnosed and persistent ITP.

**Methods**

The PLATON study collected real-world practice data from Central and Eastern Europe (CEE), i.e. Slovakia, Slovenia, Bulgaria, Russia, and Czech Republic, between December 2010 and July 2017. The planned sample size of 180 patients could not be reached and 100 patients were included. Details of the study design, the statistical methods, and a description of the results in the overall study population, as well as by country of enrolment, were previously reported by Mihaylov et al. [19].

**Study design**

PLATON was a single-arm, ambidirectional, observational, noninterventional cohort study of adult patients (≥18 years) within the romiplostim indication approved at the time of study conduct (i.e. in primary ITP as second-line therapy after splenectomy or failure of other therapies, or where surgery was contraindicated). The planned observation period per patient was 24 months.

**Objectives**

The primary objectives of PLATON and the respective results were reported elsewhere [19]. The aim of the present ad hoc analysis was to assess the effectiveness and safety of romiplostim within 24 weeks after initiation by duration of ITP: ‘newly diagnosed’, ‘persistent’, and ‘chronic’ – as defined by the ASH 2019 guidelines [12] – in the real-world setting in participating CEE countries.

**Statistical methods**

The statistical analysis was descriptive in nature. Categorical variables were reported as number, percentage, and exact two-sided 95% confidence intervals (CI). Continuous variables were summarized as mean, 95% CI, standard deviation (SD), median, interquartile range (IQR), and range. Data were analysed as documented with no imputation for missing data.

Time to first platelet response was defined as the time to first platelet count ≥50 × 10^9/L during weeks 2–24 after romiplostim initiation and overall platelet response was defined as having at least one platelet measurement ≥50 × 10^9/L during weeks 2–24 after romiplostim initiation. Patients achieved a durable platelet response when ≥75% of all recorded platelet measurements were ≥50 × 10^9/L during weeks 14–24. In patients receiving rescue medication, the analysis of these outcome measures included all platelet measurements occurring before rescue therapy; follow-up was censored on the date of rescue therapy receipt. Rescue therapy was defined as (1) receiving rescue therapy after an initial platelet response and subsequent loss of platelet response; or (2) receiving a new type of therapy after no platelet response was observed; or (3) introducing therapies for active bleeding. Adverse drug reactions were collected as reported, causality of the events to romiplostim was not assessed. No formal between-group statistical analyses were performed.

**Results**

**Participants and baseline characteristics**

A total of 100 patients were included in the study. Baseline characteristics for the overall population have been reported previously [19].

At romiplostim initiation, 22.0% of patients had newly diagnosed ITP, 17.0% had persistent ITP, and 61.0% had chronic ITP. Baseline characteristics across these 3 groups are shown in Table 1. Baseline platelet counts were lowest in the newly diagnosed setting (median 7.5 × 10^9/L; IQR: 4.0, 16.0) and increased with duration of ITP (Table 1). Few patients with newly diagnosed (4.5%) or persistent ITP (11.8%) had undergone splenectomy prior to romiplostim initiation, whereas 32.8% of chronic ITP patients were splenectomised. The percentage of patients experiencing at least one bleeding event within 6 months prior to romiplostim initiation was highest in newly diagnosed ITP patients (68.2%), with 41.2% of persistent and 29.5% of chronic ITP patients experiencing a prior bleeding event.
Overall platelet response
group (Table 1).
The median time from the start of bleeding to romiplostim were lower in the newly diagnosed and persistent groups. Included the following bleeding types: abnormal vaginal bleeding, central nervous system bleeding with neurologic symptoms, haematemesis, haematuria, and/or melena.

Platelet counts closest to the first prior bleeding event were lowest in the newly diagnosed and persistent groups than in chronic ITP patients (Table 1, Table S1). The median time from the start of bleeding to romiplostim initiation was shortest in the newly diagnosed group (Table 1).

The initial median romiplostim dose was 1 μg/kg body weight in all groups. The average median weekly romiplostim dose across the entire observation period was lowest in newly diagnosed patients (2.17 μg/kg; IQR: 1.06, 4.61). The median duration of exposure to romiplostim was similar in persistent and chronic ITP patients and approached the planned duration of observation of 24 months in these two groups; the median (IQR) exposure in newly diagnosed patients was 18.60 months (3.84, 24.15). Table S2 summarizes romiplostim exposure data.

### Effectiveness

The percentage of patients achieving an overall platelet response to romiplostim exceeded 80% and did not differ according to response definition (i.e. achievement of ≥30 × 10⁹ platelets/L or ≥50 × 10⁹ platelets/L at least once) or ITP duration, ranging from 81.8% to 88.2% across groups. The time to first platelet response, counted after the first week of romiplostim treatment, was shortest in the persistent ITP group and ranged from 15.0 to 27.0 days (Table 2). Fifty percent (95% CI: 28.2–71.8%) of newly diagnosed ITP patients achieved a durable platelet response, while 35.3% (95% CI: 14.2–61.7%) of those in the persistent group and 31.1% (95% CI: 19.9–44.3%) of those in the chronic group met the durable platelet response criteria. The percentage of patients able to discontinue all non-romiplostim ITP medications was highest in the newly diagnosed group (31.8%) compared with 17.6% and 16.4% in the persistent and chronic groups, respectively. The percentages of patients in each group that required rescue therapy was similar and ranged from 9.8% to 13.6%. The incidence of patients experiencing bleeding events requiring emergency treatment was 13.6% in newly diagnosed patients, 5.9% in persistent and 4.9% in chronic ITP patients (Table 2).

### Safety

Of the 100 patients, 4.0% experienced an adverse drug reaction. A detailed summary of adverse drug

| Outcome | Duration of ITP |
|---------|----------------|
|         | <3 months (N = 22) | 3–12 months (N = 17) | >12 months (N = 61) |
| Overall platelet response ≥30 × 10⁹/L, n (%) [95% CI] | 18 (81.8) | 15 (88.2) | 52 (85.2) |
| [59.7, 63.6, 73.8, 94.8, 98.5, 93.0] | |
| Overall platelet response ≥50 × 10⁹/L, n (%) [95% CI] | 18 (81.8) | 15 (88.2) | 52 (85.2) |
| [59.7, 63.6, 73.8, 94.8, 98.5, 93.0] | |
| Durable platelet response, n (%) [95% CI] | 11 (50.0) | 6 (35.3) | 19 (31.1) |
| [28.2, 14.2, 19.9, 71.8, 61.7, 44.3] | |
| KM median [95% CI] time to first platelet response (after day 7), days | 27.0 | 15.0 | 22.0 |
| [15.0, 15.0, 22.0] | |
| Discontinuation of all non-romiplostim ITP treatments, n (%) [95% CI] | 7 (31.8) | 3 (17.6) | 10 (16.4) |
| [13.9, 3.8, 43.4, 8.2, 28.1] | |
| Any rescue therapy, n (%) [95% CI] | 3 (13.6) | 2 (11.8) | 6 (9.8) |
| [2.9, 3.4, 15.6, 8.0, 3.7, 20.2] | |
| Specific types of bleeding, n (%) [95% CI] | 3 (13.6) | 1 (5.9) | 3 (4.9) |
| [0.1, 22.8, 0.4, 11.3] | |
| Bleeding requiring emergency treatment, n (%) [95% CI] | 2 (9.5) | 0 (0.0) | 2 (3.3) |
| [2.9, 3.4, 0.1, 28.7, 0.1, 13.7] | |

Cl: confidence interval of percentage (calculated by exact test); ITP: immune thrombocytopenia; KM: Kaplan-Meier estimates.

*Overall platelet response ≥30 × 10⁹/L: proportion of weekly measurements ≥30 × 10⁹ platelets/L during weeks 2–24 after romiplostim initiation in the absence of rescue therapy.

*Overall platelet response ≥50 × 10⁹/L: proportion of weekly measurements ≥50 × 10⁹ platelets/L during weeks 2–24 after romiplostim initiation in the absence of rescue therapy.

*Durable platelet response: ≥75% of all recorded measurements ≥50 × 10⁹ platelets/L during weeks 14–24 after romiplostim initiation in the absence of rescue therapy.

*Included the following bleeding types: abnormal vaginal bleeding, central nervous system bleeding with neurologic symptoms, hemorrhage, melena.
To first-line treatment. In this trial, 93% of patients (n = 70) receiving romiplostim achieved a platelet response (platelet count ≥50 × 10^9/L) after a median time of 2.1 weeks on treatment.

A number of observational studies and case reports demonstrate that romiplostim has already been used in the newly diagnosed and persistent settings in clinical practice (although off-label at the time) [21]. This real-world evidence from unselected daily practice supports finding from clinical trials that romiplostim is effective and well tolerated in patients <1 year from ITP diagnosis (see review by Lozano et al. [21]). For example, Snell Taylor et al. [18, 23] recently reported that 32% of 64 newly diagnosed, 53% of 50 persistent, and 49% of 226 chronic ITP patients achieved a durable platelet response (same definition as used within our study) and all non-romiplostim ITP medications were discontinued in 74% of newly diagnosed and over half of persistent (69%) and chronic (51%) ITP patients.

In recent guidelines [1, 12–14], TPO-RAs are generally recommended as a second-line treatment in the persistent phase of ITP (after three months). A key potential benefit of using romiplostim earlier in the treatment paradigm (rather than in the chronic setting) is to help avoid unnecessary adverse events associated with prolonged use of steroids, thereby potentially improving quality of life [21]. Indeed, guidelines recommend keeping the initial treatment period with corticosteroid-associated side effects to no longer than 8 weeks [1, 12–14]. In patients with no adequate response to the initial corticosteroid dose within two weeks, prednisolone should be tapered rapidly and then stopped [13]. In cases of life-threatening bleeding, TPO-RAs are also recommended in the newly diagnosed ITP phase. In the present study, 68.2% of newly diagnosed patients had at least one bleeding event prior to romiplostim initiation (compared with 41.2% of persistent and 29.5% of chronic ITP patients), suggesting that these newly diagnosed patients were initiated on romiplostim for emergency care. Similar findings were also observed by Snell-Taylor et al. who found a history of prior bleeding in 75% of newly diagnosed patients, compared to 50% in persistent and 39% of chronic patients [18].

Use of TPO-RAs in refractory patients with ITP of shorter duration may also lead to achievement of prolonged treatment-free periods. In the above-mentioned trial by Newland et al. [22], 32% of patients with ≤6 months of ITP duration at romiplostim initiation achieved a treatment-free remission (platelet counts ≥50 × 10^9/L for 24 weeks without ITP medications). Of these, 79% maintained platelet counts ≥100 × 10^9/L and 54% maintained platelet counts ≥150 × 10^9/L. In their integrated analysis of studies that were not designed to assess remission, Kuter et al [17] found a rate of treatment-free remission of 16% in patients with ≤1 year of ITP duration at
romiplostim initiation and 6% in patients initiated at >1 year. Treatment-free duration was defined as maintaining platelet counts ≥50 × 10⁹/L without any ITP mediation for ≥6 months. In the present study, treatment-free remission was collected as end-of-study status under the term ‘remission’ and/or as reason for discontinuation (as ‘haemostatic platelet range. No further treatment necessary’) per physician assessment from a drop-down menu, with no precise definition in terms of a specific platelet range for a certain duration. Overall, 25.0% of patients met this definition of remission at study end; 23.0% discontinued romiplostim because of ‘haemostatic platelet range’ with no further treatment necessity.

Real-world studies have several limitations as most are descriptive in nature and lack a control group. Therefore, inference of causal relationships should be avoided due to the potential risk of systematic errors (selection bias, information bias, and confounding) that may have affected the estimates [24]. Controlling for all possible confounding variables in studies in routine clinical practice for a rare disease, such as primary ITP, is challenging. Despite these limitations, the real-world data presented herein broadens the totality of evidence around the patient populations who are receiving romiplostim, and the effectiveness and safety of romiplostim in real-world clinical practice, both on- and off-label with results generally aligned with findings from randomized, controlled trials. Kuter et al. [17] analysed seven randomized, controlled trials by duration of ITP (≤1 year versus >1 year) and found substantially higher response rates by any definition evaluated in patients receiving romiplostim compared to placebo/standard-of-care.

Conclusions

In CEE clinical practice, romiplostim was effective and well tolerated, irrespective of ITP duration at the time of romiplostim initiation. Prescribing romiplostim in early ITP was considered as off-label at the time of the conduct of the study. The fact that one-in-five patients received romiplostim in the early stage of ITP demonstrates the need for treatment in this patient population, including in the CEE region.

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Authors contribution

BS, ZS, NT, and GM were responsible for patient data collection and acquisition of data. KB was responsible for data cleaning and site queries. JH planned the presented post hoc analysis. All authors interpreted the data and reviewed and critically appraised the manuscript.

Data availability statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/

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