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Enzalutamide for Primary Immune Prostate Cancer in Routine Clinical Practice: Results from a Rare Metastasis Study in Japan

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ABSTRACT

Introduction: The effectiveness and safety of romiplostim were evaluated by immune thrombocytopenia (ITP) phase (newly diagnosed/persistent/chronic) at romiplostim initiation.

Methods: This is a post hoc analysis of a prospective, Japanese, multicentre, observational study in adults with ITP who received ≥ 1 dose of romiplostim. Follow-up data were collected for ≤ 2 years. Outcomes included overall platelet response (≥ 1 platelet count $\geq 50 \times 10^9/L$ at 2–24 weeks after romiplostim initiation) or durable platelet response ($\geq 75\%$ of measurements $\geq 50 \times 10^9/L$ at 14–24 weeks) and adverse drug reactions (ADRs), evaluated by ITP phase.

Results: Data from 96 patients were analyzed (newly diagnosed, $n = 18$; persistent, $n = 25$; chronic, $n = 53$). During the 2- to 24-week follow-up, overall platelet response was achieved in 100% (95% confidence interval: 81.5–100), 100% (86.3–100), and 96.2% (87.0–99.5) of patients with newly diagnosed, persistent, or chronic ITP, respectively, and platelet responses were durable in 88.2% (63.6–98.5), 65.0% (40.8–84.6), and 69.4% (54.6–81.7) of patients. During the 2-year follow-up, ADRs occurred in 24.0–35.8% of patients across phases. Two patients with chronic ITP experienced bone marrow ADRs; no thrombotic ADRs occurred.

Conclusion: Romiplostim was effective and well tolerated in patients with newly diagnosed, persistent, or chronic ITP in routine clinical practice.

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Introduction

Primary immune thrombocytopenia (ITP) is a rare autoimmune disease characterized by low platelet counts (12 months) [1]. This update in the clinical definition of ITP has posed a number of challenges in terms of treatment decisions as initial drug indications, and associated clinical trial data were based on the old definition. Current guideline recommendations include corticosteroids, intravenous immunoglobulin (IVIg), or anti-D as first-line treatment options for newly diagnosed ITP, with romiplostim considered a second-line treatment option [2-4]. Romiplostim is a thrombopoietin-receptor agonist (TPO-RA) that binds to the TPO receptor, activating the JAK2/STAT5 pathway and ultimately leading to increased platelet production [5]. Romiplostim has demonstrated sustained platelet responses together with low toxicity in patients with chronic ITP, with some patients experiencing treatment-free responses [6-8]. While

romiplostim was initially approved for second line treatment of chronic ITP in patients who are refractory to other treatments, such as corticosteroids, evidence from clinical [9,10] and real-world studies indicated that it could also produce durable platelet responses in patients with newly diagnosed or persistent corticosteroid-refractory ITP [9,11-15]. Furthermore, in an integrated analysis of nine studies, treatment-free responses to romiplostim were more likely in patients who had ITP for ≤ 1 year than in those with ITP for > 1 year [8]. Recently, as a result of the evidence, the US Food and Drug Administration and the European Medicines Agency removed the restriction of “chronic” from their romiplostim indications for adult patients with ITP in 2019 and 2021, respectively [16,17]. Following extension of the regulatory label, romiplostim is now indicated in Europe for the treatment of primary ITP in adult patients who are refractory to other treatments (e.g., corticosteroids and immunoglobulins) [17]. This updated label is aligned with major international and regional guidelines that advocate the second-line use of romiplostim within 1 year of ITP diagnosis. The American Society of Hematology

recommends TPO-RAs as treatment options in patients with ITP for ≥ 3 months who are corticosteroid dependent or have no response to corticosteroids [3]. Similarly, the Joint Working Group of European Hematology Societies in Japan, Austria, and Switzerland recommends that TPO-RAs should be offered as second-line therapy, and that they may be considered for all patients who do not respond to first-line therapy, regardless of disease duration [2]. Decision-making surrounding the optimal treatment pathway for patients with ITP can be challenging in clinical practice. To guide future recommendations and improve outcomes for patients, further real-world data on the use of romiplostim in the newly diagnosed and persistent phases of ITP are warranted. This study describes a population of adults with ITP treated with romiplostim in routine clinical practice in Japan; in particular, the effectiveness and safety of romiplostim were evaluated according to the three phases of ITP.

Materials and Methods

Study Design

This was a post hoc analysis of a prospective, multicentre, single arm, observational study that was conducted in Japan at academic and non-academic clinical practices throughout the country to ensure a representative population of patients. The results from the full study population have been presented previously [18]. Data were collected on the first patient in January 2010, and data of the last patient were collected in July 2016. The original study design is depicted in Figure 1. Patients were followed for 2 years (median [Q1, Q3]: 104.0 [100, 104] weeks) from the day of romiplostim initiation or until death, loss to follow-up, or withdrawal of informed consent (whichever occurred first). Patients were observed for the full period irrespective of continuation of therapy with romiplostim. **Study Population** The study population included patients aged ≥ 18 years with a diagnosis of ITP (according to the Joint Working Group of European Hematology Societies in Japan, Austria, and Switzerland, American Society of Hematology, or British Committee for the Standards in Hematology criteria) who had received at least one dose of romiplostim [2,4,19]. Patients were treated according to routine clinical practice, and the decision to treat was freely undertaken by the clinician. Exclusion criteria were treatment (or planned treatment) with platelet-related products (e.g., pegylated recombinant human megakaryocyte growth and development factor, recombinant human TPO, other TPO-RAs, or related platelet products), simultaneous participation in other clinical studies, initiation of romiplostim treatment prior to commercial availability in Japan, and hypersensitivity to romiplostim, its excipients, or *Escherichia coli*-derived proteins [2,4,19]. All patients provided informed consent. **Study Variables and Outcomes** Following the first dose of romiplostim, follow-up data were collected at 3-monthly intervals for up to 2 years using a standardized electronic clinical response form (eCRF) at all sites. Baseline demographics, patient characteristics, and ITP-specific medical history were abstracted from medical records. Data were also collected for prior ITP-related hospitalizations, defined as those that occurred within a 2-year period before initiation of romiplostim treatment. Reasons for hospitalization included red blood cell transfusion, platelet transfusion, ITP treatment administration, bleeding event, infection, splenectomy, or others. Data on bleeding events up to 6 months prior to initiation of romiplostim were abstracted from medical records. Bleeding events were classified according to the World Health Organization scale [24]. Data collected after initiation of romiplostim included romiplostim dose, number of doses, duration of treatment, adverse drug reactions (ADRs), platelet count over time, bleeding events,

ITP-related hospitalization, and discontinuations. Outcomes included the proportion of patients with an overall platelet response (≥ 1 platelet count measurement $\geq 50 \times 10^9$ /L during 2–24 weeks after romiplostim initiation); the proportion of patients with a durable platelet response ($\geq 75\%$ of all platelet count measurements $\geq 50 \times 10^9$ /L during 14–24 weeks after romiplostim initiation); time to first platelet response ($\geq 50 \times 10^9$ /L) during 2–24 weeks after romiplostim initiation; median platelet count during 2–24 weeks after romiplostim initiation; and the proportions of patients with ITP therapies, bleeding events, transfusion, or Interrelated hospitalization. All ADRs (including thrombotic and bone marrow ADRs) that occurred from the day after initiation of romiplostim therapy through 2 years were evaluated, irrespective of causality to treatment (coded according to Common Terminology Criteria for Adverse Events [CTCAE]).

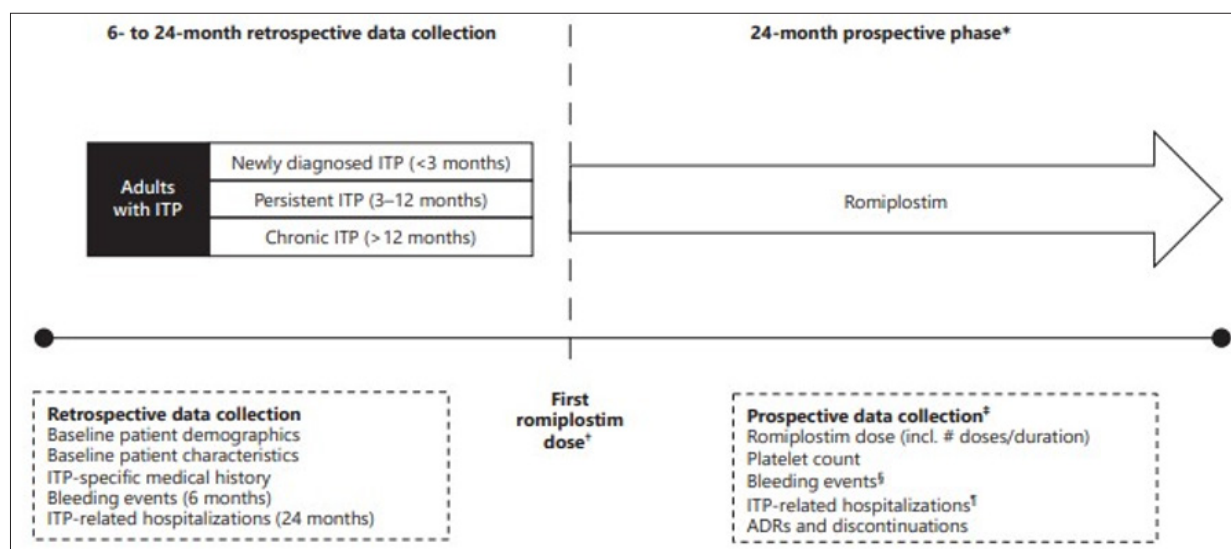


Figure 1: Study design. *Patients were followed for 2 years or until death, loss to follow-up, or withdrawal of informed consent

Statistical Analysis

This was a post hoc analysis of an observational study with no formal hypotheses and hence no power calculations; the planned sample size of approximately 150 patients to enroll into the study was based on the cumulative exposure to romiplostim. Analyses were conducted in patients who met the study eligibility criteria and with known dates for ITP diagnosis and romiplostim initiation. Baseline was defined as the time of romiplostim initiation. All outcomes were analysed by ITP phase at romiplostim initiation: newly diagnosed, persistent, or chronic ITP was defined as time from ITP diagnosis to romiplostim initiation of 12 months, respectively (i.e., as defined by the International Working Group in 2009) [1]. Analyses were descriptive in nature. In each ITP phase, categorical outcomes were summarized using frequencies and percentages (with 95% confidence intervals [CIs] where appropriate), and continuous data were summarized using mean and standard deviation (or 95% CI where appropriate) or median and interquartile range (IQR). Additionally, unweighted mean dose and median platelet count were calculated for each patient over the follow-up period. Missing data were not imputed, except for start/end dates for ADRs and medication. Where a start date for an ADR/medication was partial or missing, the following imputation rules were applied: if the day portion was missing, it was set to day 1; if the month portion was missing, it was set to January 1; if the date was completely missing or if the imputation date was prior to the first dose date, the date was set to the first dose date. Where an end date for an ADR/medication was partial or missing for ADRs that were resolved (end date was not imputed for not resolved ADRs), the following imputation rules were applied: if the day portion was missing, the date was set to the last day of the month; if the month portion was missing, the date was set to December 31; if the date was completely missing or if the imputation date was after the end of the patient's observational period, the date was set to the date of discontinuation.

Results

Baseline Demographics and Patient Characteristics

A total of 159 patients were enrolled at 38 sites in Japan and were included in the study; 22 patients were excluded met [n = 12], inclusion criteria not met [n = 3], documentation incomplete/not valid [n = 4], and screening failure [n = 3]). The ITP phase for 41 patients could not be determined due to a missing date of ITP diagnosis, and these patients were also excluded from the analyses

met [n = 12], inclusion criteria not met [n = 3], documentation incomplete/not valid [n = 4], and screening failure [n = 3]). The ITP phase for 41 patients could not be determined due to a missing date of ITP diagnosis, and these patients were also excluded from the analyses.

Romiplostim Use and Administration during the 2-Year Follow-Up Period

Over the 2-year follow-up, patients with persistent ITP received a lower median number of romiplostim administrations (37 administrations) across a lower median number of weeks (87 weeks) compared with patients with newly diagnosed or chronic ITP.

Platelet Count during the 24-Week Follow-Up Period

CI, confidence interval; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; Q, quartile. * Newly diagnosed ITP: 12 months from diagnosis. † Patients for whom there were no data on the number of platelets or the timing of the platelet measurement were censored. ‡ An overall platelet response was defined as having ≥ 1 platelet count measurement $\geq 50 \times 10^9/L$ during 2–24 weeks after romiplostim initiation. § A durable platelet response was defined as having $\geq 75\%$ of all platelet count measurements $\geq 50 \times 10^9/L$ during 14–24 weeks after romiplostim initiation. II Three patients required transfusions. One patient required transfusion.

Concomitant ITP Therapy

Following initiation of romiplostim treatment, at least one concomitant ITP therapy was administered in over half of the patients with newly diagnosed ITP (61.1%) and less than half in patients with persistent and chronic ITP (28.0% and 39.6%, respectively). The most frequently administered medications to patients with newly diagnosed, persistent, and chronic ITP were corticosteroids and IVIg.

Discussion/Conclusion

The aim of this post hoc analysis of an observational study was to describe the population of adult patients with ITP who received romiplostim in routine clinical practice in Japan and to gain insights into the effectiveness and safety of romiplostim according to the phase of ITP in these patients. The results of our study showed that clinically meaningful platelet responses were achieved

and sustained in the majority of romiplostim-treated patients in all ITP phases. Romiplostim was well tolerated regardless of ITP phase at romiplostim initiation, with minimal discontinuations due to ADRs. Our study sample was representative of the general Japanese ITP population, as shown by comparison to patients in a national survey (2016–2017) [21].

In both study cohorts, over 50% of patients had chronic ITP (>12 months); corticosteroids and IVIg were the most frequently used treatments prior to romiplostim initiation. Similarly, rates of splenectomy were relatively low across all ITP phases in this study and the national survey [21]. Over half of the patients in all ITP phases underwent bone marrow biopsy prior to romiplostim treatment. This is important to note, as patients with chronic ITP who undergo bone marrow biopsy after diagnosis have more severe disease and are at greater risk of potentially serious complications [22]. Notably, in the present study, romiplostim was initiated within the first year following ITP diagnosis in almost half of the patients, despite the chronic indication included in the European label at the time of the study. A substantial proportion of patients with newly diagnosed or persistent ITP have also been treated with romiplostim in other European countries, as demonstrated in real world studies [12,14,23,24].

This real-world usage in earlier treatment lines is aligned with Joint Working Group of European Hematology Societies in Japan, Austria, and Switzerland guidelines, which recommend the use of TPO-RAs in all patients who do not respond to first-line therapy, regardless of ITP stage, and with the American Society of Hematology guidelines, which recommend the use of TPO-RAs in adults with ITP for ≥ 3 months who are corticosteroid dependent or unresponsive to corticosteroids [2,3]. Platelet responses to romiplostim were achieved rapidly and consistently by patients in all ITP phases. The time to first platelet response was generally consistent across ITP phases, ranging from 7 days in patients with persistent or chronic ITP to 8.5 days in those with newly diagnosed ITP. Moreover, patients with newly diagnosed and persistent ITP achieved high rates of overall platelet responses (100%) and high rates of durable platelet responses (65.0–88.2%), suggesting effectiveness of romiplostim within 1 year of ITP diagnosis, as well as in patients with chronic disease. Our findings were similar to those reported from clinical studies, which indicate that romiplostim can lead to sustained platelet responses in the majority of patients regardless of whether they have newly diagnosed, persistent, or chronic ITP [6,8,9,15].

Platelet response definitions can be highly variable between different ITP studies; however, the same platelet count threshold of $\geq 50 \times 10^9 /L$ used in this study has also been used in previous studies of romiplostim and other ITP therapies [6,8,9,15, 25–29]. Although neither a dosing algorithm nor a target platelet count was pre-defined in this observational study, the majority of patients across all ITP phases were treated with an initial dose of 1 $\mu g/kg$ in line with the recommended dose for patients from the European label (noting that a substantial proportion, 15–24%, started above this dose) [17]. Furthermore, the median weekly romiplostim dose during the first 24 weeks of romiplostim treatment (1.4–2.4 $\mu g/kg$) corresponds well to the median dose used in the registrational trials (i.e., 2–3 $\mu g/kg$) [17].

The results from this study confirm the established favorable safety profile of romiplostim from previous clinical studies and real-world studies [6–9, 12–14]. The proportion of patients with an ADR leading to romiplostim withdrawal was low (4%), no

patients experienced thrombotic ADRs, and bone marrow-related ADRs were reported in only 2 patients (both with chronic ITP). In the overall study population, the rate of time-adjusted bleeding events of at least grade 3 in severity prior to romiplostim was 7.2/100 patient-years [13]. This time-adjusted rate decreased to 4.0/100 patient-years following initiation of romiplostim [13]. In contrast, corticosteroid use is associated with a number of side effects, such as weight gain, hypertension, increased risk of infection, and osteoporosis [2]. Despite guidelines warning that first-line corticosteroids should be used for a limited period of time (e.g., to a maximum of 6 weeks for prednisolone), there is an over-reliance on corticosteroids in routine clinical practice [2,3,4]. Therefore, the earlier second line use of romiplostim may help to avoid side effects associated with corticosteroid use and decrease the need for other subsequent therapies, such as splenectomy, that may have long-term health risks [30–32].

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Author Contributions

All authors contributed to the analysis or interpretation of the data, revision of the manuscript, and approved the final version.

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