1. ABSTRACT

- **Title**

Primary Immune Thrombocytopenia Treated With Romiplostim in Routine Clinical Practice: A Retrospective Study From the United Kingdom Immune Thrombocytopenia Registry

- **Keywords**

Nplate®, romiplostim, immune thrombocytopenia, ITP, registry

- **Rationale and Background**

Primary immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura; ITP) is a rare autoimmune blood disorder, which is characterised by a platelet count < 100 x 10^9/L in the absence of any other disorders associated with thrombocytopenia. First-line treatment for primary ITP includes corticosteroids, intravenous immunoglobulin (IVIg), and Rh_o(D) immune globulin (anti-D); the latter is not available in the European Union. Patients who are unresponsive to these drugs are considered for second-line treatments such as danazol, mycophenolate mofetil, azathioprine, cyclosporine, rituximab, and thrombopoietin receptor agonists (TPO-RA). Romiplostim (Nplate) is a TPO-RA approved in Europe for adults with chronic ITP that is refractory to other treatments (eg, corticosteroids and IVIg). Since 2011, patients in the United Kingdom may receive romiplostim in accordance with its marketing authorization as recommended by the National Institute for Health and Care Excellence (NICE).

The efficacy of romiplostim in clinical trial populations has already been published but there is limited published evidence about its use in real-life settings in the United Kingdom. This study therefore aims to describe the use of romiplostim in patients with primary ITP in routine clinical practice within the United Kingdom, to describe the demographic and clinical characteristics of patients with ITP receiving romiplostim in the United Kingdom, and to report the use of ITP medications, platelet counts, and bleeding events before and after romiplostim initiation. Moreover, this study also describes the pattern of rituximab administration in patients who received romiplostim as an exploratory analysis to investigate the level of use of this drug as second-line therapy.

- **Research Question and Objectives**

Primary Objectives

- to describe the demographic and clinical characteristics of patients with primary ITP receiving romiplostim
- to describe the use of ITP medications and platelet counts before and after romiplostim initiation

Secondary Objectives

- to describe the pattern of romiplostim administration
- to estimate the rate of bleeding events before and after romiplostim initiation
- to estimate the rates of all cause and cause-specific hospital admissions before and after romiplostim initiation
- to estimate the rate of rescue medications used before and after romiplostim initiation

Exploratory Objectives

- to describe the pattern of rituximab administration in patients who have received romiplostim
- to describe the primary and secondary endpoints in the study population categorised by splenectomy status at romiplostim initiation

- **Study Design**

This study was a retrospective cohort study that used data from the United Kingdom Immune Thrombocytopenia (UKITP) Registry.

- **Setting**

The study was conducted using data from the UKITP Registry, which retrospectively and prospectively collects demographic and ITP-related clinical data on patients with primary ITP enrolled by consent through a network of 68 centres throughout the United Kingdom. The index date for the current study was the first use of romiplostim. Follow-up started at first exposure to romiplostim and continued after the index date until a patient exited the study for any reason (eg, leave study registry, death, or loss to follow-up) or the end-of-study period (ie, end of December 2014), whichever occurred first.

- **Patients and Study Size, Including Dropouts**

All adults (≥ 18 years) within the UKITP Registry diagnosed with primary ITP and who had received at least 1 dose of romiplostim after launch in the United Kingdom in October 2009 were included in the study. Patients identified with secondary ITP or familial ITP or who participated in any romiplostim clinical trial were excluded.

- **Variables and Data Sources**

Data were retrieved from the UKITP Registry for the following: demographic and clinical characteristics, pattern of romiplostim administration, platelet counts, bleeding events, hospitalisations, and pattern of rituximab administration.

Data within the UKITP Registry are collected from the patient's medical notes, hospital electronic records, and from the data received from the patient's general practitioner at different time points (at the time of enrolment, as the data become available, or at a minimum annually during the follow-up). Certain information is also directly reported by the patients to their clinician who can directly enter information onto the data collection forms. All collected data are entered in the registry's online database and backed up regularly.

- **Results**

At the time of data extraction from the UKITP Registry (31 January 2015), 1440 patients with ITP were registered and the 118 adult patients with primary ITP who were treated with romiplostim during routine clinical practice in the United Kingdom since October 2009 were considered eligible for this study.

The median age at ITP diagnosis of the romiplostim cohort was 58.5 years (interquartile range [IQR]: 35.8, 73.1). Patients in the romiplostim cohort had been diagnosed with ITP since 1980, with 50% diagnosed between 2010 and 2014. The median time from ITP diagnosis to romiplostim initiation was 3.3 years (IQR: 0.9, 8.1). Almost three-quarters of patients (72.9%) initiated romiplostim ≥ 1 year from ITP diagnosis, and 27.1% of patients initiated romiplostim within 1 year of ITP diagnosis (with 11.9% within 3 months, 5.9% between 3 and 6 months, and 9.3% between 6 months and 1 year).

Most patients (77.1%) had received at least 3 different ITP medications before romiplostim. The most common ITP treatments before romiplostim initiation were steroids (89.8%), IVIg (77.1%), and rituximab (56.8%). All patients had at least 1 course of romiplostim, defined as a cluster of romiplostim prescriptions in which the time between 2 prescriptions was no longer than 3 weeks. The median duration for the first course of romiplostim was 1.4 months (IQR: 0.2, 6.5), with a median maximum weekly romiplostim dose of 3.0 μg/kg (IQR: 2.0, 6.0). After initiation of romiplostim, additional ITP therapy was prescribed or continued. The most frequently administered of these medications were steroids (32.2%), IVIg (27.1%), and eltrombopag (24.6%). Overall, 82.2% of patients had 2 or fewer ITP medications after romiplostim initiation.

The mean platelet count within 2 weeks before romiplostim initiation was 38.1 x 10^9/L (SE: 5.8), which rose to 102.9 x 10^9/L (95% CI: 89.4, 116.4) within 1 month of romiplostim treatment and thereafter was maintained in the 50 x 10^9/L to 150 x 10^9/L range through up to 3 years of follow-up.

During the observation period (time from romiplostim initiation until end of follow-up), 82 patients (69.5%) had at least 1 ITP-related hospital admission (including day case admission) (852.3 per 100 patient-years). Thirty-four (28.8%) patients had at least 1 bleeding event (at any site) (234.9 events per 100 patient-years within 6 months of romiplostim initiation). The most frequent bleeding manifestations during the observational period were external bleeding (skin) (22 of 118 patients [18.6%]), epistaxis (10 of 118 patients [8.5%]), other gastrointestinal bleeding (non-oral) (7 of 118 patients [5.9%]), haematoma (6 of 118 patients [5.1%]), and oral bleeding (6 of 118 patients [5.1%]) after romiplostim initiation in the overall population.

- **Discussion**
  - This study was conducted to provide a better understanding of the treatment of primary ITP patients with romiplostim in routine clinical practice in the United Kingdom. Despite limitations such as potential selection bias into the registry, the small sample size, and the heterogeneous nature of the selected cohort, the UKITP Registry provides a valuable insight in the real-world ITP patient population prescribed with romiplostim in the United Kingdom.
  - Among the 118 adult romiplostim-treated patients with primary ITP in this study, most patients (77.1%) had received at least 3 different ITP medications before romiplostim. Most patients (82.2%) initiated romiplostim after 6 months from ITP diagnosis and nearly one-fifth of patients (17.8%) initiated romiplostim within 6 months from ITP diagnosis. After romiplostim initiation, mean platelet counts were maintained above 50 x 10^9/L during the study.
  - The number of different types of ITP therapeutic treatments used before and after romiplostim initiation within this UKITP cohort highlights the complexity of ITP treatment in routine practice. The initiation of romiplostim at different ITP disease phases, with most patients initiating treatment during the chronic disease phase and some initiating treatment with romiplostim earlier (within 6 months of diagnosis with primary ITP), highlights the diversity of romiplostim administration in routine clinical practice.

- **Marketing Authorization Holder**

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

- **Names and Affiliations of Principal Investigator**

Dr Drew Provan
Blizard Institute
Barts and The London School of Medicine and Dentistry
Queen Mary's University London
London