



Full Length Article

Epidemiology and management of primary immune thrombocytopenia: A nationwide population-based study in Korea



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ABSTRACT

Introduction: The epidemiology of immune thrombocytopenia (ITP) is not well characterized in an Asian population. **Materials and methods:** From July 2010 to June 2014, ITP patients were identified using the Korean Health Insurance Review and Assessment Service database.

Results: The overall incidence rate of ITP was 5.3 per 100,000 person-years (95% CI: 5.1–5.5). The overall incidence rate ratios of children under 15 years old to adults and females to males were 3.8 (95% CI: 3.7–3.9) and 1.3 (95% CI: 1.2–1.4), respectively. Of the total 10,814 patients, 3388 patients (31%) needed treatment for ITP; of these, 54% continued treatment for more than three months. First-line therapy consisted of corticosteroids (CS) in 42%, immunoglobulin (IVIg) in 35%, CS with IVIg in 19%, and other immunosuppressive agents (ISA) in 4%. Among treated patients, 75% of adults and 33% of children continued treatment for more than three months. After three months, the most frequently used drug was CS alone in 63% of patients. Only 104 patients underwent splenectomy; of these, 51% received salvage treatment after a median of one month after surgery (range: 0–27). The proportion of patients who received platelet transfusions of 12 units or more per month for at least two consecutive months was significantly higher among patients treated for more than three months compared with patients who completed treatment within three months.

Conclusions: This population-based study is the first to describe the incidence of ITP and its treatment reality for patients in Korea.

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1. Introduction

Immune thrombocytopenia (ITP) is an autoimmune-mediated condition that results from antibody-mediated destruction of platelets and impaired platelet production of megakaryocytes [1,2]. Primary ITP is defined as an isolated platelet count $< 100 \times 10^9/l$, in the absence of any underlying cause or disorder [3]. Most epidemiologic studies have been conducted in Europe, and data remain limited in Asian populations. ITP incidence is estimated to be between 3.0 and 5.3 per 100,000 person-years in children and between 1.6 and 3.9 per 100,000 person-years in adults [4–9]. A registry-based study reported an overall incidence rate of ITP in Japan of 2.2 per 100,000 person-

years [10]. However, the epidemiology of ITP has not been characterized using a nationwide population-based dataset, particularly in Asian populations.

Management options for patients with ITP have evolved substantially over the past decade [11]. With recent advances in treatment, including rituximab and thrombopoietin-receptor agonists (TPO-RAs), a larger proportion of patients are able to maintain platelet counts with acceptable tolerability and safety [12–14]. Knowledge about incidence and real world treatment patterns of ITP has important implications for public health, hospital resource utilization, and clinical research. The few national surveys conducted to investigate the patterns of practice for ITP treatment showed great variation in the management of patients with ITP, although these data may not be easily generalized [15,16]. Recently, Michel et al. described the current clinical practice for adults with ITP, but this study was limited by its focus on hospitalized patients [17]. Korea operates a unified mandatory national health insurance system. Its claim data and review records are sufficient to analyze the real-world treatment of specific diseases. In this study, we aim

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to investigate the nationwide incidence and practice patterns of ITP using the Korean Health Insurance Review and Assessment Service databases.

2. Material and methods

2.1. Korean Health Insurance Review and Assessment Service (HIRA) databases

The National Health Insurance (NHI) is the only public medical insurance system operated by the Ministry for Health, Welfare and Family Affairs in Korea [18,19]. The NHI program of Korea covers the entire Korean population as a compulsory social insurance system, including medical aid covering 2.9% of beneficiaries in 2012. The HIRA is a government-affiliated organization created to build an accurate claims review and quality assessment system for the NHI [20]. HIRA databases are open for all investigators with academic purposes.

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital and the need for informed consent from each patient was waived, as the authors did not have access to identified information.

2.2. Study population

The study population consisted of ITP patients of all ages. Diagnoses were codified according to the 5th and 6th Korean Classification of Disease (KCD-5 in 2010; KCD-6 from 2011 to 2014). KCD-5 and KCD-6 are modified classification systems from the International Classification of Disease-10 (ICD-10). The selection process followed several steps (Fig. 1). First, 26,084 patients coded as having a diagnosis of ITP (KCD-5 code D693 and KCD-6 codes D693 or D6938) as the main or related disease were selected from 2010 to 2014. Second, we excluded 7450 cases that shared other bleeding disease codes between the time of first encoding of ITP through the six months following the ITP diagnosis. These codes were D690, D691, D692, D694, D695, D696, D698, or D699. The most frequently excluded cases had unspecified thrombocytopenia of D696 (Table S1). Third, 2107 patients with whom ITP was associated with malignancies, including lymphoproliferative disorders, a chronic viral infection, or systemic autoimmune diseases, were classified as secondary ITP, according to an international working group and excluded from the study (Table S2) [3]. Last, we restricted patients to those with a date of diagnosis after July 1, 2010, as we could not assess whether an ITP diagnosis during the first half of 2010 was prevalent or incident. We also excluded patients with a date of diagnosis after June 30, 2014, because we could not ascertain the presence or absence of other D69 codes during the six months following diagnosis. Finally, a total of 10,814 incident ITP cases (diagnosed between July 1, 2010 and June 30, 2014) were selected for this study.

We searched for the medication codes at both hospital admission and outpatient clinic visits, looking for administration of systemic corticosteroids (CS), intravenous immunoglobulin (IVIg), including anti-D immunoglobulin, and immunosuppressive agents (ISA) including danazol, azathioprine, cyclosporin A, dapsone, mycophenolate mofetil, cyclophosphamide, vinblastine and vincristine. Drug therapies were divided into four categories: CS, IVIg, CS with IVIg, and ISA. The ISA group included ISA alone or in combination with CS and/or IVIg. We also evaluated the procedure codes for splenectomy and platelet transfusion. One unit of platelet apheresis is considered to be six units of platelet concentrate (PC). We defined the heavy transfusion requirement as 12 units of PC or more per month for at least two consecutive months. Data around the use of rituximab or TPO-RA were not available, as these drugs were not reimbursable in HIRA system during the study period. Instead, we identified information about patients who used their own finances to receive TPO-RA through the Korean Orphan Drug Center (KODC) during the study period.

2.3. Statistical analysis

The overall incidence rate was calculated as the number of patients who developed ITP divided by the total beneficiaries of medical security based on the 2012. The total population according to data from the NHI was 51,169,141 in 2012 (25,647,133 males and 25,522,008 females) [21]. Ages were grouped as follows: <1, 1–4, 5–9, 10–14, 15–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years of age. Descriptive analyses were used to compare children (aged <15 years) with adults (aged ≥15 years). A 95% confidence interval (CI) of the incidence rate and differences in the incidence of ITP by age and sex were estimated using Poisson distributions. Comparisons between groups were performed by chi-square tests. Significance was defined as $P < 0.05$ for all analyses.

3. Results

3.1. Incidence of whole and treated ITP in Korea

We identified 10,814 patients with incident ITP during the 4-year study period (Fig. 1). The overall incidence of ITP was 5.3 per 100,000 person-years (95% CI: 5.1–5.5). The incidence rate for children was statistically significantly higher than adults (14.3 per 100,000 person-years [95% CI: 13.4–15.1] vs. 3.7 per 100,000 person-years [95% CI: 3.5–3.9], $P < 0.0001$), with an estimated incidence rate ratio of children relative to adults of 3.9 (95% CI: 3.7–3.9). We observed a higher incidence of ITP among females relative to males (6.0 per 100,000 person-years [95% CI: 5.7–6.3] vs. 4.5 per 100,000 person-years [95% CI: 4.3–4.8], $P < 0.0001$), with an estimated incidence rate ratio comparing women with men of 1.3 (95% CI: 1.2–1.4). We found 3388 patients receiving treatment with an incidence of 1.7 per 100,000 person-years (95% CI: 1.5–1.8). Among treated patients, patterns of the predominance of child and female patients still persisted; the estimated incidence rate ratios comparing children with adults and women with men were 3.7 (95% CI: 3.2–4.2) and 1.2 (95% CI: 1.1–1.4), respectively.

Fig. 1a shows the age and sex distribution of all ITP patients. The age-specific incidence of total ITP patients appeared to have a bimodal distribution for men, with the first peak incidence observed among boys under 10 years old (19.6 per 100,000 person-years [95% CI: 17.9–21.4]) and the second peak among men aged 80 or older (9.2 per 100,000 person-years [95% CI: 5.9–12.6]). For women, incidence rates peaked in patients under 10 years old (15.9 per 100,000 person-years [95% CI: 14.3–17.6]). Significant differences in sex-specific incidence were observed among patients aged 20–29, 30–39, 40–49, and 50–59, with the incidence among women being 2.7 times (95% CI: 2.3–3.1), 3.4 times (95% CI: 3.0–3.9), 2.2 times (95% CI: 1.9–2.4), and 1.8 times (95% CI: 1.6–2.0) greater than among men, respectively. However, among age groups under 10 years old, the pattern was reversed, with a higher incidence among boys relative to girls (1.2 times, 95% CI: 1.2–1.3). In addition, an excess of incident male cases at the oldest ages (≥80 years) was observed (1.7 times, 95% CI: 1.3–2.2). We identified two subgroups with a considerable predominance of boys, those under one year old (1.4 [95% CI: 1.2–1.5]) and those aged 1–4 (1.3 [95% CI: 1.1–1.4]) (Fig. 1b). Among the 3388 treated patients, the significant predominance of males under the age of five and females aged 20–59 persisted, but the male predominance of seniors aged 80 or above disappeared (Fig. 1c and d). There were no significant seasonal or monthly variations in the incidence of ITP in either adults or children (data not shown).

3.2. Patterns of treatment

A total of 3388 (31%) patients received treatment, with a median follow-up duration of 29 months (range, 0–54 months). Treated patients were followed significantly longer than untreated patients (30 months [range, 0–54 months] vs. 28 months [range, 0–54 months]; $P = 0.02$).

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