Chronic immune thrombocytopenia in Denmark, Sweden and Norway: The Nordic Country Patient Registry for Romiplostim

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ABSTRACT

Background: Population-based cohorts of immune thrombocytopenia (ITP) are useful for understanding occurrence, clinical characteristics and long-term clinical course. This paper describes the content of the Nordic Country Patient Registry for Romiplostim (NCPRR) and provides prevalence and incidence estimates of chronic ITP (cITP).

Methods: The NCPRR, a cohort study established in 2009, includes all adult (≥18 years) patients in Denmark, Sweden and Norway with cITP (defined as ITP lasting >12 months and platelet count <100 × 10^9/L), combining data from national health registries and medical records. The NCPRR currently includes prevalent cITP patients diagnosed before 2009 and incident cITP patients diagnosed during 2009–2016. The registry obtains clinical information for cITP patients, including comorbidities, treatments, laboratory values, and complete follow-up for various outcomes.

Findings: The NCPRR currently includes 3831 patients with cITP (1258 prevalent; 2573 incident). In 2009, the prevalence of registered cITP was 10/100,000 (95% CI: 9–11) adult persons in Denmark and 10/7100,000 (95% CI: 9–11) adults in Sweden. During 2009–2016, the incidence rates of cITP per 100,000 person-years were 2.8 (95% CI: 2.6–3.0), 1.8 (95% CI: 1.7–2.1) and 2.1 (95% CI: 1.9–2.2) in Sweden and Norway, respectively. Fifty-eight percent of cITP patients were women. At NCPRR inclusion, 30.2% were aged ≥70 years, 23% had a platelet count <50 × 10^9/L, 17.4% were splenectomized, 41% had prior ITP therapy, and 8.6% had severe comorbidity.

Interpretation: The NCPRR provides population-based data on the epidemiology and characteristics of almost 4000 cITP patients and is a valuable resource for research.

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1. Introduction

Primary immune thrombocytopenia (ITP) is a rare autoimmune disorder that leads to decreased production and peripheral destruction of platelets [1]. Incidence of ITP in adults ranged from 1.6 to 3.9 per 100,000 person-years in previous studies conducted in Denmark, Sweden, France, Japan, Korea, Taiwan, and the United Kingdom (UK) [2–10]. Prevalence of ITP was reported to be between 4.5 and 23.6 per 100,000 persons in two US studies [11,12]. Previous estimates of incidence and prevalence used various definitions of ITP and have not been confirmed in a contemporary population-based multinational cohort study.

Although ITP can follow a self-limiting course in some patients, for the majority of adults diagnosed with ITP, the disorder is persistent (lasting 3–12 months) or chronic (lasting >12 months) [13]. Large population-based cohorts with comprehensive clinical information are valuable to examine the incidence and clinical course of persistent or chronic ITP and the effectiveness and long-term safety of new or existing treatments, particularly given the condition’s rarity. The Nordic Country Patient Registry for Romiplostim (NCPRR) was established in 2009 as a post-authorization safety study to assess long-term safety and to monitor long-term outcomes in all adult patients with chronic ITP (cITP).

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Research in context

Evidence before this study

We searched PubMed for articles published in English using the search string “Immune thrombocytopenia” AND (“Registry” OR “Population-based”). No date restrictions were applied. Reference lists of relevant studies were reviewed to identify other relevant studies. Studies were included if they provided data on incidence or prevalence of immune thrombocytopenia in a well-defined population. Our review showed that incidence of ITP has been reported in previous studies in different countries, while data on prevalence of ITP is limited to two US studies.

Added value of this study

The Nordic Country Patient Registry for Romiplostim (NCPRR) currently follows the largest chronic immune thrombocytopenia (cITP) cohort in the world with detailed data on almost 4000 adults with confirmed cITP in Denmark, Sweden and Norway excluding transient ITP. This contemporary population-based study confirmed findings from the previous smaller studies on incidence and contributed new data on prevalence of cITP. The study included information on characteristics of cITP patients, including results from reassessment of routinely collected bone-marrow biopsies showing that only a small proportion of patients had increased reticulin and collagen content at cohort inclusion.

Implications of all available evidence

Large multinational patient cohorts are critical resources for studies of treatment practices, disease burden, and outcomes in routine clinical practice for patients with a rare disease like cITP.

Our aims herein are to describe: (1) the establishment and data content of the NCPRR; (2) the prevalence and incidence of adult cITP in the Nordic countries based on the NCPRR data thus far; and (3) the demographic and clinical characteristics of cITP patients included in the NCPRR.

2. Methods

2.1. Study Design and Setting

The NCPRR was established in April 2009 as a cohort study of all adult cITP patients in Denmark, Sweden and Norway (combined adult population = 15.4 million persons) with study inclusion continuing through 2019. The three countries have tax-funded health care systems. ITP patients are referred by their general practitioners to hospital-based hematological specialists. Hospitals are required to report data on all hospital visits to nationwide hospital registries [14–16]. Virtually complete follow-up for hospitalizations, outpatient clinic visits, and death among ITP patients is available through the countries nationwide hospital and population registries, linkable through the personal identification number (PIN) assigned to all residents of each country [17,18].

2.2. Data Sources

The NCPRR makes use of data from the National Health Registry System of each country and from medical record review.

The Danish National Patient Registry (DNPR) contains data on all hospitalizations in Denmark since 1977 and on outpatient clinic visits and emergency room visits since 1995 [14]. Variables include, among others, dates of hospital admission/discharge or outpatient contact, diagnoses coded according to the International Classification of Diseases, Tenth Edition (ICD-10) since 1994, and major procedures and treatments performed. The Danish Civil Registration System, established in 1968, includes data on vital status (deceased, alive, emigrated), country of birth, and place of residence of all Danish residents [17].

The Swedish Population Register contains information on all inpatient admissions to public hospitals since 1987 and on outpatient visits since 2001 [16]. Available data are similar to those in the DNRP, except for coding of diagnoses, which are based on the ICD-9 until 1997 and ICD-10 thereafter. The Swedish Population and Address Register includes data on vital status and emigration [18].

The Norwegian Patient Registry, established in 1997, has included PINs since 2008 [15]. The Registry contains data of hospital admission/discharge and outpatient contacts, diagnoses coded according to ICD-10, and major procedures performed. The Norwegian Central Population Register includes data on vital status and emigration.

In addition to the registry sources described above, patients’ original paper and electronic medical records are manually reviewed to obtain clinical data on treatments, bleeding episodes requiring hospitalization, height, weight, and laboratory results. Variables are listed in Appendix 1.

2.3. ITP Patients

Patients are eligible in the NCPRR if they (1) were alive at or after cohort establishment on 1 April 2009, (2) had at least two inpatient or outpatient diagnoses of ITP or other primary thrombocytopenia separated by more than six months during the period from 1 January 1996 to 31 December 2016, (3) were aged 18 years or older on the date that the criteria for cITP were fulfilled, and (4) did not have any diagnosis consistent with secondary ITP or other causes of thrombocytopenia within 5 years preceding cITP diagnosis. Diagnosis codes are provided in Appendix 2. Patients also are required to be actively followed in the health care system, i.e., to have at least one hospital contact with an ITP diagnosis in the study period. We reviewed the medical records on all eligible patients to confirm the ITP diagnosis by at least one documented platelet count below 150 × 10^9/L and by an ITP diagnosis noted in their medical records reflecting that the treating physician considered the patient to have primary ITP.

The NCPRR inclusion date is the date that a patient fulfils the criteria for cITP, defined as the date of the first ITP-related hospital contact occurring more than 6 months after an initial ITP diagnosis. This definition is consistent with the cITP definition used when the study was planned [1]. In this paper we further restricted to patients with cITP according to the current recommended cITP definition, i.e., ITP lasting greater than 12 months with any platelet count < 100 × 10^9/L [13]. For the current analyses, the study inclusion was the first ITP-related hospital contact occurring more than 12 months after the initial ITP diagnosis.

2.4. Patient Characteristics

Data on age, sex, conditions included in the Charlson Comorbidity Index [19], and splenectomy are obtained from the national health registries.

2.5. Bone Marrow Reassessment

Bone marrow sampling (aspirations or biopsies) performed in routine clinical practice is ascertained from medical records in Sweden and Norway, and from the Danish Pathology Registry in Denmark [20]. The NCPRR has access to all routinely performed bone marrow specimens in the three countries that are archived after evaluation in...
regional departments of pathology. The NCPRR retrieves, retains and reassesses the most recent bone marrow biopsy before study inclusion and all subsequent biopsies performed during the study period for reticulin and collagen content, and grades them according to the European consensus of grading bone marrow fibrosis (MF) by an experienced hematopathologist in each country [21].

2.6. Other Outcomes

For all patients in the cohort, we review medical records annually to identify worsening thrombocytopenia, thrombosis, anemia, bleeding requiring hospitalization, and/or use of rescue medication with intravenous immunoglobulin (IVIG), intravenous Rho immunoglobulin, or intravenous glucocorticoids. The Registry also obtains data annually from the national patient registries to assess other outcomes, including thrombotic/thromboembolic events, hematological malignancies, and acute renal failure.

2.7. Statistical Analyses

The prevalence of cITP in Denmark and Sweden was computed by dividing the number of living persons with cITP at study start on 1 April 2009 by the total adult population alive on 1 January each year in each country, as provided by national websites with data on population statistics. As Norway did not collect data on cITP diagnoses before 2008, prevalence could not be estimated for this country. Analyses of prevalence were stratified by combinations of sex and age group (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+ years). We computed 95% confidence intervals (CIs) using Jefferys Prior [22].

The incidence of cITP in Denmark, Sweden and Norway was computed as the number of incident cITP patients in the study period divided by person-years of follow-up, assuming that the entire adult population alive on 1 January 2009 was followed during the study period. Analyses of incidence were stratified further by combinations of sex and age group (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+ years). We computed 95% CIs assuming a Chi-squared distribution.

For all prevalent and incident cITP patients included in the cohort, we tabulated demographic variables, comorbidity level, individual chronic diseases, and clinical characteristics at study inclusion.

We also tabulated the number and proportion of patients with a bone marrow biopsy and the MF grading of the most recent bone marrow biopsy obtained before study inclusion, overall and stratified by age (≤ 60 versus > 60 years).

We repeated the analyses with cITP defined according the NCPRR study inclusion criteria as at least 6 months ITP duration and at least one platelet count < 150 × 10^9/L.

2.8. Ethical Considerations

The study was approved by Ethics Committees in Denmark (record number N-20080040), Sweden (record number 2009/1597-31/4 and 2013/182-32), Norway (record number REK sør øst 2012/1444) and the Data Protection Agency in Denmark (record number 2015-57-0002/ Aarhus University record number 2016-051-000001 - 387). The Ethics Committees granted permission to abstract data from medical records without patients’ informed consent, but individual hospital departments could waive participation in the Registry.

2.9. Role of the Funding Source

Amgen contributed to the funding and design of the NCPRR, but was not involved in the design of the current analyses. Amgen approved the current publication, but the decision to publish was at the initiative of the collaborators from Denmark, Sweden, and Norway.

3. Results

To date, a total of 6955 patients with potential adult cITP have been identified. After excluding patients with a other cause of thrombocytopenia (n = 514, 7.4%), patients without an ITP diagnosis during the study period (n = 1187), those whose participation was waived by their hospital or who lacked review of their medical record (n = 380), those whose ITP was not confirmed in the medical record (n = 344), and those with ITP lasting 6–12 months or platelet count 100–149 (n = 640), the current cohort comprises 3831 adults with confirmed cITP (Fig. 1).

Among these 3831 cITP patients, 1258 had prevalent cITP on April 1, 2009 and 2573 had incident cITP diagnosed after this date. Prevalent cITP patients were included at a median of 64 months [interquartile range (IQR) 35–95 months] after their first ITP diagnosis, while incident cITP patients were included at a median of 15 months (IQR 13–23 months) after their first ITP diagnosis.

3.1. Prevalence and Incidence of cITP

On 1 April 2009, the prevalence of confirmed adult cITP requiring specialist care within a 13-year period (1996–2009) was 10.0 per 100,000 persons in Denmark (95% CI: 9.1–11.0) and 10.7 per 100,000 persons in Sweden (95% CI: 9.9–11.4).

The prevalence of cITP stratified by sex and age in Denmark and Sweden is illustrated in Fig. 2. The prevalence was higher in women than in men and increased with age in both countries. While the prevalence was high among women < 40 years old, it was highest for persons of both sexes aged 70 years or older.

The incidence of adult cITP after 1 April 2009 was 2.8 per 100,000 person-years in Denmark (95% CI: 2.6–3.0) and 1.8 per 100,000 person-years in Sweden (95% CI: 1.7–1.9) and 2.1 per 100,000 person-years in Norway (95% CI: 1.9–2.3). The number of new cITP patients joining the cohort has averaged 332 per year.

Incidence stratified by sex and age in Denmark, Sweden and Norway is illustrated in Fig. 3. The lowest incidence occurred in patients aged 40–49 years and the highest in elderly patients aged 70 years or older. In all three countries, particularly high incidence was found in men aged 80 years or older (Fig. 3).

3.2. Characteristics at Cohort Inclusion

The current cohort of 3831 cITP patients includes 2215 (57.8%) women and 1616 (42.2%) men. Older cITP patients aged ≥ 70 years comprise 30–2% of the cohort (Table 1).

At study inclusion, 31–6% of prevalent cITP patients were splenectomized; the corresponding percent for incident cITP patients, whose disease duration is shorter, was 10–4% (Table 2).

A high comorbidity level, reflected by a Charlson Comorbidity Index score ≥ 3, was present in 8–6% of patients at study inclusion. Frequent comorbidities were solid tumor (7–9%), diabetes (9–3%) and hypertension (18–1%). Of the 3831 cITP patients, 317 (8.3%) had a history of bleeding severe enough to require hospital contact in the year before study inclusion (9–2% of prevalent patients and 7–8% of incident cITP patients). The proportion of patients with a platelet count below 30 × 10^9/L within 90 days before study inclusion was 11–2% in the overall cohort and 10–7% among incident cITP patients (Table 2). The prevalence of patients with a platelet count below < 30 × 10^9/L at any time before study inclusion was 60–9% in the overall cohort, 62–5% among prevalent cITP patients, and 60–2% among incident cITP patients (Table 2). The proportion without any previous platelet count recorded was 2–8% (Table 2); ranging from 1–3% in Norway to 3–9% in Denmark.

Types of ITP medication used within 6 months before study inclusion are shown in Table 3. The proportion receiving any ITP medication within 6 months before study inclusion was 32–6%. Most frequently, patients had received prednisolone and other oral
glucocorticoids (25.8% of patients), followed by rituximab (3.0%), dexamethasone (1.6%), azathioprine (2.2%), eltrombopag (2.0%), and romiplostim (0.9%) (Table 3).

3.3. Reassessment of Bone Marrow Biopsies

Among the 1258 prevalent cITP patients, 769 (61.1%) had a recorded bone marrow examination; 748 had a bone marrow biopsy and 21 had only a bone marrow aspirate (Table 4). Among the 769 prevalent cITP patients with a bone marrow biopsy, 40 patients had their biopsies (5.2%) reassessed and MF-graded.

Among the 2573 incident cITP patients, 1778 (69.1%) had a recorded bone marrow examination; 1305 (50.7%) had a bone marrow biopsy and 473 (18.4%) had a bone marrow aspirate only (Table 4). Among the 1305 incident cITP patients with a bone marrow biopsy, 626 had their biopsies (48.0%) reassessed and MF-graded. In
patients with reasessed bone marrow biopsies, an MF grade of 0 was present in 571 patients and 55 patients (2.1% of all incident cITP patients) had a MF grade of 1. No incident cITP patients had an MF grade of 2 or 3 before study inclusion.

Among the 1187 incident cITP patients aged over 60 years, 930 (77.7%) had a recorded bone marrow sample before study inclusion including 267 (22.3%) with a bone marrow aspiration only. In the

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**Table 1** Patient characteristics at study inclusion [date of chronic ITP (cITP) diagnosis in incident cITP patients and April 1, 2009 in prevalent cITP patients].

| Patient characteristics | Prevalent cITP on April 1, 2009 | Incident cITP after April 1, 2009 | All ITP patients |
|-------------------------|----------------------------------|----------------------------------|-----------------|
|                         | N %                              | N %                              | N %             |
| Total                   | 1258 100 00                       | 2573 100 00                       | 3831 100 00     |
| Age group in years      |                                  |                                  |                 |
| 18–29                   | 151 12 00                         | 478 18 58                        | 629 16 42       |
| 30–39                   | 186 14 79                         | 300 11 66                        | 486 12 69       |
| 40–49                   | 159 12 64                         | 266 10 34                        | 425 11 09       |
| 50–59                   | 159 12 64                         | 293 11 39                        | 452 11 80       |
| 60–69                   | 226 17 97                         | 457 17 76                        | 683 17 83       |
| 70–79                   | 217 17 25                         | 441 17 14                        | 658 17 18       |
| 80+                     | 160 12 72                         | 338 13 14                        | 408 13 00       |
| Year of study entry     |                                  |                                  |                 |
| 2009                    | 1258 100 00                       | 299 11 62                        | 1557 40 64      |
| 2010                    | 0 0                              | 374 14 54                        | 374 9 76        |
| 2011                    | 0 0                              | 404 15 70                        | 404 10 55       |
| 2012                    | 0 0                              | 345 13 41                        | 345 9 01        |
| 2013                    | 0 0                              | 334 12 98                        | 334 8 72        |
| 2014                    | 0 0                              | 343 13 33                        | 343 8 95        |
| 2015                    | 0 0                              | 272 10 57                        | 272 7 10        |
| 2016                    | 0 0                              | 202 7 85                         | 202 5 27        |
| Sex                     |                                  |                                  |                 |
| Women                   | 772 61 37                        | 1443 56 08                       | 2215 57 82      |
| Men                     | 486 38 63                        | 1130 43 92                       | 1616 42 18      |
| Country                 |                                  |                                  |                 |
| Denmark                 | 430 34 18                        | 942 36 61                        | 1372 35 81      |
| Sweden                  | 790 62 80                        | 1040 40 42                       | 1830 47 77      |
| Norway                  | 38 3 02                         | 591 22 97                        | 629 16 42       |
| Year of cITP diagnosis  |                                  |                                  |                 |
| 1996–2000               | 97 7 71                          | 0 0                             | 97 2 53         |
| 2001–2005               | 526 41 81                        | 0 0                             | 526 13 73       |
| 2006–2010               | 635 50 48                        | 673 26 16                        | 1308 34 14      |
| 2011–2016               | 0 0 00                          | 1900 73 84                       | 1900 49 60      |

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**Table 2** Comorbidity and disease characteristics at study inclusion [date of chronic ITP (cITP) diagnosis in incident cITP patients and April 1, 2009 in prevalent cITP patients].

| Comorbidity and disease characteristics | Prevalent cITP on April 1, 2009 | Incident cITP after April 1, 2009 | All ITP patients |
|----------------------------------------|----------------------------------|----------------------------------|-----------------|
| Charlson Comorbidity Index score       |                                  |                                  |                 |
| 0                                      | 857 68 12                        | 1730 67 24                       | 2587 67 53      |
| 1–2                                    | 312 24 80                        | 602 23 40                        | 914 23 86       |
| 3+                                     | 89 7 07                          | 241 9 37                        | 330 8 61        |
| Specific comorbidities within 5 years before study inclusion | | | |
| Solid tumor                            | 96 7 63                          | 201 7 97                        | 301 7 86        |
| Diabetes                               | 118 9 38                          | 219 9 29                        | 357 9 32        |
| Peptic ulcer                           | 5 0 40                            | 36 1 40                        | 41 1 07         |
| Hypertension                           | 219 17 41                        | 474 18 42                       | 693 18 09       |
| Prior splenectomy                      | 198 31 64                        | 267 10 38                       | 665 17 36       |
| Bleeding requiring hospital contact within 1 year before study inclusion | 116 9 22 | 201 7 81 | 317 8 27 |
| Anergy within 1 year before study inclusion | 44 3 50 | 154 5 99 | 198 5 17 |

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**3.4. cITP According to NCPRR Inclusion Criteria**

A total of 4471 cITP patients were included in the analyses with cITP defined according the broader NCPRR study inclusion criteria are shown in Appendix 4. As expected, prevalence and incidence was slightly higher and more patients received ITP treatments within 6 months before study inclusion (Appendix 4).

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**4. Discussion**

The NCPRR currently follows the largest cITP cohort in the world with detailed data on almost 4000 adults with confirmed cITP. We found that the prevalence of cITP was similar in Denmark and Sweden, and that the incidence of cITP was higher in Denmark than in Sweden or Norway. While glucocorticoids were the most frequently used ITP treatment, patients received a wide range of ITP therapies during the six months before study inclusion. Two thirds of incident cITP patients had a recorded bone marrow sample. Only a small proportion of the reassessed bone marrow biopsies had an MF grade ≥ 1 at study inclusion.

The NCPRR is the only multinational population-based ITP cohort for patients with cITP. The UK ITP registry has enrolled 1618 patients with ITP from 70 centers in the UK [65]. Despite inclusion of all ITP patients, and not only cITP patients, the UK ITP registry has the same
treated patients received glucocorticoid prior to cITP, but fewer in
ried out analyses for the 2002
required [12]. The
rated by at least 14 days, decreasing to 4
100,000 population among patients with two ITP diagnoses sepa-
both from the US. Segal et al. found an ITP prevalence of 9
their study found an even lower incidence (1·6–7.1 per 100,000 person-years),
due to the requirement of both a platelet count of <50 × 10^9/L and a
bone marrow examination [24]. Mouliès et al. reported an ITP inci-
dence rate of 2·94 per 100,000 person-years in France based only on
hospital diagnosis [5]. In Japan, the reported incidence rate of ITP was
2·16 per 100,000 person-years among patients with a platelet count
<100 × 10^9/L [7]. In Korea and Taiwan the incidence of diagnosed ITP
in adults has been reported to be 3·7, 2·9 and 2·59 per 100,000 person-
years, respectively [8–10].

Data on presence of increased reticulin (MF grading ≥1) in the bone
marrow of ITP patients are conflicting [25–30], and the natural history of
reticulin levels is unknown. While few patients in our cohort had a
reassessed biopsy showing MF grading ≥1, previous studies report that
up to 40% of ITP patients have bone marrow reticulin deposits (defined as
European bone marrow fibrosis grading MF ≥1 or Bauermeister grading ≥2)
before exposure to thrombopoietin receptor agonists [25–30]. The difference
could be explained by the indication for bone
marrow biopsy as previous studies assessed the proportion among
patients with a bone marrow biopsy. The indication may have differed
in earlier studies compared with our study, given varying study periods
and study populations, with differences in age, sex, disease duration,
and platelet level – all associated with bone marrow reticulin content
[28,30]. Despite differences between countries and dependency on clin-
ical judgment, bone marrow examinations are frequent among patients
in the NCPRR. Almost 80% of patients above age 60 provide a bone mar-
row sample before cITP diagnosis, as recommended in an international
consensus report [31].

It is an important strength that the NCPRR operates within the
population-based, tax-supported health systems of the Nordic coun-
tries, allowing virtually complete follow-up of a large multinational
cohort. Nevertheless, some limitations need to be considered. First,
we may have underestimated the incidence of cITP, as not all medical
records were available for review.

Second, the NCPRR may not capture all cITP patients with asympto-
matic disease who are not hospitalized or seen by specialists during
the study period. In the Nordic countries, patients with ITP usually
undergo a hospital-based diagnostic work-up and most primary cITP
patients are followed at hospital-based clinics. However, general
practitioners may handle follow-up for asymptomatic patients and it
remains possible that this occurred for some patients before they
became eligible for the current study.

Third, inclusion of patients in the NCPRR is dependent on the
accuracy of diagnostic coding during hospital admissions and outpa-
tient clinic visits. The positive predictive value of the ITP diagnosis
is as high as 93% in Denmark [32]. The sensitivity of the algorithm was
increased by adding diagnoses of other primary thrombocytopenia
and by not excluding all potential causes of thrombocytopenia, e.g.,
patients with a history of solid tumor. However, the specificity was

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Table 3

| ITP treatment | Prevalent cITP on April 1, 2009 | Incident cITP after April 1, 2009 | All ITP patients |
|---------------|-------------------------------|----------------------------------|-----------------|
|               | N %                           | N %                              | N %             |
| Total         | 1258 100 00                    | 2573 100 00                      | 3831 100 00     |
| Any ITP treatment within 6 months before study inclusion | 386 30 68 | 864 33 58 | 1250 32 63 |
| Prednisolone or other oral glucocorticoid (except dexamethasone) | 280 22 26 | 710 27 59 | 990 25 84 |
| Duration | 0–2 months | 61 4 85 | 222 8 63 | 283 7 39 |
| 2–4 months | 38 3 02 | 72 2 80 | 110 2 87 |
| 4–6 months | 181 14 39 | 416 16 17 | 597 15 58 |
| N/A | 978 77 74 | 1863 72 41 | 2841 74 16 |
| Dexamethasone | 16 1 27 | 47 1 83 | 63 1 64 |
| Cyclic high-dose methylprednisolone | 0 0 | 5 0 19 | 5 0 13 |
| Intravenous immunoglobulin (IVIg) | 33 2 62 | 89 3 46 | 122 3 18 |
| Danazol | 9 0 72 | 5 0 19 | 14 0 37 |
| Azathioprine | 47 3 74 | 37 1 44 | 84 2 19 |
| Cyclophosphamide | 6 0 48 | 0 0 0 | 6 0 16 |
| Vinca alkaloids | 0 0 0 | 0 0 0 | 0 0 0 |
| Mycophenolate | 6 0 48 | 7 0 27 | 13 0 34 |
| (mycophenolatmofetil) Cyclosporine | 15 1 19 | 13 0 51 | 28 0 73 |
| Rituximab | 36 2 86 | 78 3 03 | 114 2 98 |
| Romiplostim | 0 0 | 34 1 32 | 34 0 89 |
| Eltrombopag | 4 0 32 | 72 2 80 | 76 1 98 |
| Dapson | 6 0 48 | 5 0 19 | 11 0 29 |
| Tranexamic acid | 37 2 94 | 62 2 41 | 99 2 58 |
| Other ITP drugs* | 4 0 32 | 8 0 31 | 12 0 31 |

* Other ITP drugs included desmopressin, hydrocortisone with unspecified route of administration, and mercaptopurine.

The proportion of patients aged 18–30 (18%) as the NCPRR, but fewer patients aged 50–70 years [23]. In both cohorts, most of medically
treated patients received glucocorticoid prior to cITP, but fewer in
the UK ITP Registry received rituximab [23].

The prevalence of ITP has not previously been described in a uniform
population-based setting and the only two former studies were
both from the US. Segal et al. found an ITP prevalence of 9·5 per
100,000 population among patients with two ITP diagnoses sepa-
rated by at least 14 days, decreasing to 4·5 per 100,000 persons
when at least 180 days between diagnoses was required [12]. The
study was limited by inclusion criteria restricted to patients aged
0–65 years and by capture of ITP diagnoses only during one calendar
year. In an attempt to overcome these limitations, Feudjo-Tepie car-
rried out analyses for the 2002–2006 period in the US. He reported a
prevalence rate of 23·6 per 100,000 adults after excluding patients

Table 4

Distribution of latest European consensus bone marrow fibrosis (MF) grade before study inclusion date* in patients with chronic ITP (cITP).

| | Prevalent cITP on April 1, 2009 | Incident cITP after April 1, 2009 | All patients |
| | N % | N % | N % |
| Total | 1258 100 00 | 2573 100 00 | 3831 100 00 |
| No BM biopsy or aspiration performed | 489 38 87 | 795 30 90 | 1284 33 52 |
| Only aspiration performed | 21 1 67 | 473 18 38 | 494 12 89 |
| MF-0 | 32 2 54 | 571 22 19 | 603 15 74 |
| MF-1 | 6 0 48 | 55 2 14 | 61 1 59 |
| MF-2 | 1 0 8 | 0 0 0 | 1 0 03 |
| MF-3 | 0 0 0 | 0 0 0 | 0 0 0 |
| Not graded yet | 686 54 53 | 617 23 98 | 1303 34 01 |
| Unknown | 23 1 83 | 62 2 41 | 85 2 22 |

* The study inclusion date was cITP diagnosis date in incident patients and April 1, 2009 in prevalent ITP diagnosis before this (prevalent patients).
increased by reviewing medical records to confirm the ITP diagnosis and a low platelet count.

Fourth, it must be noted that the NCPRR cohort is comprehensive and includes cITP patients both with and without need for ITP medication. Two thirds of incident cITP patients had not received any ITP therapy within 6 months before the date of their cITP diagnosis. This suggests that the disease did not require treatment or went into remission after a short course of treatment administered more than 6 months before the cITP diagnosis date.

In general, comorbidities and outcomes obtained from the national health registries are coded with a high positive predictive value [14,19]. Data from medical records are obtained for the NCPRR by trained study staff using a standardized data abstraction manual. With detailed data on almost 4000 cITP patients and virtually complete follow-up through linkage to national registries in the three countries, the NCPRR is a valuable resource for studies of treatment practices, disease burden, and outcomes for cITP patients in routine clinical practice.

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Authorship Contributions

CFC, HTS and MN designed the study plan for the current analysis. CFC wrote the first draft. NR was responsible for data management and conducted the statistical analyses. SB, WG, HF, KK, SS and JA critically reviewed and contributed to the content of the manuscript. All authors reviewed the manuscript and approved the final version. The corresponding author has access to the data in the study and had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

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Data Sharing

Individual participant data will not be shared in order to protect patient privacy.

Appendix A Supplementary data. Appendix 1-4

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2019.07.015.

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