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

Christian Fynbo Christiansen\textsuperscript{a,}\textsuperscript{*}, Shahram Bahmanyar\textsuperscript{b}, Waleed Ghanima\textsuperscript{c}, Nickolaj Risbo\textsuperscript{a}, Charlotta Ekstrand\textsuperscript{b}, Scott Stryker\textsuperscript{d}, John Acquavella\textsuperscript{a}, Karynsa Kilpatrick\textsuperscript{d}, Henrik Frederiksen\textsuperscript{a,}\textsuperscript{e}, Norgaard Mette Nørgaard\textsuperscript{a}, Sorensen Henrik Toft Sørensen\textsuperscript{a}

\textsuperscript{a} Department of Clinical Epidemiology, Aarhus University Hospital, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
\textsuperscript{b} Clinical Epidemiology Unit & Center for Pharmacoepidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
\textsuperscript{c} Department of Medicine, Bispebjerg Hospital Trust and Department of Hematology, Institute of Clinical Medicine, University of Oslo, Norway
\textsuperscript{d} Center for Observational Research, Amgen Inc., United States of America
\textsuperscript{e} Department of Hematology, Odense University Hospital, Odense, Denmark

\textbf{A B S T R A C T}

\textbf{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).

\textbf{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 x 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.

\textbf{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: 9.1–11.0) adult persons in Denmark and 10.7/100,000 (95% CI: 9.0–11.4) 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: 1.7–2.0) and 2.1 (95%CI: 1.9–2.3) in Denmark, 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 x 10^9/L, 17.4% were splenectomized, 41% had prior ITP therapy, and 8.6% had severe comorbidity.

\textbf{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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\textsuperscript{*} Corresponding author at: Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Alle 43-45, DK-8200 Aarhus N, Denmark.

E-mail address: cfc@clin.au.dk (C. Fynbo Christiansen).

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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).
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. 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.

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. 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.

The Swedish Patient Register contains information on all inpatient admissions to public hospitals since 1987 and on outpatient visits since 2001. Available data are similar to those in the DNPR, 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.

The Norwegian Patient Registry, established in 1997, has included PINs since 2008. The Registry contains data on 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 the 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 $150 \times 10^9/L$ 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 fulfills 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. 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 $< 100 \times 10^9/L$. 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, 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. 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, thrombocytosis, 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 Jeffreys 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 to 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 2,573 had incident cITP diagnosed after this date. Prevalent cITP patients were included at a median of 64 months (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), 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: 1.9–2.2). 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, 36.1% 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
Potential adult cITP* patients  
N=6955

Potential adult primary cITP†  
n=6441

ITP hospital contact in the study period‡  
n=5254

Yearly medical record reviews performed  
n=4880

Confirmed cITP  
n=4471

cITP > 12 months and platelet count < 100  
n=3831

Diagnosis of potential secondary cause of ITP  
n=514

No hospital contact in the study period§  
n=1187

Medical records not available‖  
n=380

Not cITP based on record review¶  
n=344

No recorded platelet <150 available‖  
n=65

cITP duration 6-12 months or lowest platelet count 100-149  
n=640

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

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**Fig. 1.** Patient flow chart of the Nordic cohort of adult patients with chronic ITP requiring health care in Denmark, Sweden and Norway, 2009–2016. *Two or more ITP diagnoses more than 6 months apart between January 1, 1996 and December 31, 2016, among patients alive on April 1, 2009. †Restricted to patients with a hospital contact for ITP between April 1, 2009 and December 31, 2016, because these patients were considered to have been actively followed during the study period. Hospital contacts include hospital admissions, outpatient specialist clinic visits, and emergency room visits. ‡Including 123 patients in non-participating hospitals and 257 patients with records from smaller hospitals with few patients diagnosed with ITP and without hematological services. The number of unavailable records was 299 in Sweden, 33 in Denmark and 48 in Norway. §ITP could not be confirmed by record review because of secondary thrombocytopenia, primarily due to connective tissue disease, myelodysplastic syndrome, myelofibrosis, gestational thrombocytopenia, or thrombotic thrombocytopenic purpura. ¶At least one documented platelet count < 150 × 10⁹/L is required, but may not be available if it was measured several years before study inclusion.

**Fig. 2.** Prevalence (per 100,000 inhabitants) of immune thrombocytopenia in Denmark and Sweden by age group and sex.
patients with reassessed bone marrow biopsies, an MF grade of 0 was present in 571 patients and 55 patients (2.1% of all incident cITP patients) had an 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

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].

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Prevalent cITP on April 1, 2009</th>
<th>Incident cITP after April 1, 2009</th>
<th>All ITP patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>1258</td>
<td>100 0</td>
<td>2573</td>
</tr>
<tr>
<td>Age group in years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>151</td>
<td>12.0</td>
<td>176</td>
</tr>
<tr>
<td>30-39</td>
<td>186</td>
<td>14.7</td>
<td>438</td>
</tr>
<tr>
<td>40-49</td>
<td>159</td>
<td>12.6</td>
<td>266</td>
</tr>
<tr>
<td>50-59</td>
<td>159</td>
<td>12.6</td>
<td>293</td>
</tr>
<tr>
<td>60-69</td>
<td>226</td>
<td>17.9</td>
<td>457</td>
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<tr>
<td>70-79</td>
<td>217</td>
<td>17.5</td>
<td>441</td>
</tr>
<tr>
<td>80+</td>
<td>160</td>
<td>12.7</td>
<td>338</td>
</tr>
<tr>
<td>Year of study entry</td>
<td></td>
<td></td>
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<tr>
<td>2009</td>
<td>1258</td>
<td>100 0</td>
<td>299</td>
</tr>
<tr>
<td>2010</td>
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<td>0</td>
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</tr>
<tr>
<td>2016</td>
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<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Women</td>
<td>772</td>
<td>61.7</td>
<td>1443</td>
</tr>
<tr>
<td>Men</td>
<td>486</td>
<td>38.3</td>
<td>1130</td>
</tr>
<tr>
<td>Country</td>
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<td></td>
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<tr>
<td>Denmark</td>
<td>430</td>
<td>34.8</td>
<td>942</td>
</tr>
<tr>
<td>Sweden</td>
<td>790</td>
<td>62.8</td>
<td>1040</td>
</tr>
<tr>
<td>Norway</td>
<td>38</td>
<td>3.0</td>
<td>591</td>
</tr>
<tr>
<td>Year of cITP diagnosis</td>
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<td></td>
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<tr>
<td>1996-2000</td>
<td>97</td>
<td>7.7</td>
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<td>2006-2010</td>
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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].

<table>
<thead>
<tr>
<th>Comorbidity and disease characteristics</th>
<th>Prevalent cITP on April 1, 2009</th>
<th>Incident cITP after April 1, 2009</th>
<th>All ITP patients</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>1258</td>
<td>100 0</td>
<td>2573</td>
</tr>
<tr>
<td>Charlson Comorbidity Index score</td>
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<tr>
<td>0</td>
<td>857</td>
<td>68.1</td>
<td>1730</td>
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<tr>
<td>1-2</td>
<td>312</td>
<td>24.8</td>
<td>602</td>
</tr>
<tr>
<td>3+</td>
<td>89</td>
<td>7.0</td>
<td>241</td>
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<tr>
<td>Specific comorbidities within 5 years before study inclusion</td>
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<td></td>
<td></td>
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<tr>
<td>Solid tumor</td>
<td>96</td>
<td>7.6</td>
<td>205</td>
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<tr>
<td>Diabetes</td>
<td>118</td>
<td>9.3</td>
<td>219</td>
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<tr>
<td>Peptic ulcer</td>
<td>5</td>
<td>0.4</td>
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<tr>
<td>Hypertension</td>
<td>219</td>
<td>17.4</td>
<td>474</td>
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<tr>
<td>Prior splenectomy</td>
<td>398</td>
<td>31.7</td>
<td>667</td>
</tr>
<tr>
<td>Bleding requiring hospital contact within 1 year before study inclusion</td>
<td>116</td>
<td>9.2</td>
<td>201</td>
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<tr>
<td>Aneurysm within 1 year before study inclusion</td>
<td>44</td>
<td>3.5</td>
<td>154</td>
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<tr>
<td>Lowest platelet count within 90 days before study inclusion (&lt;10^11/l)</td>
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<tr>
<td>&lt;50</td>
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<td>50-49</td>
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<td>755</td>
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<td>Lowest platelet count at any time before study inclusion (&lt;10^11/l)</td>
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<tr>
<td>&lt;50</td>
<td>786</td>
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<tr>
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<td>27</td>
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</table>

1376 incident cITP patients aged ≤60 years, 848 (61.6%) had a bone marrow sample before study inclusion. Of these, 230 (16.7%) only had a bone marrow aspiration. There was virtually no difference in the proportion of incident cITP patients with an MF grade of 0 or 1 in patients aged >60 years compared with patients aged ≤60 years (Appendix 3).

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).

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 [23]. Despite inclusion of all ITP patients, and not only cITP patients, the UK ITP registry has the same

Fig. 3. Incidence rate (per 100,000 person-years) of immune thrombocytopenia in Denmark, Sweden and Norway by age group and sex.
treated patients received glucocorticoid prior to cITP, but fewer in
prevalence rate of 23
ried out analyses for the 2002
study was limited by inclusion criteria restricted to patients aged
rated by at least 14 days, decreasing to 4
both from the US. Segal et al. found an ITP prevalence of 9
Cyclic high-dose
methylprednisolone
Intravenous immunoglobulin
(VIG)
Danazol
Azathioprine
Cyclophosphamide
Vincristine
Mycophenolate
(mycophenolate mofetil)
Cyclosporine
Rituximab
Ruxolitinib
Elotuzumab
Dapsonie
Tranexamic acid
Other ITP drugs

* Other ITP drugs included desmopressin, hydrocortisone without specified route of administration, and mercaptopurine.

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 uni-
population-based setting and the only two former studies were
uniform from both 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-
ried 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).

<table>
<thead>
<tr>
<th>MF Grade</th>
<th>Prevalent cITP on April 1, 2009 N (%)</th>
<th>Incident cITP after April 1, 2009 N (%)</th>
<th>All patients N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No BM biopsy or aspiration assessed</td>
<td>1258 (100.00)</td>
<td>2573 (100.00)</td>
<td>3831 (100.00)</td>
</tr>
<tr>
<td>Only aspiration performed</td>
<td>489 (38.87)</td>
<td>795 (30.90)</td>
<td>1284 (33.52)</td>
</tr>
<tr>
<td>MF-0</td>
<td>21 (1.67)</td>
<td>473 (18.38)</td>
<td>494 (12.89)</td>
</tr>
<tr>
<td>MF-1</td>
<td>32 (2.54)</td>
<td>571 (22.19)</td>
<td>603 (15.74)</td>
</tr>
<tr>
<td>MF-2</td>
<td>6 (0.48)</td>
<td>55 (2.14)</td>
<td>61 (1.59)</td>
</tr>
<tr>
<td>MF-3</td>
<td>1 (0.08)</td>
<td>0 (0.00)</td>
<td>1 (0.03)</td>
</tr>
<tr>
<td>Not graded yet</td>
<td>868 (64.53)</td>
<td>617 (23.98)</td>
<td>1303 (34.01)</td>
</tr>
<tr>
<td>Known</td>
<td>23 (1.83)</td>
<td>62 (2.41)</td>
<td>85 (2.22)</td>
</tr>
</tbody>
</table>

* The study inclusion date was cITP diagnosis date in incident patients and April 1, 2009 in prevalent patients.

with potential secondary ITP [11]. Neither study required laboratory or medical record confirmation of ITP diagnoses.

Our findings on incidence of cITP in Nordic countries are consist-
ent with previous studies. The higher estimates found in some stud-
ies could be explained by lack of medical record or laboratory
confirmation and inclusion of ITP of any duration and different plate-
let threshold [2–7,11,12]. Similar to our study, Frederiksen and
Schmidt reported an ITP incidence rate of 2–7 per 100,000 person-
years in Funen, Denmark, during 1973–1995 indicating that the inci-
dence of ITP has not changed during the last 20 years in Denmark [3].
Abrahamson et al. reported an incidence rate of 3.9 per 100,000 person-
years during 1992–2005 using the UK Clinical Practice Research
DataLink (CPRD) [6]. However, ITP cases identified by READ codes in the
CPRD were not confirmed by reduced platelet count, repeated ITP
coding or record review. Schoonen et al. reported an ITP incidence of
3.9 per 100,000 person-years using the UK CPRD and reported that
66% of ITP patients had a platelet count < 100 × 10^9/L [4] Another UK
study found an even lower incidence (1–6 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]. Mouli 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 per-
son-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 (defi-
ned as European bone marrow fibrosis grading MF ≥1 or Bauermeister
grading ≥B) 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-
cal 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 asym-
ptomatic 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

Table 3

Treatments for ITP within 6 months before study inclusion [date of chronic ITP (cITP) diagnosis in incident cITP patients and April 1, 2009 in prevalent cITP patients].

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Prevalent cITP</th>
<th>Incident cITP</th>
<th>All ITP patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone or other oral glucocorticoid</td>
<td>280 (22.26)</td>
<td>710 (27.59)</td>
<td>990 (25.84)</td>
</tr>
<tr>
<td>Duration</td>
<td>0–&lt;6 months</td>
<td>61 (22.6)</td>
<td>222 (53.8)</td>
</tr>
<tr>
<td>6–24 months</td>
<td>38 (13.4)</td>
<td>72 (17.8)</td>
<td>110 (13.1)</td>
</tr>
<tr>
<td>24–60 months</td>
<td>181 (66.2)</td>
<td>416 (16.7)</td>
<td>597 (15.8)</td>
</tr>
<tr>
<td>N/A</td>
<td>978 (37.7)</td>
<td>1863 (72.4)</td>
<td>2841 (74.6)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>16 (1.27)</td>
<td>47 (1.83)</td>
<td>63 (1.64)</td>
</tr>
<tr>
<td>Cyclic high-dose methyprednisolone</td>
<td>0 (0)</td>
<td>5 (0.19)</td>
<td>5 (0.13)</td>
</tr>
<tr>
<td>Intravenous immunoglobulin (VIG)</td>
<td>33 (2.62)</td>
<td>89 (3.46)</td>
<td>122 (3.18)</td>
</tr>
<tr>
<td>Danazol</td>
<td>9 (0.72)</td>
<td>5 (0.19)</td>
<td>14 (0.37)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>47 (3.74)</td>
<td>37 (1.44)</td>
<td>84 (2.19)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>6 (0.48)</td>
<td>0 (0)</td>
<td>6 (0.16)</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>6 (0.48)</td>
<td>7 (0.27)</td>
<td>13 (0.34)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>15 (1.19)</td>
<td>13 (0.51)</td>
<td>28 (0.73)</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>36 (2.86)</td>
<td>78 (3.03)</td>
<td>114 (2.98)</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>4 (0.32)</td>
<td>72 (2.80)</td>
<td>76 (1.98)</td>
</tr>
<tr>
<td>Dapsonie</td>
<td>6 (0.48)</td>
<td>5 (0.19)</td>
<td>11 (0.29)</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>37 (2.94)</td>
<td>62 (2.41)</td>
<td>99 (2.58)</td>
</tr>
<tr>
<td>Other ITP drugs</td>
<td>4 (0.32)</td>
<td>8 (0.31)</td>
<td>12 (0.31)</td>
</tr>
</tbody>
</table>

* Other ITP drugs included desmopressin, hydrocortisone without specified route of administration, and mercaptopurine.
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.

Acknowledgments

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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. Appendices 1-4

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