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ABSTRACT

Objectives: To describe routine treatment and clinical characteristics of patients with chronic ITP (cITP).

Methods: We used data from Danish nationwide registers and medical records to examine routine clinical care, including splenectomy and medical treatment, of Danish patients with chronic immune thrombocytopenia (cITP, defined as two or more ITP diagnoses at least 6 months apart), i.e. treatment initiation before cITP diagnosis and treatment initiation within one year post-diagnosis for treatment-naïve patients.

Results: Nearly half of all 964 cITP patients diagnosed during 2009–2015 initiated treatment between initial ITP diagnosis and chronic onset; 43% received glucocorticoids, 12% received IVIG and 18% received rituximab. Within one year post-diagnosis, 9.2% of previously untreated patients commenced therapy, most often corticosteroids and rituximab.

Discussion: Our results are in line with findings of recent studies from other countries.

Conclusion: We found that corticosteroids, IVIG, and rituximab are common first-choice of ITP drugs. Bleeding events occurred in nearly one third of treated patients in the year before cITP diagnosis and in 5% of the treatment-naïve patients. A substantial number of patients do not need treatment during the first 6–12 months. However, some of these patients will subsequently need treatment as the disease may worsen, indicating the need for continuous follow-up of these patients.

KEYWORDS

Purpura; thrombocytopenic; Idiopathic; therapeutics; disease progression

Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by platelet destruction and decreased production [1]. However, patients with similarly low platelet counts may present with a spectrum of symptoms, ranging from being asymptomatic to severe bleeding diathesis [2]. Severe bleeding events occur in about 10% of adult ITP patients [3]. Corticosteroids alone or in combination with intravenous immunoglobulin (IVIG) are considered as the first-line therapies in ITP, whereas splenectomy, immunosuppressive treatment and Thrombopoietin receptor agonists (TPO-RA) are used in patients failing steroids [4]. Treatment is recommended for patients with bleeding symptoms or at high risk of bleeding. In adults, initiation of treatment is recommended if platelet counts fall below 30 × 10^9/L [4,5].

In the current study, we described the routine treatment and clinical characteristics of patients with chronic ITP (cITP) in the year after chronicity.

Methods

Setting and data sources

This population-based cohort study was conducted in Denmark. The Danish National Health Service provides universal tax-supported access to hospitals, free of charge, for the entire population [6].

The Danish National Patient Registry (DNPR) contributes data to the Nordic Country Patient Registry for Romiplostim (NCPRR) in Denmark [7]. The DNPR has recorded information on all non-psychiatric inpatient hospitalizations since 1977 and on outpatient and emergency room visits since 1995. Data has been coded using the International Classification of Diseases, Eighth Revision (ICD-8) through 1993 and the Tenth Revision (ICD-10) thereafter [8]. The Danish Civil Registration System records information on migration and vital status for the entire population using the unique civil registration number assigned to each Danish resident [9]. The registries can be linked unambiguously using the patient civil registration number, which is
recorded at every hospital contact. This number additionally allows for identification of patient medical records for abstraction of clinical information.

**Study population**

All Danish patients aged 18 years or older with incident cITP, defined as two or more ITP diagnoses at least 6 months apart between 1 April 2009 and 31 December 2015, were identified from the NCPRR. To avoid including patients with prevalent ITP, we excluded patients who had an ITP diagnosis between 1 January 1996 and 1 April 2009. We also excluded patients with secondary ITP defined as ITP associated with other diseases and conditions, such as systemic lupus erythematosus (SLE), human immunodeficiency virus (HIV) infection, hepatitis C virus infection, liver cirrhosis, hematological malignancies, diagnosed within 5 years before ITP. The NCPRR also contains data manually abstracted from electronic or paper medical records at all hospital departments treating ITP patients, including inpatient units, outpatient specialist clinics, and emergency departments. Medical records were reviewed to confirm ITP diagnosis. Bleeding events were abstracted from medical records by type and month of event.

We only included serious bleeding events requiring hospital contact. Laboratory data included abnormal hemoglobin and white blood cell counts recorded in medical records as laboratory tests taken within 28 days of each other. Anemia was defined as a hemoglobin level below 8.1 mmol/L (13 g/dl) for males and below 7.4 mmol/L (12 g/dl) for females. Leukocytosis was defined as a total leukocyte count above $10^9$/L.

**Follow-up and treatment**

The date of a second ITP diagnosis coding occurring more than 6 months after a first ITP diagnosis was considered the cITP diagnosis date. Patients were followed for 12 months after their cITP diagnosis date, with censoring at emigration or death.

Data on treatments were abstracted from medical records, except for splenectomy, which was defined by surgical codes recorded in the DNPR. Treatments before and after each patient’s cITP diagnosis date included prescriptions for corticosteroids (prednisolone or other oral glucocorticoid, dexamethasone, or high-dose methylprednisolone), rituximab, intravenous immunoglobulin (IVIG), danazol, azathioprine, cyclophosphamide, dapsone, mycophenolate (mycophenolate mofetil), TPO-RA (eltrombopag or romiplostim), supportive treatment (including tranexamic acid and platelet transfusion), and other treatments including vinca alkaloids, cyclosporine, desmopressin, and mercaptopurine.

**Statistical analysis**

We calculated the distribution of patients by age group on the cITP diagnosis date, gender, Charlson comorbidity index score, prevalent comorbidities on the cITP diagnosis date, nadir platelet count within 90 days before the cITP diagnosis date and the percentage of patients who experienced ≥1 bleeding-related hospital contact within one year before their cITP diagnosis date. We then computed the overall proportions of patients treated with ITP drugs, splenectomy, and supportive treatment between their initial ITP diagnosis date and their cITP diagnosis date. We also calculated the cumulative proportion of patients who were treatment-naive on their cITP diagnosis date and initiated therapy during the subsequent 12 months, accounting for death as a competing risk. In a sensitivity analysis, we changed the definition of cITP to two or more ITP diagnoses at least 12 months apart, in accordance with the most recent guideline [5].

**Results**

The study included 964 cITP patients (57% female, median age 58 years, interquartile range (IQR): 36–71 years). Median time from first ITP diagnosis to cITP diagnosis date was 7 months (IQR: 6–10 months) (Table 1). Nearly half ($n = 469, 49\%$) of patients were treated between their initial ITP diagnosis date and their subsequent cITP diagnosis date. Of the total cohort, 43% had a record of treatment with corticosteroids, 18% with rituximab, 12% with IVIG, 3.7% with splenectomy, 3.1% with TPO-RA, and 12% with supportive treatment (Table 2).

Among the 495 patients who were not treated prior to cITP diagnosis date, 6.5% had a nadir platelet count within 90 days before their cITP diagnosis date of $<30 \times 10^9$/L; 13.3% had a count of 30–50; 44% had a count of 50–150 $\times 10^9$/L; and 7.1% had a count $>150 \times 10^9$. Values were unavailable for 29% of patients. For those treated prior to their cITP diagnosis date, corresponding proportions were 19%, 9.8%, 24%, and 34%, respectively, with values unavailable for 14%. Bleeding events within one year before the cITP diagnosis date were reported in 32% of treated patients and for 5.3% of patients who were not treated before their cITP diagnosis date (Table 1).

For patients who were treatment-naive (any type of treatment including supportive treatment) on their cITP diagnosis date ($n = 495$), 9.2% (95% confidence interval (CI): 7.7%, 11.0%) ($n = 43$) initiated therapy during the subsequent 12 months. The 12-month risk of specific treatment was 6.3% (95% CI: 5.1%, 7.7%) for corticosteroids, 5.3% (95% CI: 4.4%, 6.3%) for rituximab, 3.1% (95% CI: 2.4%, 4.0%) for IVIG, 1.7% (95% CI: 1.2%, 2.3%) for TPO-RA, and 3.7% (95% CI: 2.9%, 4.5%) for splenectomy (Table 2).
Changing the definition of cITP to ≥2 ITP diagnoses separated by >12 months reduced the cohort to 848 patients. The proportion of patients treated between their ITP and cITP diagnosis dates increased from 49% to 55% and a bleeding-related hospital contact in the year before cITP diagnosis decreased from 5.3% to 1.8%.

### Discussion

We found that 51% of all Danish patients diagnosed with cITP were treatment-naïve at the time of chronicity. In the 12 months after cITP diagnosis, 9.2% of previously untreated patients commenced therapy. More patients initiated corticosteroid or rituximab treatment than underwent splenectomy or initiated IVIG or TPO-RA treatment.

The strengths of our study included its use of data from routine clinical practice. In the NCPRR, data are abstracted from healthcare registries enriched with medical record data serving a national population with uniform tax-supported access to healthcare. This eliminates selection bias stemming from selective inclusion of specific hospitals, insurance plans, or age groups. Furthermore, the data in these registries provide almost complete follow-up, thereby reducing information bias [8]. A weakness was lack of information on treatment lines and on treatment compliance and the restriction to treatments within one

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Table 1. Descriptive characteristics of Danish patients with chronic immune thrombocytopenia (cITP) diagnosed between 2009 and 2015 in Denmark.

|                           | All N (%) | Treated before cITP date N (%) | Treatment-naïve at cITP N (%) |
|---------------------------|-----------|-------------------------------|-------------------------------|
| Total                     | 964 (100.0) | 469 (100.0)                  | 495 (100.0)                   |
| **Age group in years**    |           |                               |                               |
| 18–30                     | 180 (18.7) | 92 (19.6)                     | 88 (17.8)                     |
| 31–50                     | 218 (22.6) | 105 (22.4)                    | 113 (22.8)                    |
| 51–70                     | 305 (31.6) | 148 (31.6)                    | 157 (31.7)                    |
| 70+                       | 261 (27.1) | 124 (26.4)                    | 137 (27.7)                    |
| **Median (IQR)**          | 58 (36–71) | 58 (34–71)                    | 57 (36–72)                    |
| **Year of cITP diagnosis**|           |                               |                               |
| 2009                      | 94 (9.8)   | 54 (11.5)                     | 40 (8.1)                      |
| 2010                      | 166 (17.2) | 94 (20.0)                     | 72 (14.5)                     |
| 2011                      | 135 (14.0) | 63 (13.4)                     | 72 (14.5)                     |
| 2012                      | 136 (14.1) | 60 (12.8)                     | 76 (15.4)                     |
| 2013                      | 138 (14.3) | 66 (14.1)                     | 72 (14.5)                     |
| 2014                      | 136 (14.1) | 62 (13.2)                     | 74 (14.9)                     |
| 2015                      | 159 (16.5) | 70 (14.9)                     | 89 (18.0)                     |
| **Time from initial ITP-diagnosis to cITP diagnosis in months (median, IQR)** | 7 (6–10) | 7 (6–9) | 7 (6–10) |
| **Gender**                |           |                               |                               |
| Female                    | 545 (56.5) | 261 (55.7)                    | 284 (57.4)                    |
| Male                      | 419 (43.5) | 208 (44.3)                    | 211 (42.6)                    |
| **Splenectomy**           |           |                               |                               |
| Yes                       | 36 (3.7)   | 36 (7.7)                      | 0 (0.0)                       |
| No                        | 928 (96.3) | 433 (92.3)                    | 495 (100.0)                   |
| **Lowest platelet count within 90 days of cITP (×10⁹/L)** | 32 (6.5) | 87 (18.6) | 32 (6.5) |
| <30                       | 119 (12.3) | 87 (19.6)                     | 32 (6.5)                      |
| 30–50                     | 112 (11.6) | 66 (13.3)                     | 56 (11.3)                     |
| 50–150                    | 333 (34.5) | 113 (24.1)                    | 220 (44.4)                    |
| 150+                      | 193 (20.0) | 158 (33.7)                    | 35 (7.1)                      |
| Missing                   | 207 (21.5) | 65 (13.9)                     | 142 (28.7)                    |
| **Lowest platelet count within 1 year of cITP (×10⁹/L)** | 35 (12.4) | 84 (17.0) | 35 (12.4) |
| <30                       | 464 (48.1) | 380 (81.0)                    | 84 (17.0)                     |
| 30–50                     | 149 (15.5) | 36 (6.4)                      | 119 (24.0)                    |
| 50–150                    | 270 (28.0) | 28 (6.0)                      | 242 (48.9)                    |
| 150+                      | 35 (3.6)   | 23 (4.9)                      | 12 (2.4)                      |
| Missing                   | 46 (4.8)   | 8 (1.7)                       | 38 (7.7)                      |
| **Charlson Comorbidity Index score** | 361 (72.9) | 361 (72.9) | 361 (72.9) |
| 0                         | 682 (70.7) | 321 (68.4)                    | 361 (72.9)                    |
| 1–2                       | 226 (23.4) | 116 (24.7)                    | 110 (22.2)                    |
| 3+                        | 56 (5.8)   | 32 (6.8)                      | 24 (4.8)                      |
| **Leukocytosis within 1 year before cITP** | 56 (11.3) | 146 (31.1) | 55 (11.1) |
| 308 (32.0)                | 252 (53.7) | 56 (11.3)                     |
| Anemia within 1 year before cITP | 201 (20.9) | 146 (31.1) | 55 (11.1) |
| Bleeding-related hospital contact within 1 year before cITP | 174 (18.0) | 148 (31.6) | 26 (5.3) |
| Any ITP treatment between first ITP diagnosis and cITP | 469 (48.7) | 469 (100.0) | 0 (0.0) |
| Corticosteroids           | 414 (42.9) | 414 (86.3)                    | 0 (0.0)                       |
| IVIG                      | 112 (11.6) | 112 (23.9)                    | 0 (0.0)                       |
| Rituximab                 | 176 (18.3) | 176 (37.2)                    | 0 (0.0)                       |
| TPO-R                     | 30 (3.1)   | 30 (6.4)                      | 0 (0.0)                       |
| Danazol                   | <5         | <5                            | 0 (0.0)                       |
| Azathioprine              | 12 (1.2)   | 12 (2.6)                      | 0 (0.0)                       |
| Cyclophosphamide          | 0 (0.0)    | 0 (0.0)                       | 0 (0.0)                       |
| Mycophenolate             | 9 (0.9)    | 9 (1.9)                       | 0 (0.0)                       |
| Supportive treatment      | 112 (11.6) | 112 (23.9)                    | 0 (0.0)                       |
| Splenectomy               | 36 (3.7)   | 36 (7.7)                      | 0 (0.0)                       |
| Other                     | 9 (0.9)    | 9 (1.9)                       | 0 (0.0)                       |
year of cITP diagnosis. We relied on data from routine clinical care in which platelet count may not always be measured regularly in stable patients. While most patients had a platelet count within 90 days before study inclusion, 21.5% patients had no such measurement in that 90-day period (and almost 30% of the treatment-naïve patients). When we included all measurements within one year of cITP, the proportion of patients without a measurement dropped to 4.1% (and 1.7% for treated patients). Although we have virtually complete data on platelet count if we extended the look-back period, we consider the 90-day window the most clinical relevant with regard to subsequent treatment.

Our results are consistent with recommended treatment for cITP [5], and also in line with findings of recent studies from other countries. For example, Lee et al. reported that 31% of 10,814 Korean patients with primary ITP received treatment during 2010–2014 [10]. Data from the United Kingdom Immune Thrombocytopenia Registry reported that 80% of all patients were treated at any time during the course of their disease, most often with prednisolone (70%) and IVIG (13%) in the period 1990–2015 [11], and that most patients receiving romiplostim received it ≥1 year after first ITP diagnosis [12]. Similar findings from Sweden showed that 65% of 587 patients with cITP, defined as two ITP hospital-based diagnoses at least 12 months apart, were treated during the 2009–2014 study period, most often with corticosteroids and IVIG (personal communication, 2017).

We found that corticosteroids, IVIG, and rituximab are common first-choice of ITP drugs [13]. In this large Danish population-based cohort study, only half of the cITP patients received ITP medication between ITP and cITP, and the chance of initiating treatment in previously untreated patients within the first year of cITP was only 9%. Corticosteroids, IVIG, and rituximab were the most common first-choice of ITP drugs. Bleeding events occurred in nearly one third of treated patients in the year before cITP diagnosis and in 5% of the treatment-naïve patients. A substantial number of patients do not need treatment during the first 6–12 months. However, some of these patients will subsequently need treatment as the disease may worsen, indicating the need for continuous follow-up of these patients.

**Disclosure statement**

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