Pharmacological agents preceding a diagnosis of immune thrombocytopenia in adult patients developing the chronic form: A Swedish national register study

Lukas Löfling\textsuperscript{a,⁎}, Marie Linder\textsuperscript{a}, Charlotta Ekstrand\textsuperscript{a}, Honar Cherif\textsuperscript{b}, Helle Kieler\textsuperscript{a}, Shahram Bahmanyar\textsuperscript{a}

\textsuperscript{a} Centre for Pharmacoepidemiology, Department of Medicine - Solna, Karolinska Institutet, Stockholm, Sweden
\textsuperscript{b} Department of Medical Science, Haematology, Uppsala University, Uppsala, Sweden

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ABSTRACT

Patients with primary chronic immune thrombocytopenia (cITP) have been reported to use more anti-infective medications, even before diagnosis of immune thrombocytopenia (ITP). The more common use of anti-infective medications may be due to general health problems, requiring medication in the early stages of cITP and before the diagnosis is set, rather than infections preceding the disease. Accordingly, cITP may not only be associated with use of anti-infective medications but also with medications for more general symptoms.

Objective: To investigate use of medications for general symptoms, such as analgesics and vitamin supplements in patients with ITP developing the chronic form, the year preceding their first primary diagnosis in comparison with such use in the general population.

Method: Swedish Health Registers were used to identify adult patients (n = 1087) with primary cITP during 2006–2012 and data on medications. Standardized Incidence Ratios (SIRs) and 95% confidence intervals (CI), were estimated as a measure of relative risk.

Results: The association for overall studied medications was SIR = 1.36 (95% CI 1.32–1.41). A majority of the point estimates were above unity.

Conclusion: In patients with cITP, prescription fills for medications used to treat pain conditions and vitamin deficiencies are more common in the year preceding their first diagnosis as compared with prescription fills in the general population. Our results suggest that patients later diagnosed with cITP receive treatment due to symptoms that could be signs of an early ITP. Accordingly, in investigations for unspecific pain symptoms and vitamin deficiencies, cITP should be considered as a differential diagnosis.

1. Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a low platelet count\textsuperscript{[1–3]}. Platelet counts below $100 \times 10^9$ platelets per liter of blood (100 G/L) are considered pathological and are usually investigated\textsuperscript{[4,5]}. There is an increased risk of bleeding and bleeding related complications at platelet counts below 20–30 G/L. The decreased number of platelets are due to an antibody or cell mediated destruction of platelets, and decreased platelet production from the megakaryocytes in the bone marrow\textsuperscript{[2,5–7]}. Primary ITP, thrombocytopenia without any known underlying cause is an exclusion diagnosis and can be confirmed only when other causes of the thrombocytopenia have been ruled out. ITP is more common among those of middle age and slightly more common among women than men (ratio 1.2–1.7:1)\textsuperscript{[8]}, and the incidence of primary ITP has been estimated to 3.3 per 100,000 person-years worldwide\textsuperscript{[9,10]}. Chronic ITP (cITP), the most common clinical manifestation of primary ITP, is ITP which lasts > 12 months\textsuperscript{[5]}.

In two recent studies from France\textsuperscript{[11]} and Sweden\textsuperscript{[12]} the incidences of primary cITP in adult patients were reported to be 1.61 and 2.30 per 100,000 person-years, respectively.

In a recent study from our research group, it was observed that patients with cITP have an increased risk of a diagnosis of infection in the years preceding their first ITP diagnosis\textsuperscript{[12]}. It was also found that patients with cITP more often filled prescriptions for anti-infective medications during the year prior to the cITP diagnosis, compared with the general population. These findings suggest that infection may not only be related to the immunomodulation treatment used in treatment.
of ITP, but also to the disease itself. However, as for many other autoimmune diseases, ITP may be associated with other symptoms than bleeding, which may trigger contact with healthcare [13]. The life quality of ITP patients has been found to be worse than that of patients with hypertension, arthritis and some malignancies [14]. The less specific and early symptoms of the disease like fatigue, general body pain and illness symptoms, as well as iron deficiency and anaemia would suggest that at this stage of the disease more symptomatic medications are prescribed. Accordingly, these patients may more often be diagnosed with infection and the treatment of infections may be a secondary finding. If this hypothesis is correct cITP should also be associated with increased filling of prescriptions of other non-chronic medications, such as analgesics, before being given their first ITP diagnosis.

We used information from the Swedish national health registers to investigate the pattern of filled prescriptions with medications used to treat general symptoms of diseases, symptoms that also can be early symptoms of ITP, in adult patients with primary cITP during the year before their first primary ITP diagnosis.

2. Material and methods

The Swedish National Patient Register (NPR) was used to identify adult patients (aged ≥18 years at time of the second ITP diagnosis) with two or more ITP diagnoses during the study period between July 2006 and December 2012. The date of a diagnosis was the date as recorded in the NPR. That is the date of a visit or admission to a hospital. Those with at least 12 months between the ITP diagnoses were defined as having cITP, and therefore included in the study (Fig. 1).

The NPR started collecting data in 1964 and has national coverage since 1987 [15]. Since 2001, information on outpatient visits are also covered for a large majority of the patient population. The NPR records information about health care establishment, date and duration of care, personal data (sex, age, personal identification number, and place of residence), main and secondary diagnosis using the International Classification of Diseases (ICD) codes, the tenth revision (ICD-10) is used since 1997. The ICD-10 codes D69.3 (immune thrombocytopenia) and D69.4 (other primary immune thrombocytopenia) recorded in NPR (inpatient, outpatient care or day surgery) were used to identify patients. Patients with secondary ITP were identified and excluded from the study base, using specified diagnoses from the NPR. Secondary ITP was defined as ITP associated with other diseases or conditions (5). ICD-10 codes used to identify patients with secondary ITP are listed in the supplementary (Table S-1).

Data on medications were obtained from the Swedish Prescribed Drug Register (PDR). The register contains data from July 2005 and includes information on filled prescriptions (substance, product name, formulation, and amount), patient characteristics (sex, age, personal identification number, place of residence), date of prescribing and date of filling the prescription, and the prescriber’s profession [16]. The PDR does not contain information on over-the-counter (OTC) medications, or medications administered in hospitals or nursing homes. The medications investigated in this study are medications that are mainly used to treat general symptoms of diseases, symptoms that also can be early symptoms of ITP. The Anatomical Therapeutic Chemical (ATC) codes A11-12 (vitamins and mineral supplements), B03A (iron preparations) M01-M03 (musculo-skeletal system), and N02A-B (analgesics, excluding antimigraine preparations), were used to identify medications used within one year prior to the first primary ITP diagnosis, that is the first ITP diagnosis out of two that an individual had to be classified as having chronic ITP (see Fig. 1).

Information for censoring of individuals who died or emigrated were retrieved from the Cause of Death Register and the Total Population Register. The cause of Death Register provides information about the main and contributory causes of death since 1961 [17]. The Total Population Register contains sociodemographic information on all Swedish residents [18].

This study was approved by the regional ethical board in Stockholm, Sweden (record number 2009/1597-31/4 and 2013/182-32).

2.1. Statistical analysis

The Standardized Incidence Ratio (SIR), the ratio of the observed number of ITP patients with a filled prescription to the expected number of ITP patients with a filled prescription, was estimated as a measure of relative risk for medication during the year preceding the first primary ITP diagnosis [19,20]. The expected number used in SIR calculations is the observed rate in the comparator population times the observed person-time in the study population. The study population was the ITP patients and for comparison we used the total Swedish population. To control for confounding, the SIR was stratified by age, sex and year of filling the prescription. For each drug, we used strata with information on observed number of fillings and person-time for both the study and the comparator population. Within each strata the comparator population rate was calculated as the observed number of fillings divided by the observed person-time. The expected number of fillings in the study population was then calculated as the comparator population rate times the observed person-time in the study population. Finally, observed and expected number of fillings were summed over strata and the ratio of the sums were calculated to yield the SIR.

The expected number of filled prescriptions in the ITP cohort was calculated by adding all observed person-years from the ITP population within each strata defined by sex, age group (15–85 + by five-years) and calendar year (2001–2012) of observation. Each stratum specific sum of person-times were then multiplied by the corresponding stratum-specific filling rate for the entire Swedish population. The filling rate was the number of patients with a filled prescriptions divided by number of observed person-years in the Swedish population, calculated as 365 times the stratum specific total population size, assuming observation during the whole year. An example of the calculation of SIR is given in Table S-2.

For the Swedish general population (comparator group) only...
aggregated data was available, i.e. no individual matching was carried out, instead we used standardization by age, sex and year of filling the prescription as adjustment. The 95% confidence intervals (CI) were calculated assuming that the observed events followed a Poisson distribution [21]. Medications with 10 or more observed events are presented in the result section.

All data were analysed with SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

Between July 2006 and December 2012 there were 3121 adult patients identified with an ITP diagnosis in the NPR (Fig. 2). Of those, 1852 were excluded as they did not fulfil the criteria of chronic disease (cITP); 1039 only had one registered ITP diagnosis, 813 had < 12 months between the diagnoses, and 182 further patients were excluded due to having secondary ITP.

In total, the study included 1087 adult patients with primary cITP. Patient characteristics are presented in Table 1. In the cohort of 1087 primary cITP patients, 44.2% had at least one filled prescription with a study medication within one year prior to their first primary ITP diagnosis. For men, this number was 37.7% and for women it was 50.4%. Males were older at the time of cITP diagnosis compared with women (mean age 61 versus 54 years).

Table 2 shows SIRs for the medications one year prior to the first primary ITP diagnosis for the ATC-codes (down to 4th ATC-code level) studied with 10 or more observed events, for SIRs for ATC-code down to 5th level see supplementary (Table S-3). The SIR, for overall medications investigated in the study, during the year before the first primary ITP diagnosis was 1.36, (95% CI 1.32–1.41).

A majority of the medications in the study that only includes medications that requires a prescription had a point estimate above unity, but only opioids (N02A) were found significant on a 95% level (Table 2). All of the medications that also includes medications available without a prescription had a point estimate above unity, and a majority were significant on a 95% level.

4. Discussion

In this population-based study, we found that it was more common for patients with cITP to fill a prescription with analgesics, vitamins, mineral supplements, or with substances used for symptoms from the musculoskeletal system prior to their first diagnosis than among the general population. The SIR for filling a prescription with anyone of the studied medications was 1.36 when compared with the general Swedish population, this is of similar magnitude as that reported for anti-infective medications [12].

Earlier studies have found that ITP patients have higher occurrence of comorbid diseases, such as diabetes, renal failure, vascular events, and infections, before their ITP diagnosis as compared with non-ITP individuals [12,22,23]. A higher prevalence of comorbid diseases before diagnosis among ITP patients is in accordance with what has been observed, before or at diagnosis, in other autoimmune disorders such as multiple sclerosis and rheumatoid arthritis [24–27]. The higher prevalence of comorbidity could be a possible reason for the augmented filling of prescriptions among the primary cITP patients during the year before their first primary ITP diagnosis, either for treating the comorbidity itself or in order to treat symptoms of the comorbidity. Another possible reason for the higher filling of a prescription with one of the studied medications is ascertainment bias, this since people with

Table 1

| Characteristics of the adult, chronic immune thrombocytopenia (cITP), patients. |
|-----------------|-----------------|-----------------|
|                  | Total, n (%)    | Male, n (%)     | Female, n (%) |
| All patients     | 1087 (100)      | 531 (100)       | 556 (100)     |
| Age at cITP diagnosis, year |
| 18-25            | 109 (10.0)      | 40 (7.5)        | 69 (12.4)     |
| 26-30            | 17 (5.8)        | 63 (16.2)       | 46 (10.5)     |
| 31-40            | 126 (11.6)      | 45 (8.5)        | 81 (14.6)     |
| 41-50            | 109 (10.0)      | 49 (9.2)        | 60 (10.8)     |
| 51-60            | 121 (11.1)      | 64 (12.1)       | 57 (10.3)     |
| 61-70            | 208 (19.1)      | 122 (23.0)      | 86 (15.5)     |
| 71-80            | 210 (19.3)      | 114 (21.5)      | 96 (17.3)     |
| 81-90            | 129 (11.9)      | 72 (13.6)       | 57 (10.3)     |
| 91+              | 12 (1.1)        | 8 (1.5)         | 4 (0.7)       |
| Mean (SD\(^a\)) | 57.3 (20.7)     | 61.0 (19.5)     | 53.8 (21.3)   |

Number of medications per ITP-patient

<table>
<thead>
<tr>
<th>Number of medications</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>607 (55.8)</td>
</tr>
<tr>
<td>1</td>
<td>184 (16.9)</td>
</tr>
<tr>
<td>2</td>
<td>133 (12.2)</td>
</tr>
<tr>
<td>3</td>
<td>63 (5.8)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>100 (9.2)</td>
</tr>
</tbody>
</table>

\(^a\) Standard deviation.

Fig. 2. Flow chart of included individuals.
symptoms who fills a prescription are expected to visit their doctor more frequent, and therefore are more likely to have a low platelet count identified and receive an ITP diagnosis. A third possible explanation is, as hypothesized earlier, that the ITP patients are seeking health care due to early symptoms of ITP (e.g. general body pain and illness symptoms, as well as iron deficiency and anaemia) and that they receive treatments for those symptoms.

Strengths of this population study includes use of the Swedish national health registers and the Swedish Total Population Register with high quality and close to complete coverage of the total Swedish population, which contributed to the quality of the study [28–30]. The accuracy of diagnoses in the Patient Register is generally between 85 and 95%, but can vary by disease and we are not aware of any published study investigating accuracy of ITP diagnosis in the register. We used register data to exclude patients with secondary ITP or Evans syndrome. The prospectively collected data from the national registers gave the study a large sample size, encompassing all adults with primary chronic ITP in Sweden, and no concern regarding recall bias. The Swedish general population was used as the comparison group and receive treatments for those symptoms of the disease and before platelet counts are reduced to levels indicating the disease.

5. Conclusion

Exposure to analgesics, vitamins and mineral supplements, and substances used for the musculoskeletal system is higher in adult patients with primary cITP during the year before their first diagnosis compared with the general Swedish population, when adjusted for age, sex and calendar year. Patients with cITP may seek help due to early symptoms of the disease and before platelet counts are reduced to levels indicating the disease.
Authorship contribution

Marie Linder and Lukas Löflling performed the statistical analysis. Lukas Löflling wrote the first draft of the manuscript. All authors participated in designing the study, interpreting the results and preparing the manuscript. Shahram Bahmanyar and Helle Kieler were responsible for acquisition of data.

Disclosure of conflicts of interest

LL, ML, CE, HK and SB are employees at the Centre for Pharmacoepidemiology, which receive grants from several entities (pharmaceutical companies, regulatory authorities and contract research organizations) for performance of drug safety and drug utilization studies. This study is an extension of a project granted by Amgen. Amgen had no role in the data collection and analysis and were not involved in the interpretation of results, writing, revision, or approval of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2017.10.014.

References