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Exposure to non-corticosteroid treatments in adult primary immune thrombocytopenia before the chronic phase in the era of thrombopoietin receptor agonists in France. A nationwide population-based study

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ABSTRACT

The objective of this study was to describe the exposure to non-corticosteroid treatments in adult primary immune thrombocytopenia (ITP) patients before the chronic phase at a nationwide level.
Study population is derived from the 2009–2011 cohort of the French Adult Immune Thrombocytopenia: a French pHarmacoepidemiological study (FAITH, no. ENCEPP 4574). The FAITH cohort includes all incident and persistent or chronic adult primary ITP patients treated in France. It was built through the nationwide French health insurance database, called SNIIRAM. For the present study, we included FAITH patients who were followed by at least 12 months and who had at least one exposure to a non-corticosteroid treatment before the ITP chronic phase. Exposure to non-corticosteroid treatments was searched through in- and out-hospital dispensing. Predictors of the choice among first-line non-corticosteroid treatments (rituximab, splenectomy or other drugs) were studied using a multinomial regression.
The study population included 443 patients. Non-corticosteroid treatments used in more than 10% of the patients at any time before the chronic phase were: rituximab (57.8%), splenectomy (22.1%), TPO-RAs (16.8%), repeated intravenous immunoglobulin (IVIg) courses (15.0%), danazol (14.4%) and dapsone (10.8%). Rituximab was the most used first-line non-corticosteroid treatment (45.4%). TPO-RAs and dapsone were more frequently used after 65 years of age (respectively, 24.8% versus 12.8%, $p = 0.01$ and 17.6% versus 7.2%, $p = 0.0008$), unlike splenectomy (16.4% versus 25.2%, $p = 0.03$). Age over 65 years was the sole independent predictor of first-line non-corticosteroid treatment choice.
In conclusion, rituximab was the leading non-corticosteroid treatment used before the chronic phase. TPO-RAs were mainly used in accordance with their labeling. IVIgs were consistently used as a chronic non-corticosteroid treatment.

1. Introduction

Immune thrombocytopenia (ITP) is a rare autoimmune disorder due to humoral and cell-mediated immune response directed against platelets and megakaryocytes [1,2]. First-line treatment of ITP is based on corticosteroids [3,4]. In adults, ITP becomes persistent in 70% of the cases [5]. Persistency phase is defined by a disease duration of more than 3 months and less than 12 months. Later, ITP is said to be chronic [6]. In face to persistent ITP, non-corticosteroid treatments are often prescribed. Such treatments may also be employed earlier in the disease course in case of contra-indication to corticosteroid or face to a resistant disease. Guidelines differ regarding the treatments that should be used before the chronic phase. The 2011 American Society of Hematology guidelines recommended splenectomy, and rituximab or thrombopoietin receptor agonists (TPO-RAs) as an alternative to splenectomy if contraindicated or not wished by the patient [4]. In contrast, an international consensus published in 2010 indicated as possible most available non-corticosteroid treatments without any grading. These include splenectomy, rituximab, TPO-RAs, danazol, dapsone or immunosuppressants such as azathioprine, mycophenolate or ciclosporin [3]. Intravenous polyvalent immunoglobulins (IVIgs) are recommended in face to severe bleeding in addition to corticosteroids, but not as chronic treatment [3,4].

However, no population-based study was interested in assessing non-corticosteroid treatment exposure in real-life practice. The aim of this study was to describe the exposure to non-corticosteroid

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treatments in adult primary ITP patients before the chronic phase at a nationwide level in France.

2. Methods

2.1. Study population

Study population is the French Adult Immune Thrombocytopenia: a French pHarmacoepidemiological study (FAITH) cohort. This study is part of post-authorization surveys of the European Network Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) coordinated by the European Medicine Agency (study no. 4574). Full protocol of the FAITH study has been described elsewhere [7]. Briefly, the source of data is the French Health Insurance Database, called *Système National d'Information Inter-Régimes de l'Assurance Maladie* (SNIIRAM). This database contains individualized, anonymous and linkable data. These data are prospectively recorded for every patient benefitting from health care in France, thus virtually covering the entire French population (65 million inhabitants). They include data regarding demographics, disabling diseases allowing full expenditure reimbursement, hospitalizations (with diagnoses encoded with the International Classification of Diseases, version 10 — ICD-10, procedures and costly drugs that were dispensed), out-hospital procedures and drug dispensing [8]. We extracted from the 2009–2011 SNIIRAM data those corresponding to all patients with at least one ITP code as a disabling disease or during hospital stays (D69.3 code of the ICD-10). We then excluded patients with a hospitalization or disabling disease diagnosis code starting by D69 and exclusive of ITP (D69.0, D69.1, D69.2, D69.4, D69.5, D69.7 and D69.8) during the year before and the semester after the date of first ITP code. To identify the date of diagnosis, we searched for out-hospital dispensing of ITP drugs (corticosteroids, dapsone, danazol, TPO-RAs or other immunosuppressants) before the first disabling disease or hospital stay with ITP code. Date of diagnosis was then defined as: i) the date of first ITP drug dispensing if a patient had at least 3 dispensing of ITP drugs during a sliding period of 6 months before the first LTD or hospital stay with ITP code, or ii) the first LTD or hospital stay with ITP code otherwise. We then restricted the cohort to incident patients (with no diagnosis code nor ITP treatment exposure during the first six months of the study) [7,9] and then to adults at the date of diagnosis and to primary ITP cases (no hospital or disabling disease diagnosis code for a disease associated with ITP during the year before and the semester after the estimated date of diagnosis). Lastly, we selected the persistently treated patients, corresponding to the FAITH cohort [7]. Persistent treatment was defined by an exposure to ITP drugs (corticosteroids, IVIgs, dapsone, danazol, TPO-RAs, hydroxychloroquine or other immunosuppressants) exceeding three consecutive months or exposure to rituximab or splenectomy.

For the present study, we restricted the 2009–2011 FAITH cohort to the patients followed by at least 12 months and exposed to at least one non-corticosteroid treatment to assess the respective treatment exposures before the chronic phase.

2.2. Patients' characteristics

Age, gender and disease duration were described. We searched for the presence of severe bleedings (defined as central nervous system or gastro-intestinal bleedings) as well as mucosal or internal bleeding using ICD-10 codes during hospitalization at ITP onset for patients hospitalized at diagnosis [9]. Central nervous system or gastro-intestinal bleedings require specific and costly health care and therefore the related hospital stays should be accurately encoded. We calculated the Charlson's comorbidity score [10] at diagnosis thanks to a method validated in the SNIIRAM. This method identifies comorbidities through disabling diseases and hospitalization diagnosis codes, as well as the reimbursement of some specific drugs (e.g. anti-diabetic to identify diabetes mellitus patients) [11].

2.3. Treatment exposure

We searched exposure to non-corticosteroid treatments during the year after the date of diagnosis through out-hospital dispensing and through hospital stays for splenectomy, rituximab and IVIgs. A single dispensing was sufficient to define an exposure, except for IVIgs. Indeed, at least three monthly IVIg dispensing were mandatory to define persistent exposure to IVIgs, in order to exclude prescriptions for acute serious bleeding [12].

2.4. Statistical analyses

We detailed the main characteristics of patients and their exposure to non-corticosteroid treatments by age groups, either below 65 years of age (younger group) or above 65 years of age (older group). Comparisons between age groups used the t-test or the Wilcoxon–Mann–Whitney test for quantitative variables, and the χ^2 test or the Fisher test for qualitative ones.

We then performed a multinomial regression analysis to assess the link between several covariates and exposure to three first-line non-corticosteroid treatment categories: splenectomy, rituximab or other drugs, splenectomy being the reference group. Covariates were age at diagnosis ($\geq$65 years vs. <65 years), gender, mucosal or internal bleeding at ITP onset, disease duration before the first non-corticosteroid treatments (<3 months vs. $\geq$3 months) and SNIIRAM-Charlson's comorbidity score ($\geq$1 vs. 0). Variables associated with the outcome at the threshold of 25% in univariate analyses were included in the multivariate model (backward procedure, $\alpha = 5\%$). Analyses were carried out with the SAS 9.4™ software (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Patients

The FAITH cohort included 1106 incident adult ITP patients persistently treated for ITP between the 1st July 2009 and the 31st June 2011. Twenty-seven patients died during the first year after diagnosis. Their median age at ITP diagnosis was 85 years, 51.8% of the patients were males and 59.3% had a Charlson's comorbidity score $\geq$1. Six had not been exposed to non-corticosteroid treatments, 13 had been exposed to rituximab, 7 to TPO-RAs, 2 to dapsone, 2 to azathioprine, 1 to IVIgs and 2 underwent splenectomy. Three hundred and seventy-eight other patients were also excluded because of a follow-up shorter than 12 months.

Out of the 701 remaining patients, 258 were excluded because they had not been exposed to any non-corticosteroid treatment before chronic phase. Therefore, 443 patients were included in the study.

3.2. Patients' characteristics

Patients' characteristics are described in Table 1. Mean age at diagnosis was 52.7 $\pm$ 20.8 years and 59.1% of the patients were females. Compared to younger patients, those aged over 65 years were predominantly males, they had more frequently mucosal or internal bleeding at ITP onset and they had a higher Charlson's comorbidity score.

3.3. Exposure to non-corticosteroid treatments before chronic phase

Exposure to non-corticosteroid treatments is described in Table 1. Median time from diagnosis to the first non-corticosteroid treatment was 2.23 months (interquartile range: 3.81).

Overall, non-corticosteroid treatments used in more than 10% of the patients at any time before chronic phase were rituximab (57.8%), splenectomy (22.1%), TPO-RAs (16.8%), IVIgs (15.0%), danazol (14.4%) and dapsone (10.8%). Hydroxychloroquine was used in 6.5% of the patients and immunosuppressants (azathioprine, mycophenolate or ciclosporin) in 5.9%.