Corticosteroid Risk Function of Severe Infection in Primary Immune Thrombocytopenia Adults. A Nationwide Nested Case-Control Study

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Abstract

Corticosteroid (CS)-related infection risk in immune thrombocytopenia (ITP) is unknown. The aim of this study was to assess the adjusted CS risk function of severe infection in persistent or chronic primary ITP adults. We designed a nested case-control study in the FAITH cohort. This cohort is built through the French national health insurance database named SNIIRAM and includes all treated incident persistent or chronic primary ITP adults in France (ENCePP n°4574). Patients who entered the FAITH cohort between 2009 and 2012 were eligible (n = 1805). Cases were patients with infection as primary diagnosis code during hospitalization. Index date was the date of first hospitalization for infection. A 2:1 matching was performed on age and entry date in the cohort. Various CS exposure time-windows were defined: current user, exposure during the 1/3/6 months preceding index date and from the entry date. CS doses were converted in prednisone equivalent (PEQ). The cumulative CS doses were averaged in each time-window to obtain daily PEQ dosages. Each CS exposure definition was assessed using multivariate conditional regression models. During the study period, 161 cases (9 opportunistic) occurred. The model with the best goodness of fit was CS exposure during the month before the index date (OR: 2.48, 95% CI: 1.61–3.83). The dose-effect relation showed that the risk existed from averaged daily doses ≥5 mg PEQ (vs. <5 mg: 2.09, 95% CI: 1.17–3.71). The risk of infection was mainly supported by current or recent exposure to CS, even with low doses.

Introduction

Immune thrombocytopenia (ITP) is a bleeding disorder due to an autoimmune reaction directed against platelets and megakaryocytes [1,2]. It is referred to as "primary" when not associated to another disease (about 80% of ITPs) [3]. First-line treatment is based on
corticosteroids [3,4]. In case of severe bleeding, intravenous polyvalent immunoglobulin (IVIgs) is added [5]. In adults, 70% of ITPs become persistent (lasting ≥3 months) or chronic (lasting ≥12 months) [1,6–8]. Nowadays, several corticosteroid-sparing treatments targeting the immune system are available [3,4]. Splenectomy is the reference treatment for corticosteroid dependent or resistant ITP [4]. Rituximab, a monoclonal antibody directed against CD20 has been used since the 2000s. It was the leading non-corticosteroid treatment used during the persistency phase in France between 2009 and 2011 [9]. Immunosuppressants such as azathioprine, mycophenolate or cyclosporine are less frequently used [3,9]. Lastly, IVIg is not recommended as chronic treatment [3,4]. Nevertheless they are widely used in some countries [9].

However, these second-line treatments may take time to be effective. During this time, corticosteroids-dependent patients are still exposed to corticosteroids, which are secondarily tapered. Consequently, adult ITP adults may be persistently exposed to low dose corticosteroids during the initial management of ITP.

An increased risk of infection has been demonstrated in ITP patients [10–13]. The hazard ratio for 20-year mortality caused by infection in adult ITP patients has been estimated to 2.4 (95% confidence interval -95% CI: 1.0–5.7) as compared with the general population [14]. A study carried out in the General Practice Research Datalink patients between 1992 and 2005 with 1145 ITP showed that 19% of deaths were related to infection [15].

One might suppose that this high risk of infection in ITP is related to the exposure to immunosuppressive treatments or splenectomy [12,16–18]. Surprisingly, the risk associated with corticosteroid use [19] has not been assessed in ITP, albeit corticosteroids have been the cornerstone treatment of this disease for 60 years [20]. The infectious risk of splenectomy has never been adjusted on corticosteroid exposure [16–18]. In daily practice, rituximab is often used in patients with contra-indication for splenectomy [9,21]. The risk of infection on rituximab was reassuring in the sole phase II clinical trial [22], however some reports of rituximab use in “real-life” practice raised concerns about the risk of infection [23–25]. Once again, most of the patients who experienced severe infection were also exposed to corticosteroids.

The aim of this study was to assess the risk function of corticosteroid-related severe infection in persistent or chronic primary ITP adults, adjusted for splenectomy, rituximab, other immunosuppressant and intravenous immunoglobulin (IVIg) exposures.

Materials and Methods

We performed a nested case-control study in the so-called FAITH (French Adult Immune Thrombocytopenia: a French pHarmacoepidemiological study) cohort. This study is registered in the post-authorization survey registry of the European Network Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) coordinated by the European Medicine Agency (study n°4574). Full protocol of the FAITH study has been described elsewhere [26]. STROBE checklist is indicated in S1 File.

Data Source

The source of data was the French health insurance database, named Système National d’Information Inter-Régimes de l’Assurance Maladie (SNIIRAM) [27]. 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 (66 million inhabitants). They include data regarding demographics, long-term disabling diseases (LTD) allowing full medical expenditure reimbursement, hospitalizations, out-hospital procedures and drug dispensing (dates of dispensing, drug identifiers and numbers of units dispensed). Hospitalizations data include procedures, diagnosis codes (one principal, one related...
and up to 30 associated diagnoses encoded with the International Classification of Disease, version 10 (ICD-10) and costly drugs dispensed such as rituximab or IVIg. Data regarding outpatient and in-hospital drug dispensing include the drug name, the dosage and the form, as well as the quantity delivered and the date of dispensing [27].

Population source
The patients’ selection process has been described in details elsewhere [26]. Briefly, data of all the patients with at least one ITP code as LTD or during hospital stays (D69.3 code of the ICD-10) were extracted from the SNIIRAM between 2009 and 2012. The date of diagnosis was defined as the first diagnosis code or the first dispensing of ITP drug before the first diagnosis code, if any. After excluding patients with ambiguous or contradictory codes suggesting mis-coding, and after exclusion of secondary ITP, we restricted the cohort to incident and persistently treated patients [26]. Persistent treatment was defined by the exposure to any ITP treatments exceeding three consecutive months (corticosteroids, IVIg, dapsone, danazol, thrombopoietin receptor agonists or other immunosuppressants), to splenectomy or to rituximab. Follow-up started at the first exposure to persistent treatment (entry date in the cohort) [26]. For the present study, we analyzed the sample of patients included from the 1st July 2009 to the 30th June 2012.

Case-control design
Cases were patients who experienced a severe infection after the entry date in the cohort. Severe infection was defined by an in-hospital primary diagnosis with an ICD-10 code for infection (Table A in S2 File). This list of codes of infection as primary diagnosis has a predictive positive value of 97% (95% CI: 93–100%) in the SNIIRAM data (personal data). Cases’ index date was the date of first severe infection. Controls were randomly selected among the patients without any severe infection during the follow-up and followed until the corresponding case’s index date.

Two controls were matched to each case on the age at entry date in the cohort (<65 vs. ≥65 years), the year and the month of entry date in the cohort. This latter matching condition was used to control for seasonality and epidemics. Controls’ index dates were index dates of the corresponding cases. Consequently, disease duration from entry date to index date was similar for cases and controls.

Corticosteroid exposure
For corticosteroids, we considered various time-windows: exposure at index date, exposure during 1, 3 or 6 months before the index date (defined as ever exposed during the 1/3/6 months before the index date) and any exposure from the entry date to the index date. Dispensed doses were converted in prednisone equivalent (PEQ). To assess the effect of cumulative exposure, the cumulative doses received during the quoted time-windows were averaged for each patient to obtain daily PEQ dosages.

Potential confounders
We identified splenectomy before index date through hospital procedures codes. We considered that a patient was exposed to rituximab during the six months following infusion, thus it is the period of maximal B-cell depletion with the maximal risk of infection [28]. However, we also carried out sensitivity analyses considering the 3-month and the 12-month periods after rituximab, as well as the “ever exposed” definition. For azathioprine, mycophenolate, cyclosporine
and IVIg, we searched exposure during the month before the index date. We also carried out sensitivity analyses using 3-, 6-, 12-month periods and the "ever exposed" definition.

Other covariates were gender, mucosal or internal bleeding at ITP onset (reflecting disease severity) [8] and comorbidities increasing the risk of infection: diabetes mellitus, chronic cardiac, lung, kidney and liver diseases (considered separately). Comorbidities were identified using algorithms validated in the SNIIRAM [29]. They combined LTD, in-hospital diagnosis codes, specific procedures (i.e. hemodialysis for severe chronic disease) and specific drugs dispensing (i.e. glucose lowering drugs for diabetes mellitus). Of note, patients with cancer, connective tissue disease, chronic viral infection and primary immune deficiency were considered as secondary ITP patients and were not included in the FAITH cohort [8, 26].

Statistical Analysis

We performed a model of conditional logistic regression for each corticosteroid exposure time-window. Models’ goodness of fit was compared using the Akaike criterion [30]. We also compared the corticosteroid exposure time-windows in specific models so as to compare the effect of recent versus past exposure. Lastly, we explore the dose-effect relationship in the best model. All the models were adjusted for the potential confounders quoted above.

Non-costly drug dispensing during hospitalization stays is not recorded in the SNIIRAM. Therefore, we carried out sensitivity analyses adding in the models a variable corresponding to the occurrence of a hospitalization of at least 7 days between start of follow-up and index date, i.e. hospitalization at risk for a significant unmeasured corticosteroid exposure.

Calculations were carried out using SAS 9.4™ statistical software (SAS Institute, Cary, North Carolina, USA).

Ethical considerations

This study received all mandatory authorizations according to French law (Institut des Données de Santé approval in March 2012, numbered 40; and Commission Nationale de l'Informatique et des Libertés authorization in July 2012, decision numbered DE-2012-076 regarding the request numbered 1579257).

Results

Selection of the population

During the study period, 1805 incident primary ITP adults persistently treated entered the FAITH cohort. Mean age was 57.6 ± 21.3 years with 58.9% of females. Mean follow-up was 18.5 ± 6.8 months. One hundred and sixty-four patients (9.1% of all FAITH patients) had a severe infection and were matched to 321 controls. For three cases (2 gastro-intestinal infections and 1 pneumonia), no suitable match could be identified. All other cases had 2 controls except one case (one control only). Therefore, 482 patients were included the case-control study (161 cases and 321 controls).

Characteristics of cases and controls

The main characteristics of cases and controls are detailed in Table 1. Mean disease duration from entry date until index date (date of severe infection) was 8.7 ± 6.1 months. Cases were more frequently males (57.1% vs. 44.2%, p = 0.007) and had more comorbidities. Cases were more frequently exposed to splenectomy, rituximab, immunosuppressants (azathioprine, mycophenolate or cyclosporine) and IVIg in the various time-windows, albeit not reaching
statistical significance (Table 1). Nine patients were exposed to repeated courses of rituximab before index date (including 6 cases and 3 controls).

Infections

Infections are categorized in Table 2. Localizations accounting for more than 10% of infections were the lower respiratory (33.5%), the gastro-intestinal (16.8%), and the urinary tracts (13.0%) as well as the skin (12.4%). Ten patients presented opportunistic infections: 3 zosters, 3 apergilloses, 2 pneumocytoses, 2 tuberculoses and 1 varicella. Opportunistic infections that occurred are detailed in Table B in S2 File. No Progressive multifocal leukoencephalopathy was described.

Corticosteroid risk function of infection

Results of the univariate analyses are shown in Table C in S2 File. Results of the multivariate models are described in Table 3. Considering the various time-windows of exposure to corticosteroids in multivariate models, the Akaike criterion was the lowest for exposure during the month before the index date (adjusted odds ratio: 2.48, 95% CI: 1.61–3.83). For longer time-
windows, the risk decreased nevertheless remained significant until the six-month time-window. When comparing the time-windows, there was no statistically significant increased risk among the patients exposed during the month before the index date whether current user or not at index date (adjusted odds ratio: 1.23, 95% CI: [0.63–2.40]). In contrast, there was a major risk of infection among the patients ever exposed during the 3 months prior to the index date when exposed during the month before the index date in comparison with those not exposed during the month before the index date (adjusted odds ratio: 3.42; 95% CI: [1.31–8.92]).

Then, we assessed the corticosteroid dose-effect relationship in the best model among the models previously quoted, considering corticosteroid exposure during the month before the index date. The analyses were also adjusted for corticosteroid past cumulative dose during the five months preceding the month before the index date. We identified a statistically significant association from an average daily dose ≥5 mg PEQ/day during the month before the index date (adjusted odds ratio: 2.09, 95% CI [1.17–3.71], p = 0.01). We did not find any impact of corticosteroid cumulative dose during the five months preceding the month before the index date (Table 4), as well as for corticosteroid cumulative dose from the entry date in the cohort until the month before the index date (sensitivity analysis, not shown).

Sensitivity analyses using the 3-, 6-, 12-month periods and the “ever exposed” definition for splenectomy, IVIg and immunosuppressants, as well as using the 3-month period, the 12-month period and the “ever exposed” definition for rituximab led to similar results (data not shown).

Table 2. Description of severe infections that occurred during the follow-up of the 1805 incident primary ITP adults persistently treated who entered the FAITH cohort between the 1st of July 2009 and the 30th of June 2012.

| Types of infection | n (%) |
|--------------------|-------|
| **By site**        |       |
| Pulmonary          | 54 (33.5%) |
| Gastro-intestinal tract | 27 (16.8%) |
| Uro-genital tract  | 21 (13.0%) |
| Cutaneous          | 20 (12.4%) |
| Sepsis             | 11 (6.8%) |
| ENT/ocular         | 8 (5.0%) |
| Neurological       | 2 (1.2%) |
| Pyogenic arthritis | 2 (1.2%) |
| Endocarditis       | 1 (0.6%) |
| **By microorganism** |     |
| Gram-negative bacillus | 7 (4.3%) |
| *Streptococcus pneumoniae* | 5 (3.1%) |
| Varicella-zoster virus | 4 (2.5%) |
| Influenza          | 3 (1.7%) |
| Aspergillosis      | 3 (1.7%) |
| Tuberculosis       | 2 (1.2%) |
| Pneumocystis       | 2 (1.2%) |
| *Staphylococcus*   | 2 (1.2%) |
| Cytomegalovirus    | 2 (1.2%) |
| *Haemophilus influenzae* | 1 (0.6%) |
| *Candida*          | 1 (0.6%) |
| Parvovirus         | 1 (0.6%) |
| Leishmaniosis      | 1 (0.6%) |

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Of note, male gender was associated to severe infection in all multivariate models, with odds ratio ranging from 1.55 to 1.86. It was the sole covariate associated with severe infection in the final multivariate model (Table D in S2 File). Exposure to rituximab, immunosuppressants and IVIg as well as splenectomy could be removed from all multivariate models. However, rituximab exposure during the six months before index date was near to the significance threshold in the final multivariate model (adjusted odds ratio: 1.67, 95% CI [0.96–2.90], p < 0.07; see Table E in S2 File).

Sensitivity analysis adding in the models the occurrence of hospitalization of at least 7 days led to similar results. However, this variable was independently associated with infection occurrence (Table F in S2 File).

Discussion

This study demonstrated that corticosteroid exposure was a leading factor associated with the occurrence of severe infection in incident primary ITP adults persistently treated. The risk function showed a maximal risk period in the month preceding the date of risk measure. The risk was present even in patients exposed to low, supraphysiologic daily doses (>5mg PEQ/day). This is an important finding as many physicians may have in mind that the infectious risk with corticosteroids is for short exposures above 20 mg PEQ daily, as noted in previous reports [31,32]. In contrast, past exposure prior to the month preceding the date of risk measure and past cumulative dose does not seem to play a major role in the occurrence of severe infection.

This risk function is similar to the one recently reported in older rheumatoid arthritis patients [33]. The increased risk with recent exposure might be explained by the effect of corticosteroids on innate immunity, which is rapidly reversed when the drug is stopped [19]. The increased risk for supra-physiological (>5mg PEQ/day) exposure to corticosteroids is an argument to support this finding in a pathophysiological perspective. A similar dose-effect

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**Table 3. Multivariate models* assessing the link between exposure to corticosteroids during the various time-windows and occurrence of severe infection.** Each line shows the adjusted result of exposure to corticosteroids with a given time-window period.

| Exposure to corticosteroids | OR [95% CI] | p       | Akaike criteria |
|----------------------------|-------------|---------|----------------|
| **Time-window periods**    |             |         |                |
| Exposure to corticosteroids at index date† | 2.12 [1.39–3.23] | <0.001  | 337.553        |
| Exposure to corticosteroids in the month before the index date† | 2.48 [1.61–3.83] | <0.001  | 331.921        |
| Exposure to corticosteroids in the 3 months before the index date† | 1.96 [1.25–3.09] | 0.003   | 341.189        |
| Exposure to corticosteroids in the 6 months before the index date† | 1.64 [1.01–2.64] | 0.044   | 342.859        |
| Exposure to corticosteroids from the cohort entry date until the index date† | 1.22 [0.65–2.29] | 0.53    | 346.674        |
| **Some comparisons across time-window periods** |             |         |                |
| Among patients with exposure in the month before the index date (n = 255, incl. 105 cases): current user vs. not current user at index date † | 1.23 [0.63–2.40] | 0.55    | 133.718        |
| Among patients with exposure in the 3 months before the index date † (n = 300, incl. 113 cases): exposure in the month before index date vs. no exposure in the month before the index date † | 3.42 [1.31–8.92] | 0.012   | 161.080        |
| Among patients with exposure in the 6 months before the index date (n = 345, incl. 124 cases): exposure in the 3 months before the index date † vs. no exposure in the 3 months before the index date † | 2.57 [0.95–7.00] | 0.064   | 195.633        |

*Adjusted for mucosal or internal bleeding at diagnosis, lung disease, kidney disease, cardiac disease, diabetes mellitus, exposure to rituximab in the six months before index date, to azathioprine, mycophenolate, cyclosporine and polyvalent immunoglobulin in the month before index date as well as splenectomy before index date. Age and disease duration until index date were neutralized by matching.

†Index date: date of infection for cases.

Abbreviations: 95% CI: 95% confidence interval; OR: odds ratio.

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Of note, male gender was associated to severe infection in all multivariate models, with odds ratio ranging from 1.55 to 1.86. It was the sole covariate associated with severe infection in the final multivariate model (Table D in S2 File). Exposure to rituximab, immunosuppressants and IVIg as well as splenectomy could be removed from all multivariate models. However, rituximab exposure during the six months before index date was near to the significance threshold in the final multivariate model (adjusted odds ratio: 1.67, 95% CI [0.96–2.90], p < 0.07; see Table E in S2 File).

Sensitivity analysis adding in the models the occurrence of hospitalization of at least 7 days led to similar results. However, this variable was independently associated with infection occurrence (Table F in S2 File).
Importantly, 130 patients (27.0%) were exposed to rituximab during the study period, of whom 67 (13.9%) were exposed during the six months before index date. In the univariate analysis, there was a clear trend towards an increased risk of infection in the 6 months following rituximab (odds ratio: 1.51, 95% CI [0.90–2.56], p = 0.1). This trend was confirmed in the multivariate analysis (adjusted odds ratio: 1.67, 95% CI [0.96–2.90], p < 0.07). Consequently, we cannot exclude an increased risk with rituximab due to sample size. In the previously quoted French registry stemming from referral centers, 11 infections occurred among 248 ITP patients treated with rituximab (median time to infection: 4 months; range: 1–14 months). Among them, 7 patients were also exposed to corticosteroids at the time of infection [25]. Further larger population-based studies are needed to assess the adjusted rituximab risk function of infection. Similarly, the respective weight of splenectomy and exposure to immunosuppressants (azathioprine, mycophenolate, cyclosporine and polyvalent immunoglobulin in the month before index date, as well as cumulative exposure to corticosteroids during the five months preceding the month before the index date. Age and disease duration until index date were neutralized by matching. Akaike criteria: 340.154. Index date: date of infection for cases. n: number of patients.

**Table 4. Multivariate model** assessing the dose-effect relation between exposure to corticosteroids during the month before the index date and occurrence of severe infection.

| Average daily dose of corticosteroids in the month before the index date ¹, mg PEQ | OR [95% CI]       | p    |
|---------------------------------------------------------------------------------|-------------------|------|
| Male gender                                                                     | 1.63 [1.11–2.40]  | 0.01 |
| Average daily dose of corticosteroids in the month before the index date ², mg PEQ | 0.003             |      |
| <5                                                                              | 1                 |      |
| [5–10[                                                                         | 2.09 [1.17–3.71]  | 0.01 |
| ≥10                                                                             | 1.99 [1.26–3.17]  | 0.003|

*Adjusted for gender, mucosal or internal bleeding at diagnosis, lung disease, kidney disease, cardiac disease, diabetes mellitus, exposure to rituximab in the six months before index date, to azathioprine, mycophenolate, cyclosporine and polyvalent immunoglobulin in the month before index date, as well as cumulative exposure to corticosteroids during the five months preceding the month before the index date. Age and disease duration until index date were neutralized by matching. Akaike criteria: 340.154.

Abbreviations: 95% CI: 95% confidence interval; OR: odds ratio.

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Our study points the role of gender in the risk of infection. We have no clear explanation for this latter association. Unfortunately, detailed clinical data such as tobacco exposure are not recorded in the SNIIRAM. Cases had more comorbidities than controls, particularly of chronic pulmonary and chronic kidney disease. Chronic pulmonary disease may favors lung infections (accounting for one third of the infections observed in this study), and chronic kidney disease has been demonstrated as a risk factor for infection [35,36].

The pattern of severe infection sites was consistent with data from the Danish population-based study [11]. Of note, 9/161 (5.6%) of the severe infections we observed were opportunistic. The risk of varicella-zoster, parasitic (n = 5 in our study) and fungal infections has been reported in ITP patients [37–42]. It is explained by the effect of corticosteroids on innate immunity (for instance as regards the cases of aspergillosis) and on T-lymphocytes [19].
In sensitivity analyses adding in the models a variable corresponding to the occurrence of a hospitalization of at least 7 days between start of follow-up and index date, this variable was independently associated with severe infection occurrence. Three explanations may be suggested: i) hospitalization reflects a more severe ITP, or in patients with comorbidities with a higher baseline risk for infection, ii) hospitalization in itself may increase the risk of infection and iii) this association is due to unmeasured exposure to corticosteroids.

Some limitations should be discussed. As all studies conducted in health insurance databases, the identification of ITP patients relies on diagnosis codes. Possibility of miscoding cannot be fully excluded despite all cautions [8,26]. The current study includes persistently treated primary ITP adult patients. Thus, our results cannot be extended to all ITP patients. The codes of infections corresponded mostly to infection localization rather than to the microorganism in cause. Consequently, we could not stratify the analyses on the type of microorganism. We could not exclude that the risk may be different between bacterial, viral and parasitic infections. The nested case-control design was used to assess the corticosteroids risk function of severe infection. The effect of repeated rituximab courses and of rituximab after or before splenectomy has to be investigated in the long term. Cases and controls were matched on the age and on disease duration. Consequently, we could not assess the weights of these factors that have been demonstrated as linked to hospital stay or visit for infection in a previous population-based study in ITP [11]. Out of the 1805 patients included in the FAITH cohort, 28 died during follow-up at home without any hospitalization for infection. As the cause of death is not recorded in the SNIIRAM, we cannot rule out that these patients died due to infection without being considered as cases. Similarly, the lack of clinical data available in the SNIIRAM prevented us from adjusting on some disease characteristics such as detailed bleeding score to assess disease severity [5] or tobacco exposure. Examination and lab tests results are not recorded in the SNIIRAM. Consequently, we could not adjust the analysis on platelet count, that may be associated with the risk of infection [43–45]. We did not find any protective effect of IVIg, but a channeling bias (treatment with IVIg of patients with a higher baseline risk of infection) cannot be ruled out. Lastly, we used dispensing data to model drug exposure, and compliance could not be assessed.

Conclusions
This study suggests that corticosteroids were the main immunosuppressant associated with severe infection in primary ITP adults exposed to persistent treatment. Maintaining corticosteroid even at a supra-physiological dose is associated with severe infection. In contrast, the past cumulative dose does not seem to play a major role. These results sustain the use of corticosteroid-sparing agents in persistent or chronic ITP.

Supporting Information
S1 File. STROBE Checklist.

S2 File. Supplementary Tables.
Table A. International Classification of Diseases, version 10 (ICD-10) codes used for the identification of severe infections during hospital stays.
Table B. Description of opportunistic infections that occurred during the follow-up of the 1805 incident primary ITP adults persistently treated who entered the FAITH cohort between the 1st of July 2009 and the 30th of June 2012.
Table C. Univariate models assessing the link between exposure to corticosteroids during the various time-windows and covariates with the occurrence of severe infection.
Table D. Full multivariate model assessing the link between exposure to corticosteroids during the month before index date and occurrence of severe infection. This model had the lowest Akaike criterion value (331.921).

Table E. Full multivariate model assessing the link between exposure to corticosteroids during the month before index date and occurrence of severe infection, without withdrawal from the model of the exposure to rituximab in the month before index date.

Table F. Full multivariate model assessing the link between exposure to corticosteroids during the month before index date and occurrence of severe infection: sensitivity analysis adding the variable corresponding to the occurrence of a hospitalization of at least 7 days between start of follow-up and index date.

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Author Contributions

Conceived and designed the experiments: GM AP MLM LS. Performed the experiments: GM AP. Analyzed the data: GM AP MLM LS. Contributed reagents/materials/analysis tools: GM AP. Wrote the paper: GM AP MLM LS.

References

1. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009; 113: 2386–2393. doi:10.1182/blood-2008-07-162503 PMID: 19005182

2. Lo E, Deane S. Diagnosis and classification of immune-mediated thrombocytopenia. Autoimmun Rev. 2014; 13: 577–583. doi:10.1016/j.autrev.2014.01.026 PMID: 24444701

3. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010; 115: 168–186. doi:10.1182/blood-2009-06-225565 PMID: 19846889

4. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011; 117: 4190–4207. doi:10.1182/blood-2010-08-302984 PMID: 21325804

5. Khellafi M, Michel M, Schaeffer A, Bierling P, Godeau B. Assessment of a therapeutic strategy for adults with severe autoimmune thrombocytopenic purpura based on a bleeding score rather than platelet count. Haematologica. 2005; 90: 829–832. PMID:15951296

6. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood. 1996; 88: 3–40. PMID:8704187

7. Stasi R, Slipa E, Masi M, Cecconi M, Scimò MT, Oliva F, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. Am J Med. 1995; 98: 436–442. PMID:7733121

8. Moulis G, Palmaro A, Montastruc J-L, Godeau B, Lapayre-Mestre M, Sailler L. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. Blood. 2014; 124: 3308–3315. doi:10.1182/blood-2014-05-578336 PMID: 25305203

9. Moulis G, Lapayre-Mestre M, Montastruc J-L, Sailler L. 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. Autoimmun Rev. 2015; 14: 168–173. doi:10.1016/j.autrev.2014.10.017 PMID: 25461471

10. Portielje JE, Westendorp RG, Kluijn-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood. 2001; 97: 2549–2554. PMID:11313240
11. Nørgaard M, Jensen ÅØ, Engebjerg MC, Farkas DK, Thomsen RW, Cha S, et al. Long-term clinical outcomes of patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. Blood. 2011; 117: 3514–3520. doi: 10.1182/blood-2010-10-312819 PMID: 21263148

12. Boyle S, White RH, Brunson A, Wun T. Splenectomy and the incidence of venous thromboembolism and sepsis in patients with immune thrombocytopenia. Blood. 2013; 121: 4782–4790. doi: 10.1182/blood-2012-12-467088 PMID: 23637127

13. Hu M-H, Yu Y-B, Huang Y-C, Gau J-P, Hsiao L-T, Liu J-H, et al. Absolute lymphocyte count and risk of short-term infection in patients with immune thrombocytopenia. Ann Hematol. 2014; 93: 1023–1029. doi: 10.1007/s00277-014-1024-3 PMID: 24441917

14. Frederiksen H, Maegbaek ML, Nørgaard M. Twenty-year mortality of adult patients with primary immune thrombocytopenia: a Danish population-based cohort study. Br J Haematol. 2014; 166: 260–267. doi: 10.1111/bjh.12869 PMID: 24690142

15. Schoonen WM, Kucera G, Coalson J, Li L, Rutstein M, Mowat F, et al. Epidemiology of immune thrombocytopenia purpura in the General Practice Research Database. Br J Haematol. 2009; 145: 235–244. doi: 10.1111/j.1365-2457.2009.05715.x PMID: 19245432

16. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood. 2004; 104: 2623–2634. PMID: 15217831

17. Kyaw MH, Holmes EM, Tools F, Wayne B, Chalmers J, Jones IG, et al. Evaluation of severe infection and survival after splenectomy. Am J Med. 2006; 119: 276.e1–7.

18. Thomsen RW, Schoonen WM, Farkas DK, Riis A, Jacobsen J, Fryzek JP, et al. Risk for hospital contact with infection in patients with splenectomy: a population-based cohort study. Ann Intern Med. 2009; 151: 546–555. PMID: 19841456

19. Cutolo M, Seriolo B, Pizzorni C, Secchi ME, Soldano S, Paolino S, et al. Use of glucocorticoids and risk of infections. Autoimmun Rev. 2008; 8: 153–155. doi: 10.1016/j.autrev.2008.07.010 PMID: 18703175

20. Stasi R, Newland AC. ITP: a historical perspective. Br J Haematol. 2011; 153: 437–450. doi: 10.1111/j.1365-2457.2010.08562.x PMID: 21466538

21. Ghanima W, Godeau B, Cines DB, Bussel JB. How I treat immune thrombocytopenia: the choice between splenectomy or a medical therapy as a second-line treatment. Blood. 2012; 120: 960–969. doi: 10.1182/blood-2011-12-309153 PMID: 22740443

22. Godeau B, Porcher R, Fain O, Lefrere F, Fenaux P, Cheze S, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. Blood. 2008; 112: 999–1004. doi: 10.1182/blood-2008-01-131029 PMID: 18463354

23. Arnold DM, Dentali F, Crowther MA, Meyer RM, Cook RJ, Sigouin C, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med. 2007; 146: 25–33. PMID: 17200219

24. Moulis G, Sailler L, Sommet A, Lapeyre-Mestre M, Derumeaux H, Adoue D. Rituximab versus splenectomy in persistent or chronic adult primary immune thrombocytopenia: an adjusted comparison of mortality and morbidity. Am J Hematol. 2013; 88: 41–6. doi: 10.1002/ajh.23580 PMID: 24038066

25. Khellafi M, Charles-Nelson A, Fain O, Terriou L, Viallard J-F, Cheze S, et al. Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients. Blood. 2014; 124: 3228–3236. doi: 10.1182/blood-2014-06-582346 PMID: 25293768

26. Moulis G, Sailler L, Adoue D, Lapeyre-Mestre M. Pharmacoeconomics of Immune Thrombocytopenia: protocols of FAITH and CARMEN studies. Therapy. 2014; 69: 437–448. doi: 10.2515/therapie/2014056 PMID: 25285364

27. Moulis G, Lapeyre-Mestre M, Palmaro A, Puiget G, Montastruc J-L, Sailler L. French health insurance databases: What interest for medical research? Rev Med Interne. 2015; 36:411–7 doi:10.1016/j.revmed.2014.11.009 PMID: 25547954

28. Gotteberg J-E, Ravaud P, Bardin T, Cadou P, Cantagrel A, Combe B, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum. 2010; 62: 2625–2632. doi: 10.1002/art.26755 PMID: 20506353

29. Bannay A, Chaignot C, Blotière P-O, Weill A, Ricordeau P, Alla F, et al. Score de Charson à partir des données du Sniiram: faïabilité et valeur pronostique sur la mortalité à un an. Rev DÉpidémiologie Santé Publique. 2013; 39:328–335.

30. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr. 1974; 19: 716–723.

31. Grossi O, Généreau T. Glucocorticoids and... infections, doping, surgery, sexuality. Rev Med Interne. 2013; 34: 269–278. doi: 10.1016/j.revmed.2012.12.008 PMID: 23415059
32. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis. 1989; 11: 954–963. PMID:2690289

33. Dixon WG, Abrahamowicz M, Beauchamp M-E, Ray DW, Bernatsky S, Suissa S, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis. 2012; 71: 1128–1133. doi:10.1136/annrheumdis-2011-200702 PMID: 22241902

34. Dixon WG, Kezouh A, Bernatsky S, Suissa S. The influence of systemic glucocorticoid therapy upon the risk of non-serious infection in older patients with rheumatoid arthritis: a nested case-control study. Ann Rheum Dis. 2011; 70: 956–960. doi:10.1136/ard.2010.144741 PMID: 21285116

35. Collins AJ, Chen S-C, Gilbertson DT, Foley RN. CKD surveillance using administrative data: impact on the health care system. Am J Kidney Dis Off J Natl Kidney Found. 2009; 53: S27–36.

36. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatol Oxf Engl. 2013; 52: 53–61.

37. Apostolidis J, Tsandekidi M, Kousiafes D, Pagoni M, Mitsouli C, Karmiris T, et al. Short-course corticosteroid-induced pulmonary and apparent cerebral aspergillosis in a patient with idiopathic thrombocytopenic purpura. Blood. 2001; 98: 2875–2877.

38. Nakano T, Fukuyama S, Inoue K, Inoue H, Hagimoto N, Fujita M, et al. A case of sarcoidosis and idiopathic thrombocytopenic purpura accompanied with invasive pulmonary aspergillosis. Nihon Koka Zasshi J Jpn Respir Soc. 2002; 40: 945–949.

39. Tsai H-C, Lee SS-J, Wann S-R, Chen Y-S, Wang J-S, Liu Y-C. Invasive pulmonary aspergillosis with cerebral abscess in a patient with idiopathic thrombocytopenic purpura. J Chin Med Assoc JCMA. 2006; 69: 278–281. PMID: 16863015

40. Fianchi L, Rossi E, Murri R, De Stefano V, Pagano L, Leone G. Severe infectious complications in a patient treated with rituximab for idiopathic thrombocytopenic purpura. Ann Hematol. 2007; 86: 225–226. PMID: 17031685

41. Papadopoulos A, Ntaios G, Kaima G, Gritvitis F, Charisopoulos G, Chrysosogonidis I. Fatal pulmonary and cerebral aspergillosis after a short course of corticosteroids for idiopathic thrombocytopenic purpura. Ann Hematol. 2008; 87: 685–686. doi: 10.1007/s00277-008-0452-5 PMID: 18317759

42. Nikkels AF, Frere P, Rakic L, Fassotte M, Evrard B, De Mol P, et al. Simultaneous reactivation of herpes simplex virus and varicella-zoster virus in a patient with idiopathic thrombocytopenic purpura. Dermatol Basel Switz. 1999; 199: 361–364.

43. Morrell CN, Aggrey AA, Chapman LM, Modjeski KL. Emerging roles for platelets as immune and inflammatory cells. Blood. 2014; 123: 2759–2767. doi: 10.1182/blood-2013-11-462432 PMID: 24585776

44. de Stoppelaar SF, van ‘t Veer C, Claushuis TAM, Albersen BJA, Roelofs JTH, van der Poll T. Thrombocytopenia impairs host defense in gram-negative pneumonia-derived sepsis in mice. Blood. 2014; 124: 3781–3790. doi: 10.1182/blood-2014-05-573915 PMID: 25301709

45. Wu Q, Ren J, Wang G, Li G, Anjum N, Hu D, et al. Effect of Persistent Thrombocytopenia on Mortality in Surgical Critical Care Patients: A Retrospective Study. Clin Appl Thromb Off J Int Acad Clin Appl Thromb. Forthcoming 2015.