Pharmacoepidemiology of Immune Thrombocytopenia: Protocols of FAITH and CARMEN Studies

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Abstract – Immune thrombocytopenia (ITP) is a rare condition. Its epidemiology is not well-known. First-line treatment is based on corticosteroids. ITP leads to persistency (lasting more than 3 months) in 70% of adult cases. Then, several second-line treatments (SLTs) are available, mainly splenectomy, rituximab (off-label) and thrombopoietin-receptor agonists. Their efficacy and safety have not been compared, particularly in the long-term. FAITH (French Adult primary Immune Thrombocytopenia: a pHarmacoepidemiological study) is dedicated to the building and follow-up of the cohort of all adults with primary ITP in France persistently treated (>3months) through the database of French Health Insurance system (*système national d'information interrégimes d'Assurance maladie*, SNIIRAM), in order to assess the benefit-to-risk balance of SLTs in real-life practice. CARMEN (*Cytopénies Auto-immunes : Registre Midi-PyrénéEN*) is a clinical registry of all incident adult ITP patients in the Midi-Pyrénées region. It is aimed at describing ITP clinical features, assessing SLT benefit-to-risk balance and adherence to guidelines for ITP management. FAITH is registered n°ENCEPP/SDPP/4574.

Résumé – Pharmacoépidémiologie de la thrombopénie immunologique : protocoles des études FAITH et CARMEN. La thrombopénie immunologique (TI) est une maladie rare. Son épidémiologie est mal connue. Le traitement de première intention repose sur les corticoïdes. La TI devient persistante (durant plus de trois mois) dans 70 % des cas adultes. Plusieurs traitements de seconde ligne (TSL) sont alors disponibles : essentiellement, la splénectomie, le rituximab, les agonistes du récepteur à la thrombopoïétine. Leur efficacité et leur sécurité n'a jamais été comparée. L'étude FAITH (*French Adult primary Immune Thrombocytopenia: a pHarmacoepidemiological study*) a pour but de construire dans le système national d'information interrégimes d'Assurance maladie (SNIIRAM) la cohorte des patients adultes incidents atteints de TI primaire traités de façon persistante (> 3 mois), de façon à comparer en vie réelle la balance bénéfice/risque des TSL. CARMEN (Cytopénies Auto-immunes : Registre Midi-PyrénéEN) est un registre clinique visant l'exhaustivité des TI adultes incidentes en région Midi-Pyrénées. Ses objectifs sont de préciser l'épidémiologie clinique de la TI et de comparer en vie réelle la balance bénéfice/risque des TSL. FAITH est enregistrée n°ENCEPP/SDPP/4574.

Abbreviations. See end of article.

1. Background

Immune thrombocytopenia (ITP), formerly known as idiopathic or (auto)-immune thrombocytopenic purpura is a rare condition.[1] It is mainly due to the production of autoantibodies directed against platelet antigens, but there is also an autoimmune inhibition of megacaryopoiesis.[2] These mechanisms lead to platelet destruction and therefore to bleeding, which can be life threatening. In about 20% of adult patients, ITP is secondary to chronic infectious diseases (human immunodeficiency virus, hepatitis C virus…), cancers (mainly hematological), connective tissue diseases (systemic lupus erythematosus for instance), or primary immune deficiencies.

Otherwise, ITP is defined as "primary".[1] In adults, primary ITP becomes persistent (lasting from three to 12 months) or chronic (lasting more than 12 months) in 70% of the patients.[1]

1.1. Epidemiology of ITP is not well known

ITP incidence in adults has been estimated from 1.6 to 3.9/ 100 000 inhabitants/year, mainly through reference center in-patients cohorts.[3] Few large population-based studies have been conducted to assess ITP incidence.[4-6] The largest one has been conducted in the clinical practitioner research datalink in 2009. This database is supplied by general practitioners in a United Kingdom area covering about 4 million inhabitants. ITP cases were retrospectively identified from 1990 to 2005 (1 145 incident adult ITP patients). This study assessed ITP incidence depending on gender and age.[6] However, no similar study has been conducted at a nationwide scale. Incidence of lethal bleeding (range 1.6-3.9/100 patients-year) has been assessed through in-patients cohorts that may be not representative of the entire ITP population.[7-9] Numerous questions are still unsolved, such as seasonal incidence variations or ITP triggering by some vaccines.[10] National health databases such as health insurance databases have the statistical power to assess such questions. However, they do not collect detailed clinical data. An international registry of adult ITP has being built, but it covers mainly patients stemmed from reference centers.[11] Therefore, a prospective registry aimed at completeness of recording in a given area is also needed.

1.2. Pharmacoepidemiological studies are needed to assess the use and to compare the effectiveness and the safety of ITP second-line treatments

First-line treatment of acute ITP is based on corticosteroids. In case of severe bleeding, intravenous polyvalent immunoglobulins (rarely alkaloids or anti-D immunoglobulins) are added.[12,13] In persistent or chronic ITP, second-line therapies (SLTs) are introduced to avoid long-term corticosteroid adverse drug reactions.

The reference SLT is splenectomy.[14] It has been performed for a century, so it has been thoroughly evaluated. It leads to a complete response (defined as a platelet count ≥100 g/L and no bleeding symptom)[1] rate of 85% in a few days.[15] However, about one quarter of patients relapse during a 5-year follow-up.[7,16-18] At a median follow-up of 20 years (range 10-43), about 60% of the patients remain in remission.[19] Peri-operative morbi-mortality is low in ITP patients, but there exist definitive infectious risk.[20]

Since the mid-2000s, rituximab, a chimeric monoclonal antibody directed against CD20, is currently used off-label for chronic ITP in case of failure of or contra-indication to splenectomy. It induces a 40-50% response (defined as a platelet count ≥30G/L and no bleeding symptom)[1] rate in splenectomy-candidate patients.[21-23] Relapses are frequent, so the response rate decreases to 20% at five years.[24,25] The infectious risk in the largest published cohorts seems to be low: only one serious infection (sigmoiditis) occurred during the two-year follow-up in a clinical trial including 60 patients and there was no evidence of an increased infectious risk in the five-year follow-up of 72 adult primary ITP patients.[23,25] However, these studies stemmed from reference centers, the patients were young and they had few comorbidities. In 2007, a review of published cases of ITP rituximab-treated patients concluded that 3.7% experienced severe or life-threatening events.[26] In daily practice, rituximab is used in older, co-morbid patients for whom splenectomy is avoided because of the perioperative risk. In a retrospective monocentric case-series of 43 consecutive adult primary ITP patients treated with rituximab, we observed that five patients (12%) experienced severe pneumonia with a 3-year median follow-up.[27] Only 32.4% (95%CI [17.3–47.5]) had been vaccinated against pneumococcus albeit it is recommended by French ITP management guidelines.[28,29] Rituximab is also more and more frequently used as a SLT instead of splenectomy, even in younger patients who often prefer this treatment to surgery.[30] However, the two treatments have not been compared directly in the long term for robust outcomes such as mortality, serious bleedings, serious infections and cardiovascular events.

Since 2009-2010, two drugs (romiplostim and eltrombopag) acting as thrombopoietin-receptor agonists (TPO-RAs) are marketed in Europe. In clinical trials, they led to response in more than 80% of the patients. However, the disease relapsed at TPO-RA withdrawal in almost all cases.[14] TPO-RA drugs are approved for "chronic ITP splenectomized patients who are refractory to other treatments (*e.g.* corticosteroids, immunoglobulins). [They] may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated".[31,32] Nevertheless, "contra-indication" to splenectomy is a very subjective notion and the International Society of Hematology has indicated these drugs as SLT for persistent and chronic ITP just as rituximab, splenectomy and other immunosuppressive drugs.[12] In daily practice, TPO-RAs might be increasingly used off-label as SLT.[14] Long-term TPO-RA adverse drug reactions are unknown. Signals have been detected regarding thrombo-embolic events and myelofibrosis for both drugs as well as cytolytic hepatitis with eltrombopag. A long-term risk of malignant myeloid disorder is suspected due to their mechanism.[33]

Rituximab and mostly TPO-RAs are costly drugs. As a result, there is a strong interest to assess and compare the benefit-to-risk balance of SLTs in a large cohort of ITP patients in the long-term and in real-life practice.

2. Methods/Design of FAITH (French Adult primary Immune Thrombocytopenia: a pHarmacoepidemiological study)

The FAITH study is registered within the European post-authorisation safety studies registry (EU-PAS) of the European Network
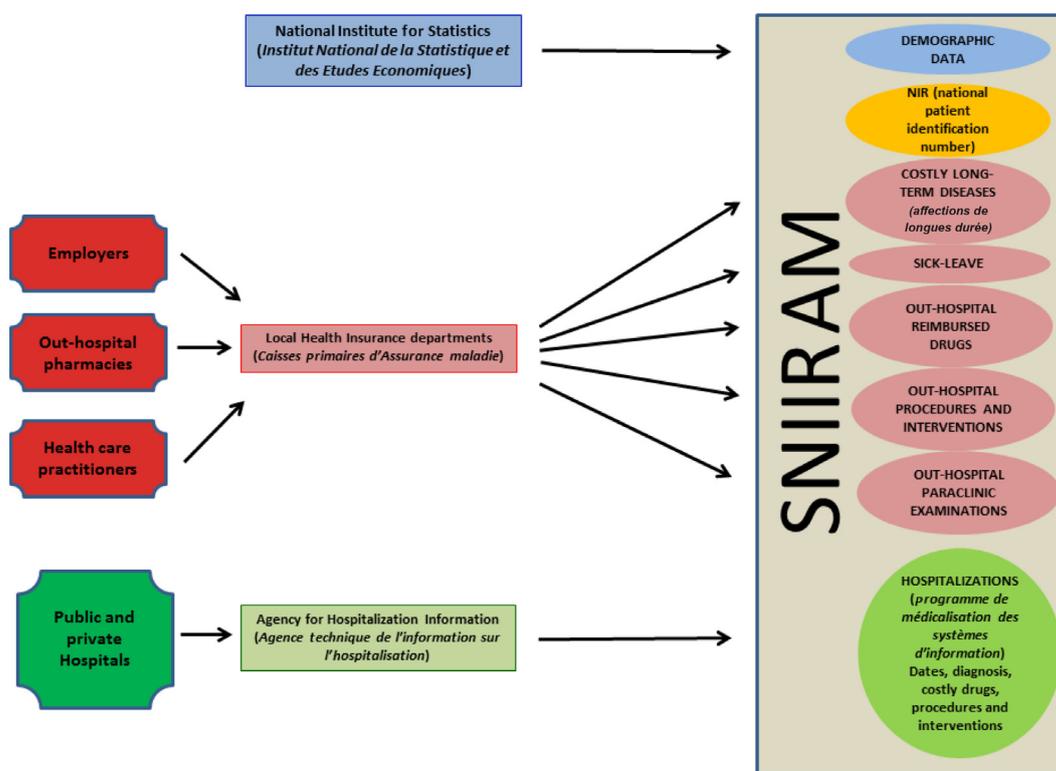
Fig. 1. Source of the *Système national d'information interrégimes de l'Assurance maladie* (SNIIRAM) data and SNIIRAM datamarts.

of Centres for Pharmacoepidemiology and Pharmacovigilange (ENCePP) coordinated by the European Medicine Agency (EMA). The FAITH study is numbered ENCEPP/SDPP/4574 and has been awarded by the ENCePP study seal approval.

2.1. Objective

The primary objective of the FAITH study is the building of a national cohort of adult incident primary ITP patients persistently treated to describe the exposure to available SLTs.

The secondary objective is to compare the effectiveness and safety of SLTs for adult primary ITP patients persistently treated in France in the long term.

2.2. Study design

FAITH is a French nationwide pharmacoepidemiological observational cohort study.

2.3. Data source of the population: the SNIIRAM

Data source is the National Health Insurance Cross-schemes Information system (*système national d'information interrégimes*

de l'Assurance maladie, SNIIRAM) which is the unique database of the French National Health Insurance System. It is handled by the French National Insurance Funds for Employees (*Caisse nationale de l'Assurance maladie des travailleurs salariés,* CNAMTS) that is the organization in charge of health care reimbursement. It collects demographic and health reimbursement expenditure data, virtually of the entire French population (65 586 600 inhabitants in January 2013). These data are individualized, anonymous, exhaustive, and linkable for a given patient.[34,35] Therefore, it is the largest medico-administrative database.[35] Therefore, the SNIIRAM has been used since the mid-2000s to conduct large epidemiological and pharmacoepidemiological post-authorization studies.[36-43] Briefly, it is constituted by several datamarts that include for each patient the following data, prospectively recorded (figure 1):

- in the administrative datamart: age, gender, department and town of residence, vital status (date of death if applicable), and insurance scheme;
- in the costly long-term disease (*affections de longue durée*, abbreviated ALD) datamart: ALD list. ALD allows full reimbursement of every health care related to the corresponding disease. They are encoded with the International classification of diseases, version 10 (ICD-10).[44] Dates of start and dates of end are recorded. Occupational diseases and sick leaves are also recorded;

– in the out-hospital drug reimbursement datamart: this data-mart contains the date of dispensing, the drug name and the dosage form encoded with the *code interpharmaceutique* (CIP) classification,[45] the quantity (number of boxes) dispensed. Prescribed dose and indication are not available. Over-the-counter dispensed drugs are not recorded because there are not reimbursed;

– in the out-hospital procedure datamart: dates of medical and paramedical procedures, names of procedures encoded with the common classification of medical acts (*classification commune des actes médicaux*, CCAM);[46]

– in the out-hospital biology datamart: it contains the date of sampling, names of dosage performed encoded with the *nomenclature des actes de biologie médicale* (NABM).[47] Results of lab tests are not recorded;

– in the hospitalization datamart, called the program medicalization of informations systems (*programme de médicalisation des systèmes d'informations*, PMSI): this datamart contains data of all hospital stays in public and private hospitals. Data are: entry and discharge dates, hospital identification code, whether the patient was admitted to intensive care unit, diagnoses (for each stay: one primary diagnosis, one related diagnosis and up to 30 associated diagnoses) encoded with the ICD-10, expensive drugs (names and dosage) dispensed during the stay encoded with the *unités communes de dispensation* (UCD) classification[45] with the quantity (number of boxes) delivered. All medical or surgical procedures and interventions are also encoded using the CCAM;[46]

– all these information are linked thanks to the patient identification number (*numéro d'inscription au répertoire*, NIR) which is the unique number identifying a given adult patient. Children of a given adult patient have the same NIR than the adult parent who gives them the right to benefit from the national Health insurance system. Nevertheless, the NIR is anonymized in the SNIIRAM so as it is theoretically impossible to identify a given patient.[35]

According to French law, available data in the current database are those of the current year and of the three previous years.[48]

In end 2012, the CNAMTS computer engineers extracted the data for all patients encoded for an ALD or a hospital stay with the ICD-10 code related to ITP (D69.3) from the 1st January 2009 to the 31st December 2011. Annual extractions until 2 022 are foreseen using the same process, along with extraction of data regarding the patients included in the cohort the previous years. Patient linkage through datamarts is performed thanks to a study number attributed by the CNAMTS computer engineers, which has been elaborated for a given patient based on its NIR, its year of birth and its gender. As a result, these study identifiers differentiate children from their parents. Twin children are differentiated thanks to another variable encoding the twinning rank.

2.4. Expected number of patients

A feasibility study with the 2009-2011 data identified 3 771 incident ITP patients in two years. Out of them, 1 106 were adult patients with persistently treated primary ITP.

2.5. Primary outcome: identification of treated adult incident cases of persistent or chronic primary ITP and description of treatment exposure at a nationwide level over time

Delivered data are raw. As a result, the building of the cohort of incident adult primary persistent or chronic ITP patients will follow several steps, summarized in figure 2. ICD-10 "D69" codes are listed in table I. "ITP drugs" used at steps 2 and 6 are defined in table II. The causes of secondary ITP used at step 5 are listed in table III. Eventually, we will restrict the cohort to persistently treated incident adult primary ITP patients. Persistent ITP treatment is defined as splenectomy, exposure to rituximab, or at least four consecutive in-hospital or out-hospital dispensing of ITP drugs in six months. Index date is defined as the date of first dispensing of persistent treatment for ITP.

Splenectomy (identified through corresponding CCAM procedure codes), exposure to rituximab and to intravenous immunoglobulins (UCD codes) will be searched through the hospitalization (PMSI) datamart. Exposure to TPO-RAs as well as exposure to corticosteroids and other immunosuppressive drugs will be searched in outpatient drug dispensing data thanks to the corresponding CIP and UCD codes. Exposure will start at the first dispensing date. We make the hypothesis that the delivered drug is effectively taken. We define the period of intake as the period from the first dispensing date to the last consecutive dispensing date plus one month, thus a drug in France is delivered for one month. Exposure will end seven median half-lives after the end of the period of intake. For rituximab exposure, several time-windows will be tested since this drug can induce durable changes in the immune system. In particular, we will define exposure as the semester following the first rituximab infusion for infection risk assessment, because in a large series of rheumatoid arthritis patients 80% of the infections occurred during this period of time.[49] We will also test the definition of exposure to rituximab as the year following the first infusion, because B-cell repopulation occurs from the sixth to the twelfth month in the huge majority of the patients.[50]

We will also assess dose-effect relations. As prescribed dose is not available in the SNIIRAM, we will assume that the delivered dose is the prescribed dose. We will part the study period by trimesters, and will assess the delivered dose during that periods thanks to defined daily dose (DDD)[51] and cumulative dose.
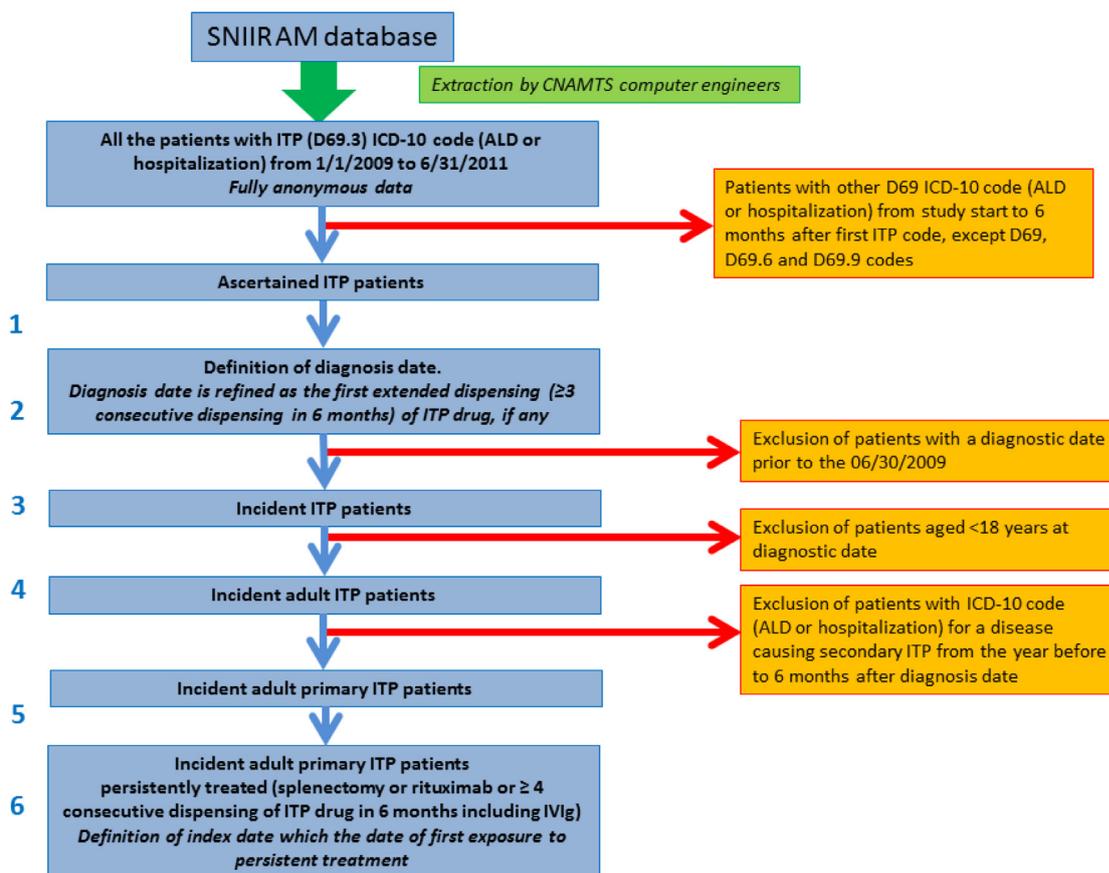
Fig. 2. Building of the FAITH cohort of adult incident primary ITP patients persistently treated. Data delivered by the CNAMTS engineers are raw but linkable data for every patient with any ITP diagnosis code (ICD-10 D69.3) for hospitalization or costly long-term disease (ALD) during the period of extractions (years 2009-2011 for the first extraction). Step 1 leads to exclusion of doubtful ITP codes. Step 2 consists in refining diagnosis date thanks to out-hospital ITP drug dispensing. The date of diagnosis is then the first event among: the first ALD ITP code, the first in-hospital ITP diagnosis code, or the first out-hospital dispensing of ITP drug in case of at least 3 dispensing in 6 months. Step 3 is the restriction to incident patients, defined by a diagnosis date after the first six months of the study period (that is, after the 30th June 2009). Step 4 is the restriction to adult patients. Step 5 is the restriction to primary ITP, excluding patients with comorbidities associated to secondary ITP (listed in table III) and Evans syndrome (with autoimmune hemolytic anemia D59.1 ICD-10 code). Step 6 is the restriction to patients persistently treated for ITP (FAITH cohort). Index date is eventually defined as the first date of persistent dispensing of ITP drugs.
ALD: costly long term disease (*affections de longue durée*); **CNAMTS**: French National Insurance Funds Employees (*Caisse nationale d'Assurance maladie des travailleurs salariés*); **ICD**: international classification of diseases; **ITP**: immune thrombocytopenia; **IVIg**: intravenous immunoglobulines.

Table I. D69 codes according to the international classification of diseases, 10th version.

Code	Condition
D69	**Purpura and other haemorrhagic conditions**
D69.0	Allergic purpura
D69.1	Qualitative platelet defects
D69.2	Other non-thrombocytopenic purpura
D69.3	Idiopathic thrombocytopenic purpura
D69.4	Other primary thrombocytopenia
D69.5	Secondary thrombocytopenia
D69.6	Thrombocytopenia, unspecified
D69.8	Other specified haemorrhagic conditions: capillary fragility (hereditary), vascular pseudohaemophilia
D69.9	Haemorrhagic condition, unspecified

Table II. List of ITP drugs affordable in the CNAMTS drug reimbursement datamarts. These are only out-hospital drugs marketed before 2013. In-hospital drugs are: rituximab, intravenous polyvalent immunoglobulins, anti-D immunoglobulins, rituximab, vinca-alkaloids such as vincristine or vinblastine.

International drug name	Anatomical therapeutic chemical classification code
Systemic glucocorticoids	
Prednisone	H02AB07
Prednisolone	H02AB06
Methylprednisolone	H02AB04
Dexamethasone	H02AB02
Betamethasone	H02AB01
Thrombopoietin receptor agonists	
Romiplostim	B02BX04
Eltrombopag	B02BX05
Immunosuppressants	
Ciclosporin	L04AD01
Azathioprine	L04AX01
Mycophenolate	L04AA06
Others	
Dapsone	J04BA02
Danazol	G03XA01

ITP: immune thrombocytopenia; **CNAMTS**: French National Insurance Funds for Employees (*Caisse nationale d'Assurance maladie des travailleurs salariés*)

Table III. Causes of secondary ITP in adults.

Cause	International classification of disease (10th version) codes
In situ neoplasms	D00-D09
Malignant neoplasms	C00-C97
Hematological malignancies	C77, C81-C96
Lymphoma	C77, C81-C86
Hodgkin lymphoma	C81
Chronic lymphocytic leukaemia of B-cell type	C91.1
Multiple myeloma and malignant plasma cell neoplasms	C90
Waldenström macroglobulinaemia	C88.0
Myelodysplastic syndromes	D46
Antiphospholipid syndrome	D68.6
Viral hepatitis C or B	B16, B18.0-B18.2
Viral hepatitis C	B18.2
Viral hepatitis B	B16, B18.0-B18.1
Human immunodeficiency virus disease	B20-B24
Connective tissue disease	M32-M35.1
Systemic lupus erythematosus	M32
Systemic sclerosis	M34
Dermatopolymyositis	M33
Sicca syndrome	M35.0
Mixed connective tissue disease	M35.1
Rheumatoid arthritis	M05, M06.0, M06.2-M06.3, M06.8-M06.9
Sarcoidosis	D86
Immunodeficiency (except HIV)	D80-D84

HIV: human immunodeficiency virus; **ITP**: immune thrombocytopenia

2.6. Secondary outcomes: comparing the effectiveness and safety of SLTs for adult primary ITP patients persistently treated in France in the long term

We will assess the overall mortality that reflects both effectiveness and safety.

Effectiveness outcomes will be serious bleedings (identified with in-hospital diagnosis codes), ITP drug withdrawal (particularly, corticosteroids), frequency and time until start of a new treatment for ITP, and cumulative dose of corticosteroids since index date. Indeed, one objective of SLTs is to get off steroids that cause many complications when used in the long-term.

Safety outcomes will be serious infections (in-hospital diagnosis codes), non-serious infections (out-hospital dispensing of antibiotics, which does not include chronic exposure to beta-lactam reflecting prophylaxis in splenectomized patients), serious cardiovascular events (in-hospital diagnosis codes), serious venous thromboembolic events (in-hospital diagnosis codes) and cancers including blood cancers (in-hospital diagnosis and ALD codes).

2.7. Controls

The incidence of outcomes will be compared among treated ITP patients according to SLT exposure, and also with two control groups.

2.7.1. Controls from the general population

Four controls for each ITP patient included in the FAITH cohort will be selected from the general population in the SNIIRAM. As it is improbable that a given adult does not benefit even once from the national health system in France during a given year, it is generally assumed that the SNIIRAM population reflects the general population. Controls are matched with FAITH cohort patients on age, gender, insurance system and department of residency at the time of data extraction by CNAMTS computer engineers. Controls will not have any ALD or hospitalization with the ITP ICD-10 code (D69.3) in the year preceding the extraction. Controls' follow-up will start (controls' index date) at the index date of the corresponding ITP patient. To allow comparison with primary ITP patients, controls with diseases potentially related to a secondary ITP (identified through ALD codes or hospital diagnoses during the year and six months after index date) will be excluded. We will check that these control patients do not develop ITP over time. If one of these patients develops ITP, he becomes a case and his follow-up as a control is censored at the date of ITP diagnosis.

2.7.2. Untreated incident adult persistent or chronic primary ITP patients

Their selection will follow the first five steps of cases' selection (figure 2). Persistent or chronic ITP is defined in these patients by ITP ALD code or at least two hospitalizations with ITP diagnosis code spaced of at least three months. These patients will not be persistently treated for ITP drug during the study period.

2.8. Statistical analyses

Estimation of incidence according to the calendar year, season, age, gender, regional geographic area will be performed. Descriptive analyses of the population will be performed (age, gender, disease duration, severe bleeding at diagnosis for in-hospital patients at diagnosis, comorbidities, ITP treatments) stratified on SLTs. Factors associated to exposure to a given strategy as SLT will be analyzed with logistic regression models leading to relative risk estimates. Those factors are age, gender, comorbidities (from study start to index date, identified with diagnosis codes of hospital satys and ALD codes) combined in the SNIIRAM-adapted Charlson score,[52] disease duration (from the date of diagnosis to the start of the treatment of interest), first-line treatment (dose and duration), history of severe bleeding (mucosal or internal bleeding) leading to hospitalization.

For secondary objectives assessment, we will perform survival analyses with Cox model leading to hazard ratio estimates. In case of low incidence of the outcome, we will carry out nested case-control studies. Drug exposure will be taken into account with time-varying analyses. All analyses will be also adjusted on the factors associated to SLT listed above. For serious bleeding assessment, analyses will be adjusted on concomitant antiagregant or anticoagulant exposure (expected effect modifier), defined as at last one reimbursement of these drugs during the month prior to hospitalization. For adverse event assessment, other adjustments will be performed: on vaccine exposure for infections, on other cardiovascular factors than age and gender (arterial hypertension identified with in-hospital diagnosis codes and ALD, diabetes identified with the same data source as well as antidiabetic drug dispensing, dyslipidemia identified with the same data source as well as hypolipemic drug dispensing).

2.9. Ethical considerations

Access to the SNIIRAM data is strictly controlled by the French law.[48] Only some CNAMTS physicians and duly authorized persons from the French regulatory authorities and from public research institutions may have access to the database. Authorization is given on a case-by-case basis by the Institute of Health Data (*Institut des données de santé*, IDS).[53] The IDS gave its approval to FAITH in March 2012 (numbered 40). The FAITH protocol foresees a prospective annual extraction during 10 years. We were authorized to store securely the FAITH data of the first five extractions by the French National Commission on Information Technologies and Liberties (*Commission nationale informatique et libertés*, CNIL). The

CNIL authorization has been obtained in July 2012 (decision numbered DE-2012-076 regarding the request numbered 1579257). We foresee prolongation of this authorization in 2016 for five new years. As this study involves fully anonymous data from existing database, it does not require any ethic committee approval.

2.10. Funding

FAITH is academic (university of Toulouse, French National Insitute of Health and Medical Research [*Institut national de la santé et de la recherche médicale*, INSERM].

3. Methods/Design of CARMEN (*Cytopénies Auto-immunes: Registre Midi-PyrénéEN*)

Data like self-medication, toxicological exposure, detailed clinical symptoms like clinical bleeding score, platelet count, and quality of life assessment are not recorded in the SNIIRAM. Consequently, a prospective registry of adult ITP patients aimed for completeness of case recording in a given area is needed. CARMEN is a clinical registry dedicated at collecting these data. CARMEN is registered in the *Portail Epidémiologie-France* registry.

3.1. Objectives

The primary objective is to describe the clinical epidemiology of adult ITP in the Midi-Pyrénées region. Secondary objectives are to assess the benefit-to-risk balance of ITP SLTs and adherence to ITP management guidelines.

3.2. Study design

CARMEN is a prospective and continuous registry aimed at completeness of adult ITP case recording in the Midi-Pyrénées region, South of France. Midi-Pyrénées is the widest region of metropolitan France (45 348 km^2) and hosts about 3 millions inhabitants. ITP patients are treated by internal medicine and hematology practitioners actually spread in one tertiary hospital (located in Toulouse and including one hematology and six internal medicine departments) and 14 peripheral public or private hospitals. All these practitioners take actively part to the network of the Midi-Pyrénées Competence Center for Autoimmune Cytopenias located in Toulouse and coordinating the CARMEN project. Investigator centers located in each department treating ITP patients are opening since summer 2013.

Each investigator collects prospectively clinical and laboratory data of every incident adult ITP patient he cares from ITP diagnosis. Inclusion criteria are recent diagnosis with ITP (<3 months), being adult (aged ≥18 years), programmed follow-up in the Midi-Pyrénées region and signed written consent for data collection in the registry. Collected data are medical history, toxic and drug exposure before ITP onset (including self-medication), examinations performed to assess ITP diagnosis and to differentiate primary from secondary ITP, bleeding symptoms, bleeding score,[54] platelet counts, treatments, adverse events, and quality of life with the SF-36 scale.[55,56] Data are prospectively collected at diagnosis, between day 15 and day 45, at 3 months, 6 months and then every 6 months. This corresponds to the usual follow-up of ITP patients. Nevertheless, these recordings occur during consultations or hospitalizations decided by the practitioner: this is a "real-life" registry and there is no visit formally requested by the protocol. Data are then transmitted by fax after anonymization with a local number attributed for each patient by the local investigator. We obtained authorization for a ten-year follow-up of the patients but extension of this authorization is foreseen. If a patient does not consent to a follow-up in CARMEN, existence of a new patient is anonymously reported without any supplementary data collection. To control data quality, 10% of the incident cases will be randomly selected each year and the corresponding medical charts consulted to check accordance with case reported data.

Every year, new cases of ITP will be extracted from the Midi-Pyrénées regional section of the SNIIRAM according to FAITH algorithm. Age, gender, residency geographic codes of these patients will be crossed with the same data from CARMEN patients in order to check for CARMEN completeness.

3.3. Expected number of patients

Based on unpublished SNIIRAM estimates, we expect between 50 and 100 patients/year.

3.4. Outcomes

Primary outcome is the description of incident ITP patients: incidence, bleeding symptoms, proportion of primary/secondary ITP, platelet counts, and SLT exposures.

To assess SLT benefit-to-risk balance, efficacy outcomes are response rate, complete response rate, mean delay to response and to complete response, response and complete response maintenance.[1] Effectiveness outcomes are overall mortality, mortality by bleeding, bleeding score, absence of need of another ITP treatment, withdrawal of corticosteroids and quality of life (SF-36 scale).[55,56] Safety outcomes are adverse drug reactions, which will also be reported by local investigators to the Midi-Pyrénées regional pharmacovigilance center where causality will be assessed.

Adherence to French ITP management guidelines[29] will be assessed as the percentage of patients who benefitted from the recommended examinations to detect secondary ITP and as the

percentage of patients who benefitted from the recommended first-line and SLT treatments.

3.5. Statistical analyses

For incidence calculation, the denominator will be the Midi-Pyrénées region population estimated in January of each year by the French National Institute of Statistics and Economic Studies (*Institut national de la statistique et des études économiques*, INSEE*).*[57] In case of non-completeness of incident case recording, a capture-recapture method will be used to assess the incidence (with the regional SNIIRAM as second source).

Descriptive analyses, with Kaplan-Meier curves when appropriate, will be performed to assess secondary outcomes. Regression model comparing SLT will be adjusted on age, gender, comorbidities (Charlson score), bleeding score, platelet count, disease duration, and treatment exposures. For secondary objective dedicated at estimated the effectiveness and safety of SLTs, analyses will be similar to those carried out in the FAITH study, in terms of outcome definitions, treatment exposure definitions, and statistical methods. The main difference regards adjustment that will be more complete in CARMEN due to the recording of clinical symptoms, platelet counts and risk factors (*e.g.* cardiovascular risk factors for cardiovascular outcomes).

3.6. Ethical considerations

CARMEN obtained authorization from the *Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé* in February 2012 (numbered 12.067) and from the CNIL in July 2012 (decision numbered 2012-438 regarding the request numbered 912339). This authorization includes the crossing process with SNIIRAM regional data. The Toulouse University Hospital ethic committee gave its approval in May 2012 (decision numbered 27-0512).

3.7. Funding

CARMEN setting up is supported by a grant from the *Délégation régionale à la recherche clinique des Hôpitaux de Toulouse* 2012 and is also granted by the French National Society of Internal Medicine (*Société nationale française de médecine interne*).

4. Discussion

4.1. Strengths and limitations of FAITH

The SNIIRAM offers a global vision of all health care provided to a given patient. The good performance of the use of in-hospital

ICD-10 diagnosis codes, crossed with specific drugs or procedure data so as to identify incident patients has been previously assessed in other diseases than ITP.[35,38]

Working in a nationwide cohort (France population: 65 millions inhabitants) during ten years, we expect the inclusion of about 7 000 incidents adult persistent or chronic primary ITP patients persistently treated with SLT, who will be prospectively followed up to 12 years. This unique cohort has the power to assess the benefit-to-risk balance of SLTs, and to investigate the factors associated to their effectiveness and their adverse events.

Data completeness as well as the possibility to build the cohort have been successfully tested in spring and summer 2013 with the 2009-2011 SNIIRAM data.

Moreover, the selection process of FAITH's patients follows several steps, beginning by the identification of ITP incident patients (figure 2). As a result, this study will add important information as regards the epidemiology of ITP in general, assessing seasonal or regional incidence variations for instance.

Some limitations are inherent to medico-administrative databases. A selection bias cannot be excluded: asymptomatic patients with persistent platelet count >30 g/L that are not treated and have never been hospitalized for ITP cannot be detected. However, these patients do not represent a clinical matter and would not have been included in the FAITH cohort by definition, since they are not persistently treated. We ensure the diagnosis of ITP by excluding all patients with another D69 ICD-10 code, but remaining errors cannot be definitively ruled out. To address this point, a study to assess the performance of FAITH algorithm is being built with clinical record review for a sample of FAITH's patients. Information biases are also expected: exposure is defined through dispensing of drugs. That does not ensure that a given patient effectively takes the drugs. We do not have detailed clinical data to assess for instance ITP severity through validated scales.[54] Lab tests results are not recorded in the SNIIRAM. As previously said, we will use a history of serious bleeding (mucosal or internal bleeding) leading to hospitalization as a proxy of ITP severity. For non-severe infections, we will use proxy like antimicrobial drug dispensing for outpatients, though this does not reflect necessarily bacterial disease. Lastly, we do not have access to some confounders or effect modifier such as smoking habit or cardiovascular history in family for cardio-vascular event assessment.

4.2. Strengths and limitations of CARMEN

CARMEN is complementary to FAITH. CARMEN is the first clinical registry aimed at completeness in a given geographic area, and therefore will add important information as regards ITP clinical epidemiology. It will explore for the first time the adherence to ITP management guidelines in the real-life practice. Clinical data, results of platelet counts, quality of life assessments while treated with the different SLTs are outcomes and adjustment variables not

collected in the SNIIRAM and therefore that cannot be assessed with FAITH. Safety outcomes will be adverse drug reactions and not adverse events as in FAITH, since causality will be calculated by the regional pharmacovigilance center.

The main expected pitfall of CARMEN is its non-completeness of incident case recording. This will be checked by crossing identifying data with the SNIIRAM. This process will detect the patients with ITP hospital code or ALD attribution not recorded in the CARMEN registry. This will allow incidence calculation by capture-recapture method and estimation of confidence level that can be attributed to secondary outcome assessment. As commonly seen in clinical registries, missing or erroneous data cannot be excluded. Nevertheless, tight check of case report forms as soon as they are received may improve the quality of the data. Tight monitoring is also foreseen to request an expected form corresponding to a next visit. As previously said, a quality data controlling 10% of the patients through medical charts will also be performed every year. Lastly, the statistical power to compare the effectiveness and safety of SLTs is much lower than with the FAITH study. Therefore, such analyses will be conducted after several years of recording in the CARMEN registry, and will concern frequent outcomes.

5. Conclusion

CARMEN and FAITH are two wide-scaled studies. They are complementary one to the other. They are designed to better know the epidemiology of ITP and to accurately assess the benefit-to-risk ratio of SLTs. Therefore, they might have an important impact for the definition of treatment algorithm in adult ITP, particularly in poorly studied groups like older patients.

Acknowledgements

Abbreviations. ALD: costly long-term disease (*affections de longue durée*); CARMEN: *Cytopénies Auto-immunes Registre Midi-PyrénéEN*; CCAM: common classification of medical acts (*classification commune des actes médicaux*); CIP: *code inter-pharmaceutique*; CNAMTS: French National Insurance Funds for Employees (*Caisse nationale d'Assurance maladie des travailleurs salariés*); CNIL: French National Commission on Information Technologies and Liberties (*Commission nationale informatique et libertés*); DDD: defined daily dose; ENCePP: European Network of Centers for Pharmacoepidemiology and Pharmacovigilance; EU-PAS: European post-authorization safety studies registries; FAITH: French Adult primary Immune Thrombocytopenia: a pHarmacoepidemiological study; ICD : international classification of diseases; IDS: Institute of Health Datas (*Institut des données de santé*); INSEE: French National Institute of Statistics and Economic Studies (*Institut national de la statistique et des études économiques*); ITP: immune thrombocytopenia; IVIg: intravenous polyvalent immunoglobulins; NABM: *nomenclature commune des actes médicaux*; NIR: patient identification number (*numéro d'inscription au répertoire*); PMSI: program medicalization of informations systems (*programme de médicalisation des systèmes d'informations*); SLT: second line treatment; SNIIRAM: National Health Insurance Cross-schemes Information System (*Système national d'information interrégimes de l'Assurance maladie*); TPO-RA: thrombopoietin-receptor agonists; UCD: *unités communes de dispensation*.

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