STUDY PROTOCOL

AITP Registry

Longitudinal Study on the Epidemiology and Treatment of

Auto-Immune Thrombocytopenia (AITP) in Algeria

(Epidemiological study, non-interventional)

Protocol Number: 20160214

AMGEN Algeria

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SYNOPSIS

Title of study	Longitudinal study on the epidemiology and management of auto-immune thrombocytopenia (AITP) in Algeria
Protocol number	20160214
Rationale	Auto-immune thrombocytopenia (AITP) is a multifactorial auto-immune disease characterized by platelets accelerated peripheral destruction by auto-antibodies and cytotoxic T lymphocytes. The etiology is unknown but a genetic origin is excluded, family forms being exceptional. Clinically, the disease onset is acute or insidious. The disease can be asymptomatic or having easy bruising or severe bleeding. AITP is suspected when the family history, physical examination, blood count and examination of peripheral blood smear do not suggest another etiology for thrombocytopenia. No reference diagnostic testing is available to establish a reliable diagnosis. A positive response to a specific therapy (intravenous immunoglobulin and/or steroids) supports the diagnosis. As for treatment, 70 to 80% are spontaneous remission without treatment within 6 months of development in children, in whom treatment ensures faster remission and allows a reduction in morbidity and increased complete remissions. Chronic AITP in children is characterized by frequent spontaneous remissions in more than 10 years of diagnostic. Meanwhile in adults, the transition to chronicity (> 6 months of evolution) is more common without treatment (80–90 %). The goal of treatment is to ensure sufficient platelets rate to prevent risk of bleeding, while a normal platelet rate is not an obligation, and that treatment is limited in intensity and duration. The medical treatment includes corticosteroids, intravenous immunoglobulin and anti-D immunoglobulin. Splenectomy is performed in patients with severe manifestations. In the case of refractory chronic AITP, corticosteroids or steroid-sparing drugs (e.g. danazol and vincristine) or immunosuppressants (e.g. azathioprine, cyclophosphamide and rituximab are suggested. Combined treatments or or bone marrow transplantations may also be prescribed. From an epidemiological perspective, the AITP occurs mainly in young adults (18–40 years), particularly women in their third or fourth decade. In France, the annual incidence of AITP is 16 to 32 cases per 1,000,000 inhabitants. However, no accurate or reliable epidemiological data on AITP are available in Algeria. In this context, the main objective of this non-interventional study is to investigate the epidemiological profile of the disease in the country (the prevalence and incidence of the AITP on national and regional levels). The study will also identify the characteristics of these patients, and their management arrangements and monitoring.
Type of study	Epidemiological, national, prospective, longitudinal study about the management of patients with auto-immune thrombocytopenia followed up by hematologists in the public sector in Algeria
Sponsor	AMGEN Algeria
Scientific approval	Conducted under the auspices of the Algerian Society of Hematology (ASHT)
CRO	Clinical Group, CRO authorized by the Ministry of Health , Population and Hospital Reform (MHPHR)
Study population	Investigators/physicians: epidemiological study proposed to the heads of the departments of hematology in Algerian hospitals

Number of patients	This study is representative and national. As the primary objective of the study is to estimate the incidence, patient recruitment will be open and no estimate of the sample size will be calculated. However, around 200 AITP patients (incident or prevalent) will be included over the 12-month inclusion period of the study. All patients diagnosed with AITP during the period of study and who gave their informed consent will be included in the study.
Participating centers	Departments of hematology in the public sector in Algeria Maximal number of hematology departments = 17
Study period	▪ Patient recruitment: 12 months from May 2017 (inclusion of first patient = first patient in) to the end of May 2018 (inclusion of the last patient = last patient in) ▪ Follow-up time for each patient: 18 months ▪ Follow-up end of the last patient (last patient out): November 2019 ± 4 weeks ▪ Total duration of study: 30 months
Study objectives	<u>Primary objective:</u> To assess the incidence of AITP diagnosed in patients aged 16 years old and over in Algeria in a 12-month period of inclusion. <u>Secondary objectives:</u> 1/ To assess the incidence by age category of AITP diagnosed in patients aged 16 years old and over in Algeria during the inclusion period. 2/ To assess the incidence by gender of AITP diagnosed in patients aged 16 years old and over in Algeria during the inclusion period. 3/ To assess the incidence by diagnosis stage (asymptomatic, easy bruising, severe hemorrhage) of AITP diagnosed in patients aged 16 years old and older in Algeria during the inclusion period. 4/ To assess the incidence by region (Wilaya) of AITP diagnosed in patients aged 16 years old and over in Algeria during the inclusion period. 5/ To assess the prevalence of AITP diagnosed in patients aged 16 years old and over in Algeria. 6/ To determine the characteristics of patients aged 16 years and over, AITP diagnosed in Algeria (age, gender, risk factors and comorbidities). 7/ To determine the evolution of the clinical evolution of AITP diagnosed patient in Algeria. 8/ To describe the treatment strategies prescribed by the Investigators.
Study endpoints	<u>Primary endpoint</u>: 1/ Number of new cases diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion. <u>Secondary endpoints:</u> 1/ Number of new cases diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion, by age categories. 2/ Number diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion, by gender. 3/ Number diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion, by diagnosis stage. 4/ Number diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion, by Wilaya (Province [Wilaya]).

	5/ Total number of cases of AITP, aged 16 years and over, previously and newly diagnosed in Algeria during the period of study. 6/ Characteristics of patients diagnosed with AITP and aged 16 years and over, in Algeria (age, gender, risk factors). 7/ Number of patients with remission of their clinical symptoms. 8/ Median time to remission from diagnosis 9/ Number of prescribed first- and second-line treatments.
Patients selection criteria	<u>Inclusion criteria:</u> 1/ Patients of both genders. 2/ Patients aged 16 years and over. 3/ Patients treated in the hematology departments in Algeria. 4/ Patients presenting with AITP during the inclusion period, whether the patient is previously diagnosed (prior to inclusion visit) or newly diagnosed (at the time of the inclusion visit). 5/ Patients who have given their written consent. <u>Criteria for non-inclusion:</u> 1/ Patients who have not given their written consent. 2/ Patients already included in the study. A patient can be monitored and treated in two different hematology departments. Hence, a coding system will be generated to avoid duplicated participations. 3/ Patients participating in another study.
Study conduct	This study will be proposed to all the heads of the departments of hematology in Algerian hospitals. Each hematologist participating in the study will respectively include eligible patients over a period of 12 months. The number of visits is not fixed since it is an observational study. Nevertheless, normal standard of care typically involves patient visits at 3, 6, 12 and 18 months. Data will be collected on a case report form (CRF) during these routine patient visits at the initial visits, 3 months, 6 months, 12, months and 18 months. These are the approximate time periods when we expect patients to visit clinical as part of their routine standard of care treatment: • Visit 1 = inclusion visit • Visit 2 = visit at 3 months (± 2 weeks) • Visit 3 = visit at 6 months (± 4 weeks) • Visit 4 = visit at 12 months (± 4 weeks) • Visit 5 = visit of end of study at 18 months (± 4 weeks) All patients presenting at the departments of hematology during a routine visit will be sequentially offered to participate in the study. In each department of hematology, the Investigator (physician) or one of his/her legal representatives will complete a case report form (CRF).
Data to be collected	**<u>Department form:</u>**

	1/ Characteristics of the department of hematology: • Wilaya (province) • City • Refusal / acceptance of participation • Ground for refusal (if applicable) • Number of patients followed up for AITP • Number of patients refusing to participate • Age and gender of patients refusing to participate • Date (dd/mmm/yyyy) or at least the month of participation refusal for these patients **CRF:** Inclusion visit: visit 1 2. Eligibility of patients 3. Signature of consent form 4. Date of signature of consent 5. Demographic characteristics of the patient: • Gender • Date of birth • Place of residence (Province) 6. Comorbidities: • Do they confer a bleeding risk or risk of injury? • If yes, specify the comorbidity: 1) Cancer 2) Pupura 3) Increased tendency to bruise 4) Neutropenia 5) Whole blood transfusion 6) Anemia 7) Iron deficiency anemia 8) Ecchymosis 9) Contusion 10) Chills 11) Rigors 12) Chemoprophylaxis 13) Hematemesis

	14) Hemoptysis 15) White blood cell disorder 16) Pneumonia 17) Respiratory disorder 18) Blister 19) Dry mouth 20) Mouth ulceration 21) Leg ulcer 22) Lethargy 23) Epistaxis 24) Dementia 25) Confusion 26) Decubitus ulcer 27) Skin ulcer 28) Dermatitis diaper 29) Oral candidiasis 30) Rush 31) Eczema gravitational 32) Pressure sore 33) Phlebitis 34) Venesection 35) Venipuncture 36) Peripheral swelling 37) Stasis dermatitis 38) Myocardial infarction 39) Unstable angina 40) Atrial fibrillation 41) Congestive cardiac failure 42) Ventricular failure 43) Intermittent claudication 44) Cerebrovascular accident 45) Oedema peripheral 46) Malaise 47) Oral pain 48) Abdominal pain 49) Hip arthroplasty

50) Dry eye
51) Keratoconjunctivitis
52) Folliculitis
53) Acarodermatitis
54) Scabies infestation
55) Diabetes mellitus non-insulin-dependent
56) Prostatism
57) Vaginal hemorrhage
58) Menorrhagia
59) Osteoporosis
60) Rectal hemorrhage
61) Gastro-oesophageal reflux disease
62) Viral infection
63) Other, specify

7. Diagnosis:
   - Date of diagnosis of AITP
   - Age at diagnosis of AITP
   - Hemorrhage score
   - Diagnosis stage (severity): asymptomatic / easy bruising / severe bleeding
   - Complete blood count
   - Examination of peripheral blood smear
8. First-line treatment:
   - Start date of treatment (if applicable)
   - Type of treatment: no treatment /corticotherapy / immunotherapy / steroid-sparing drugs / immunosuppressants / combined therapy / splenectomy / bone marrow transplantation / other (specify)
   - Route of administration

<u>Follow-up visits at 3, 6, 12 and 18 months</u>:

1. Patient lost to follow-up: yes/no
2. Date of last contact
3. Withdrawal cause (if applicable)
4. Patient relapse: yes/no
5. If yes, date of relapse
6. Diagnosis:
   - Hemorrhage score

	• Diagnosis stage (severity): asymptomatic / easy bruising / severe bleeding • Remission: yes / no • Transition to chronicity: yes / no 7. First / second-line treatment: • Line of treatment • Change of treatment since the last visit: yes/no If yes: • Reason for change • Start date of treatment (if applicable) • If yes, type of treatment: no treatment /corticotherapy / immunotherapy / steroid-sparing drugs / immunosuppressants / combined therapy / splenectomy / bone marrow transplantation / other (specify) • Route of administration
Statistical methodology	The data will be processed anonymously and confidentially. Statistical analysis will be performed using SAS software. A detailed statistical analysis plan will be prepared and validated by the Sponsor of the study before freezing of database and the beginning of the statistical analysis. This study is an estimation study, so no formal statistical testing will be performed. Missing data will not be replaced except for incomplete dates in order to allow the calculation of an interval between two dates. In this case one day and/or missing months are completed. <u>Descriptive statistics</u> ▪ Description of variables: Depending on the nature of the criteria, descriptive statistics will be performed as follow: - Continuous variables are described by their frequency, mean, standard deviation, median, quartiles 1 and 3, extreme values (minimum and maximum) and the number of missing values. - Categorical variables are described by the frequency, the percentage of each of the possible answers and the number of missing data. ▪ Description of the participating hospitals: The Provinces of hematology departments having refused to participate in the study will be compared with those who agreed to participate. The possible collected reasons for refusal will be described. ▪ Description of the population of patients: Eligible population will consist of all patients included, that is to say for whom the selection criteria will be available and who meet the eligibility criteria. A descriptive analysis of the collected variables will be conducted in this population. Incident AITP cases will be defined as all patients with an AITP diagnosed 3 months or less before the inclusion visit. All other AITP patients will be defined as prevalent cases.

	Analysis of study endpoints ▪ Analysis of the primary endpoint: Incidence will be estimated as the total number of incident cases divided by the number of Algeria inhabitants aged 15 years old or more. The two-sided 95% confidence interval (CI) will be estimated. ▪ Analysis of the secondary endpoint : The incidence will be estimated as the total number of incident cases, by age and gender. The prevalence will be estimated as the number of all included AITP (incident and prevalent) cases divided by the number of Algeria inhabitants aged 15 or more. The 95% CI will be estimated. All characteristics of the patients will be described in each group: incident and prevalent cases.
Provisional schedule of study	▪ Approval from the Ministry of Health: February 2017 ▪ Study initiation in the hematology departments: March 2017 ▪ End of data collection: July 2019 ▪ Data analysis: August 2019 ▪ Final Study Report: October 2019 ▪ Date of publication: December 2019

SOMMAIRE

ABBREVIATIONS

Abbreviation	Definition
ADELF	Association of French-Speaking Epidemiologists
AE	Adverse Effect
AITP	Auto-Immune Thrombopenia
CNPM	National Center Of Materiovigilance and Pharmacovigilance
CRF	Case Report Form
CRO	Clinical Research Organization
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practice
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ISF	Investigator Site File
MA	Marketing authorization
MHPHR	Ministry of Health, Population and Hospital Reform
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
WHO	World Health Organization

1. INTRODUCTION AND STUDY RATIONALE

Auto-immune thrombocytopenia (AITP) is a multifactorial auto-immune disease characterized by platelet accelerated peripheral destruction by auto-antibodies and cytotoxic T lymphocytes (1). The etiology is unknown but a genetic origin is excluded, family forms being exceptional (2).

Clinically, the disease onset is acute or insidious. The disease can be asymptomatic or present with easy bruising or severe bleeding. Bleeding is often mucosal (epistaxis, gingival bleeding and menorrhagia), it is rarely digestive or as gross hematuria. Intracranial hemorrhage is rare (1).

The AITP is suspected when the family history, physical examination, complete blood count and examination of peripheral blood smear do not suggest another etiology for thrombocytopenia. No reference diagnostic testing is available to establish a reliable diagnosis. A positive response to a specific therapy (intravenous immunoglobulin and/or steroids) supports the diagnosis of the disease. Achieving a myelogram is necessary after 60 years, in case of abnormality of other cell types or when thrombocytopenia does not respond to first-line treatments; it shows a normal, rich marrow megakaryocytes. It must be coupled to cytogenetic testing when myelodysplastic syndrome is suspected. The differential diagnosis includes secondary causes of AITP (drug-induced), auto-immune diseases (such as lupus erythematosus), HIV infection and hepatitis C (2).

As for treatment, 70 to 80% are spontaneous remission without treatment within 6 months of development in children, in whom treatment ensures faster remission and allows a reduction in morbidity and increased complete remissions. Chronic AITP in children is characterized by frequent spontaneous remissions in more than 10 years after diagnosis. Meanwhile in adults, the transition to a chronic (> 6 months of evolution) is more common without treatment (80–90%). The goal of treatment is to ensure sufficient platelets to prevent bleeding risk, while a normal platelet count is not an obligation, and that treatment is limited in intensity and duration. Therefore, treatment should be reserved for patients with severe thrombocytopenia to moderate bleeding or are at risk of bleeding. Patients with mild and asymptomatic thrombocytopenia should not be treated, and the patient's characteristics (e.g. physical activity, comorbidities and treatments) must be taken into account.

The therapeutic treatment includes corticosteroids (e.g. oral prednisone, intravenous methylprednisolone (1) and oral dexamethasone (3)), intravenous immunoglobulin and anti-D immunoglobulin. The splenectomy is performed in patients with severe manifestations (1). In the case of refractory chronic AITP, corticosteroids or non-steroids (ex. danazol and vincristine) or immunosuppressants (e.g. azathioprine,

cyclophosphamide and rituximab (4,5) are offered (1). Combined treatments or bone marrow transplantation may also be prescribed (1).

More recently, a study of rituximab in France, Norway and Tunisia, was published in the Lancet in April 2015 by Ghanima *et al.* Rituximab (Mabthera®, Roche) is a humanized murine monoclonal antibody, and the study has shown the benefits in second-line treatment of AITP (6).

From an epidemiological perspective, the AITP occurs mainly in young adults (18–40 years), particularly women in their third or fourth decade. Female predominance suggests that sex hormones may play a role in different aspects of the AITP. A study by Andres *et al.* in Strasbourg demonstrated that gender is likely to play a potential role in the presentation of AITP, with an impact on the score of the AITP. It does not seem to have any effect on the progression or response to therapy. However, other large randomized trials are needed to confirm these results (7).

The AITP is also one reason for more frequent in pediatric hematology, especially at the age of 5 years (2). Indeed, a chronic or acute thrombocytopenic purpura of more than 20% of patients have were noted in 2 months (January–February 2008) on the register of consultation of the pediatric department of the University Hospital of Setif in Algeria. Also, from April 2007 to April 2008, 31 patients (2 to 3 cases per month) were diagnosed and followed in that service (8).

In France, AITP annual incidence is 16 to 32 cases per 1 million inhabitants. However, Algeria does not have up to day accurate and reliable epidemiological data on AITP. In this context, the main objective of this non-interventional study is to investigate the epidemiology of the disease in the country (the prevalence and incidence of AITP on national and regional levels). The study will also identify the characteristics of these patients, and their management arrangements and monitoring.

This study will concern only the public hospitals in Algeria, as less than 5% of these patients are followed up in another type of institutions.

2. OBJECTIVES OF THE STUDY

2.1. Primary objective

The main objective of the study is to assess the incidence of patients aged 16 years and over, diagnosed with AITP in a 12-month period of inclusion.

2.2. Secondary objectives

The secondary objectives of the study are:

1) To assess the incidence by age category of AITP diagnosed in patients aged 16 years old and over in Algeria during the inclusion period.
2) To assess the incidence by gender of AITP diagnosed in patients aged 16 years old and over in Algeria during the inclusion period.
3) To assess the incidence by diagnosis stage (asymptomatic, easy bruising, severe hemorrhage) of AITP diagnosed in patients aged 16 years old and older in Algeria during the inclusion period.
4) To assess the incidence by region (Wilaya) of AITP diagnosed in patients aged 16 years old and over in Algeria during the inclusion period.
5) To assess the prevalence of AITP diagnosed in patients aged 16 years old and over in Algeria.
6) To determine the characteristics of patients aged 16 years and over, AITP diagnosed in Algeria (age, gender, risk factors and comorbidities).
7) To determine the evolution of the clinical evolution of AITP diagnosed patient in Algeria.
8) To describe the treatment strategies prescribed by the Investigators.

3. METHODOLOGY

3.1. Study design

This is a longitudinal prospective national epidemiological study on the care of patients with auto-immune thrombocytopenia followed up by hematologists in the public sector in Algeria.

3.2. Study population

3.2.1. Participating centers and Investigators

This study will be suggested to all heads of hematology departments in the public hospitals in Algeria. The maximum number of hematology departments participating in the study is 17.

3.2.2. Selection criteria of patients

- Inclusion criteria

Patients with auto-immune thrombocytopenia will be eligible to participate in the study if they meet the following inclusion criteria:

1) Patients of both genders.
2) Patients aged 16 years old and over.
3) Patients treated in the hematology departments in Algeria.
4) Patients presenting with AITP during the inclusion period, whether the patient is previously diagnosed (prior to inclusion visit) or newly diagnosed (at the time of the inclusion visit).
5) Patients who have given their written consent.

➢ Exclusion criteria

Patients with auto-immune thrombocytopenia will be not eligible to participate in the study if they have one or more of the following exclusion criteria:

1) Patients who have not given their written consent.
2) Patients already enrolled in the study. A patient can be monitored and treated in two differents hematology departments. Hence, a coding system will be generated to avoid duplicate entries.
3) Patients participating in another study.

3.3. Number of subjects

The present study is an estimation study. No formal statistical testing will be performed. All patients diagnosed with AITP during the period of study and who gave their informed consent will be included in the study.

4. WITHDRAWAL OF PATIENTS FROM THE STUDY

4.1. Criteria for withdrawal

Patients can discontinue their participation in the study at any time. The specific reasons for the interruption of participation in this non-interventional study are:

1) The patient is free at any time to terminate his/her participation in the study, without prejudice to any other treatment. Patients who prematurely withdrew from the study will not be replaced.
2) If a patient is enrolled in a clinical trial at any time during his/her participation in this study, his/her participation in the present study should be stopped.

4.2. Interruption procedures

No specific procedure exists for the cessation. Data of patients whom informed consent is withdrawn will be included in the statistical analysis of the study until the time of consent withdrawal, unless prohibited by local regulations. This information is cited in the informed consent form.

5. STUDY CONDUCT

5.1. Restrictions during the study

No specific restriction exists for this observational and epidemiological study. The prescribed medications and medical interventions must remain completely independent of the participation of the Investigator in this study.

5.2. General aspects

Before the inclusion of a patient in the study and collection of any data on the Case Report form (CRF), the following conditions should be met:

1) The written approval of the study (study protocol, CRF, informed consent form) by the Ethics Committee and the Ministry of Health, according to local regulations.
2) Formal agreements between AMGEN Algeria or its representatives and the Investigator / hospital must be signed.

5.3. Conduct of the study

This study will be proposed to all the heads of a maximum of 17 hematology departments of public hospitals in Algeria. Each hematologist participating in the study will prospectively include eligible patients over a period of 12 months.

The number of visits is not fixed since it is an observational study. Nevertheless, normal standard of care typically involves patient visits at 3, 6, 12 and 18 months. Data will be collected during these routine patient visits at the initial visits, 3 months, 6 months, 12 months and 18 months. These are the approximate time periods when we expect patients to visit clinical as part of their routine standard of care treatment:

1) Visit 1 = inclusion visit
2) Visit 2 = visit at 3 months (± 2 weeks)
3) Visit 3 = visit at 6 months (± 4 weeks)
4) Visit 4 = visit at 12 months (± 4 weeks)

5) Visit 5 = end of study visit at 18 months (± 4 weeks)

All patients presenting to the hematology department during a routine visit will be offered to participate in the study sequentially.

The investigating physician or one of his/her legal representatives in each participating hematology department will complete a CRF at each visit. The data collected will be transferred for analysis after the visit of each eligible patient to the Investigator.

5.4. Collected variables

Collected data by visit are presented below and summarized in Table 1.

5.4.1. Department form

1) Characteristics of the department of hematology:
    a. Wilaya (Province)
    b. City
    c. Refusal / acceptance of participation
    d. Groud for refusal (if applicable)
    e. Number of patients followed up for AITP
    f. Number of patients refusing to participate
    g. Age and gender of patients refusing to participate
    h. Date (dd/mmm/yyyy) or at least the month of participation refusal for these patients

5.4.2. Case Report Form

5.4.2.1. Inclusion visit: visit 1

1) Eligibility of patients
2) Signature of consent form
3) Date of signature of consent form
4) Demographic characteristics of the patients:
    a. Gender
    b. Date of birth
    c. Place of residence (Province)
5) Comorbidities:

a. Do they confer a bleeding risk or risk of injury?

b. If yes, specify the comorbidity (9):

1) Cancer
2) Pupura
3) Increased tendency to bruise
4) Neutropenia
5) Whole blood transfusion
6) Anemia
7) Iron deficiency anemia
8) Ecchymosis
9) Contusion
10) Chills
11) Rigors
12) Chemoprophylaxis
13) Hematemesis
14) Hemoptysis
15) White blood cell disorder
16) Pneumonia
17) Respiratory disorder
18) Blister
19) Dry mouth
20) Mouth ulceration
21) Leg ulcer
22) Lethargy
23) Epistaxis
24) Dementia
25) Confusion
26) Decubitus ulcer
27) Skin ulcer
28) Dermatitis diaper
29) Oral candidiasis
30) Rush
31) Eczema gravitational
32) Pressure sore

33) Phlebitis
34) Venesection
35) Venipuncture
36) Peripheral swelling
37) Stasis dermatitis
38) Myocardial infarction
39) Unstable angina
40) Atrial fibrillation
41) Congestive cardiac failure
42) Ventricular failure
43) Intermittent claudication
44) Cerebrovascular accident
45) Oedema peripheral
46) Malaise
47) Oral pain
48) Abdominal pain
49) Hip arthroplasty
50) Dry eye
51) Keratoconjunctivitis
52) Folliculitis
53) Acarodermatitis
54) Scabies infestation
55) Diabetes mellitus non-insulin-dependent
56) Prostatism
57) Vaginal hemorrhage
58) Menorrhagia
59) Osteoporosis
60) Rectal hemorrhage
61) Gastro-oesophageal reflux disease
62) Viral infection
63) Other, specify

6) Diagnosis:
    a. Date of diagnosis of AITP
    b. Age at diagnosis of AITP

c. Bleeding score
    i. Bleeding Scale of the World Health Organization (WHO) (10) (Appendix 16.3)
    ii. Khellaf bleeding score (11) (Appendix 16.4)
d. Diagnosis stage (severity) of AITP: Asymptomatic / easy bruising / severe bleeding
e. Complete blood count
f. Examination of peripheral blood smear

7) First-line treatment:
    a. Start date of treatment (if applicable)
    b. Type of treatment: no treatment /corticotherapy / immunotherapy / steroid-sparing drugs / immunosuppressants / combined therapy / splenectomy / bone marrow transplantation / other (specify)
    c. Route of administration

5.4.2.2. Follow-up visits at 3, 6, 12 and 18 months

1) Patient to follow-up: yes/no
2) Date of last contact
3) Withdrawal cause (if applicable)
4) Patient relapse: yes/no
5) If yes, date of relapse
6) Diagnosis:
    a. Hemorraghe score: WHO bleeding scale and Khellaf bleeding score
    b. Diagnosis stage (severity): asymptomatic / easy bruising / severe bleeding
    c. Remission: yes / no
    d. Transition to chronicity: yes / no
7) First / second-line treatment:
    a. Line of treatment
    b. Change in treatment since last visit: yes / no
    c. If yes:
        i. Reason for change
        ii. Start date of treatment (if applicable)
        iii. If so, type of treatment : no treatment /corticotherapy / immunotherapy / steroid-sparing drugs / immunosuppressants / combined therapy / splenectomy / bone marrow transplantation / other (specify)

iv. Route of administration

Table 1: Flowchart of data to be collected by visit

	Data collected	Visit 1 Inclusion	Visit 2 (3 months ± 2 weeks)	Visit 3 (6 months ± 4 weeks)	Visit 4 (12 months ± 4 weeks)	Visit 5 study termination (18 months ± 4 weeks)
	Signature of the the consent form	X				
Patients characteristics	Verification of the eligibility criteria of patients	X				
	Characteristics of Investigator/hematology department	X				
	Patient demographic characteristics	X				
	Comorbidities	X				
AITP Diagnosis	Complete blood count and blood smear	X				
	Date of diagnosis	X				
	Age at diagnosis	X				
	Severity of AITP	X				
Bleeding score	WHO Bleeding Scale	X				
	Khellaf bleeding score	X				
First line treatment	Start of treatment (if applicable)	X				
	Type of treatment	X				
	Route of administration	X				
Withdraw of patient of study	Loss to follow-up Date of last contact Reasons for withdrawal from the study		X	X	X	X
Relapse of patient	Date of relapse		X	X	X	X
AIT Diagnostic	Severity of AITP		X	X	X	X
	Remission		X	X	X	X
	Chronicity		X	X	X	X
Bleeding score	WHO bleeding scale		X	X	X	X
	Khellaf bleeding score		X	X	X	X
First line / second line treatment	Line of treatment		X	X	X	X
	Change in treatment since last visit		X	X	X	X
	Start of treatment (if applicable)		X	X	X	X
	Type of treatment		X	X	X	X
	Route of administration		X	X	X	X

6. STUDY ENDPOINTS

6.1 Primary endpoint

Annual incidence of AITP in Algeria: The ratio of the number of cases of diagnosed AITP aged 16 and over, in Algeria during the period of 12 months of inclusion and Algerian workforce population aged 16 years old and over.

The parameter is expressed in number of cases per 100,000 of population aged 16 years old and over.

6.2 Secondary endpoints

1) Number of new cases diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion, by age categories.
2) Number diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion, by gender.
3) Number diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion, by diagnosis stage.
4) Number diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion, by Wilaya (Province).
5) Total number of cases of AITP, aged 16 years and over, previously and newly diagnosed in Algeria during the period of study.
6) Characteristics of patients diagnosed with AITP and aged 16 years and over, in Algeria (age, gender, risk factors).
7) Number of patients with remission of their clinical symptoms.
8) Median time to remission from diagnosis.
9) Number of prescribed first- and second-line treatments.

7. STUDY MONITORING

The Sponsor (and its representatives) is responsible for contacting the Investigator regularly and will be authorized, on request, to check different patients' records, provided that the patient's confidentiality is respected, and in accordance with the local requirements.

The study Monitor is responsible for performing the quality control check of the CRFs, at regular intervals throughout the study to ensure protocol compliance and consistency of entered data (accurate, complete and consistent). The Monitor must also have access to the patient's source documents (medical records), when available, to verify the registration of relevant data on the CRF. The Investigator (or representative) agrees to cooperate with the Monitor to ensure that all errors detected during these inspections are corrected.

8. STUDY SCHEDULE AND TERMINATION TERMS OF THE STUDY

8.1 Study schedule

1) Approval from the Ministry of Health: February 2017
2) Study initiation in the hematology departments: March 2017
3) Recruitment period: 12 months
4) Date of initial inclusion (first patient in): May 2017
5) Date of last inclusion (last patient in): May 2018
6) Follow-up period for each patient: 18 months
7) End of follow-up of the last patient (last patient out): Novemver 2019 ± 4 weeks
8) Total study duration: 30 months
9) Data analysis: August 2019
10) Final Study Report: October 2019
11) Date of publication: December 2019

8.2 Study termination

The Sponsor and the Investigator reserve the right to terminate the study at any time, particularly for ethical or any other reason. By ending the study, the Sponsor and the Investigator undertake to protect the data of the study and the interests of the patient.

9. DATA MANAGEMENT

9.1 Data collection

Data collection will be done on a paper CRF. This collection format will have to be accurate and reliable. The verification of the authenticity of data will be carried out by the study Monitor, by cross-checking the CRF against source documents and according to the Good Pharmacoepidemiology Practice (GPP) (12), Good Clinical Practice (GCP) (13), and the recommendations of the Association of French-Speaking Epidemiologists (ADELF) (14).

10 to 15% of CRFs by hematology department will be verified. Following the verification, non-compliance lists will be produced and provided to the Investigators.

9.2 Study documents

9.2.1 Patient record / Case Report Form (CRF)

For each eligible patient in the study, a CRF will be filled by the Investigator or one of his/her representatives (working with the authorized Investigators of the site). This rule also applies to patients who fail to complete the study. In this case, the reason for its withdrawal should be noted on the form.

All completed forms must be readable and verifiable. Mistakes should be crossed out, not erased and the inserted correction and change initialled and dated by the Investigator (or authorized representative).

The Monitor should ensure that the entered data in the case report is accurate, complete, readable and current.

9.2.2 Source documents: patient medical record

The Investigator shall provide, upon the Sponsor's request, the required data to control, particularly

important, when reports are illegible or when data transcription errors are suspected. Access to the complete patient record, when available, must be authorized by the Investigator, provided that the patient's confidentiality is respected. In case of any particular problem, an audit request can be made.

9.2.3Archiving

The Investigator should retain records of the study for a period of 15 years after closure or early termination of the study. Beyond this period, the documents will be destroyed, according to local regulations.

These documents should be classified into two distinct categories:

- Investigators' file
- Patient source documentation
  - Investigator's file (ISF)

The Investigator's file will contain the protocol, the approval of the Ministry of Health, Population and Hospital Reform (MHPHR), the reports of Investigators meetings, copies of the reports made to the authorities, and the patient information, informed consent in French and Arabic, the participants curruculum vitae, a copy of the blank CRF, certification from the collaborating laboratory and its normal values, the declaration form of serious adverse events (SAEs), protocol violation, and the list of physicians authorized by the Principal Investigator at each site to participate in the study.

  - Source documents of patients

The patients' clinical source documents include: patient records, notes of the physician and nurses, the appointment book, reports of laboratory and evaluation reports.

In case the Investigator wishes to entrust the archiving files to another party or move them to another location, the Sponsor should be informed in advance.

If the Investigator cannot guarantee archiving of some or all documents, special arrangements may be made between the Investigator and the Sponsor to store them in a sealed container outside the site to be returned to the Investigator if regulatory audit. If the documents are required for the continued care of the patient,

appropriate copies will be made.

9.2.4 Audits and inspections

The Investigator must allow access to patient source documents included in this study, the appropriate skilled personnel, the Sponsor and its representatives and finally the local authorities after appropriate notification.

Verification of collected data at the report forms must be direct through inspection of source documents.

10. STATISTICAL ANALYSIS

10.1 Data entry

Data entry for the analysis will be done by the Clinica Group, CRO approved by the MSPRH, according to international standards of data management.

10.2 Sample size

This study is representative and national. As the primary objective of the study is to estimate the incidence, patient recruitment will be open and no estimate of the sample size will be calculated. However, around 200 AITP patients (incident or prevalent) will be included over the 12-month inclusion period of the study. All patients diagnosed with AITP during the period of study and who gave their informed consent will be included in the study.

Based on published rates of AITP in other countries, we anticipate 200 patients will be included in this study with 2 sites and 10% of the patients refusing to participate in the study.

The percentage of patients, who will refuse to participate in the study, will be estimated and the sample size is estimated to be 200 over the period of inclusion.

10.3 Statistical methods and analysis plan

The data will be processed anonymously and confidentially.

Statistical analysis will be performed using SAS software. A detailed statistical analysis plan will be prepared and validated by the Sponsor of the study before the freezing of database and the beginning of the statistical analysis.

No replacement of missing values will be performed except incomplete dates in order to allow the calculation of an interval between two dates. In this case, missing day and month will be imputed.

➢ Descriptive statistics

- Description of variables:

Dependent on the type of variables, descriptive statistics will be performed as follows:

- Continuous variables are described by their frequency, mean, standard deviation, median, quartiles 1 and 3, extreme values (minimum and maximum) and the number of missing data.
- Categorical variables are described by the frequency, the percentage of each modality and the number of missing data.

- Description of the participating hospitals:

The Provinces of hematology departments having refused to participate in the study will be compared with those of hematology departments who agreed to participate. The departments' characteristics (e.g. Province [Wilaya], city, number of patients with AITP followed up in the center) and the possible collected reasons for refusal will be described.

- Description of the population of patients:

Eligible population will consist of all patients included, that is to say for which will be available at least the selection criteria and meet the eligibility criteria.

All data collected at inclusion (see Table 1) will be classically described in incident and in prevalent cases and overall.

➢ Analysis of the evaluation criteria of the study

- Analysis of the primary endpoint:

The incidence of AITP will be estimated as the total number of included incident cases divided by the number of Algeria inhabitants aged 15 or more. The two-sided 95% confidence interval (CI) will be estimated using a Poisson distribution.

The number of Algerian inhabitants will be the official Algerian number available at the time of the analysis on the public Algerian website available at www.ons.dz. At the time of the writing of the present protocol, available data are the 2015 data. All data for the Algerian population will be data available on the website at the time of the statistical analysis or 2016 if available.

- Analysis of the secondary endpoints:

Prevallence of AITP will be calculated using the same methos as above but using all included case of ITP. A Poisson distribution will also be assumed for the prevalence.

Incidence and prevalence will also be estimated by age and by gender.

However, as some sites and some patients may refuse to participate, the estimated incidence and prevalence will be lower than the true estimates of the Algerian populations.

All other follow-up data will be summarized by group (incidence and prevalence cases) and by visit. The duration of follow-up in the study will be calculated as the date of the last visit in the study – date of inclusion +1. The interval between 2 follow-up visits will also be summarized. The number and percentage of patients withdrawn 12 months or less after inclusion will be displayed in each group.

Minimum and maximum platelet levels over the study will be estimated for each patient so as the number of available platelet determinations over the study period.

Maximum bleeding score over the study period will also be displayed in each group.

The number and percentage of patients having received steroids, immunoglobulin and other treatments at least once over the study period will be displayed in each group so as the number and percentage of patients who underwent splenectomy.

The statistical analysis of data at inclusion visit can be performed after completion of the inclusion period. No other interim analysis is planned.

11. ETHICAL ASPECTS

- Local regulations / Declaration of Helsinki:

The Investigator undertakes to ensure that the study is conducted in accordance with:

- The ethical principles of the Helsinki Declaration of 1964, revised in Seoul in 2008
- GCP guidelines of the International Conference on Harmonization (ICH-GCP E6, 7/17/96)
- And the laws and regulations of Algeria.

- Information note and written informed consent:

An information note and a consent will be given to the patient (Appendix 16.1).

12. CONFIDENTIALITY

Data on patient participation in this study may not be disclosed to third parties without written permission. The Investigator must ensure that patient confidentiality will be maintained and that their identity will be protected from unauthorized parties. Patients should not be identified by name, but by an identification code. The Investigator must keep a patient's enrolment register for identification. The Investigator must keep documents in strict confidentiality.

13. PUBLICATION

All information resulting from this study is considered confidential until the statistical analysis of the study is completed and a final report is issued by the Sponsor. The results of this study will be submitted for publication and for presentation at scientific meetings, by Amgen or by some Investigator(s) on behalf of all the Investigators.

14. REFERENCES

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9. Feudjo-Tepie MA, Le Roux G, Beach KJ, Bennett D, Robinson NJ. Comorbidities of Idiopathic Thrombocytopenic Purpura: A Population-Based Study. Advances in Hematology 2009 ; 2009, Article ID 963506, 12 pages. doi:10.1155/2009/963506
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15. SIGNATURE OF THE STUDY PROTOCOL

I undersigned,

Pr, Dr,: _____

Practicing at: _____

- Certifies have read and understood all the conditions of the study protocol:"**Longitudinal study on the epidemiology and treatment of auto-immune thrombocytopenia (AITP) in Algeria**".
- I pledge to conduct the study in compliance with international Good Clinical Practice (ICH-GCP E6, 17th/07/96), and local regulatory requirements regarding the verification of source documents, audits and inspections related in the study.
- I agree that any change to the protocol is done as an amendment and should be approved in writing by Amgen.
- I understand that any breach of protocol may result in premature termination of the study.

	Signature	**Date (dd-mmm-yyyy)**
Investigator		
Medical Manager		
Medical Director		

16. APPENDIX

16.1 Written consent form

16.2 WHO Bleeding Scale

Grade 0	No bleeding
Grade I	Petechiae
Grade II	Slight loss of blood
Grade III	Crude blood loss
Grade IV	Debilitating blood loss

16.3 Bleeding score of Khellaf

Age	
Age over 65 years	**2**
Age over 75 years	**5**
Cutaneous bleeding	
Located petechial purpura (legs)	**1**
Located ecchymotic purpura	**2**
2 locations petechial purpura (e.g. legs + chest)	**2**
Generalized petechial purpura	**3**
Generalized ecchymotic purpura	**4**
Mucosal bleeding	
Unilateral epistaxis	**2**
Bilateral epistaxis	**3**
Hemorrhagic oral bullae, sponteous gingival bleeding or both	**5**
Gastrointestinal bleeding	
Gastrointestinal hemorrhage without anemia	**4**
Gastrointestinal hemorrhage with acute anemia (> 2g hemoglobin decrease in 24 hours) and/or shock	**15**
Urinary bleeding	
Macroscopic hematuria without anemia	**4**
Gross hematuria with acute anemia	**10**
Genitourinary tract bleeding	
Major menorrhagia/metrorrhagia without anemia	**4**
Major menorrhagia/metrorrhagia with acute anemia	**10**
Central nervous system bleeding	
Bleeding from the central nervous system and/or bleeding with life-threatening prognostic	**15**
Total score	

16.4 Information regarding the management of adverse events observed in programs and / or studies which AMGEN is the Sponsor and which do not involve the live participation of patients

16.4.1 Definition of adverse events (AEs)

Any occurrence of adverse medical event in a subject exposed to a pharmaceutical product and do not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintentional sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a drug, whether or not considered related to the drug.

16.4.2 Serious and non-serious adverse events, and pregnancy exposures observed after exposure to one or more non-AMGEN drugs

The Investigator must inform the regulatory authorities and the independent ethics committees (IEC) in accordance with local requirements and ICH-GCP as soon as he/she becomes aware of the adverse events observed after exposure to a non-AMGEN drugs.

Under these conditions, the reporting of adverse events is subject to the terms of Executive Decree No. 98-192 of 8 Safar 1419 of 03 June 1998, in particular in Article 11 and Decree No. 48 of 07 October 1998 supplemented by decree No. 00200 of 25 July 2009 amending decree No 112 of 22 October 1995 establishing rules of Good Clinical Practice in Algeria.

The reporting of adverse events must be made to the Marketing Authorization (MA) holder or their representatives and/or the National Pharmacovigilance Center and Materiovigilance (CPCM).

Contact CPCM

Address: Sis Bâtiments Nouvel Institut Pasteur Dely Ibrahim, BP 247 Bab El Oued, 16009 Alger

Telephone/ Fax: +213 213 636 71/ +213 362 884

Internet site: http://www.cnpm.org.dz/jaune.php

16.4.3 Serious and non-serious adverse events, pregnancy exposures observed after exposure to one or more drugs including those for which AMGEN holds the Marketing Authorization

The Investigator must notify about all adverse events observed after exposure to a medication or several medications including those for which Amgen holds the MA.

The Investigator must complete and transmit by email / fax / mail copies of the adverse events form (Appendix: adverse events form) to AMGEN Algeria in **24 hours.**

Continuous monitoring of safety data for the use of medications for which AMGEN Algeria holds the MA will be provided by the Local Safety Officer and/or back-up, the director of the medical department, whom contacts are:

Local Safety Responsible, AMGEN Algeria

Tel: +213 …

Tel: +213 ….

Email: ….

Medical Manager, AMGEN Algeria

Tel: +213 …

Tel: +213 ….

Email: …