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 1300 AITP patients (incident and prevalent) are expected to 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 September 2017 (inclusion of first patient) to the end of August 2018 (inclusion of the last patient) , ▪ **Last patient in = last patient out = 31 August 2018** ▪ Total duration of study: 12 months
Study objectives	Primary objective: To assess the incidence of AITP diagnosed in patients aged 16 years old and over in Algeria in a 12-month period of inclusion. Secondary objectives: 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/ . 8/ .
Study endpoints	Primary endpoint: 1/ Number of new cases diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion. 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 of new cases diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion, by gender. 3/ Number of new cases diagnosed with AITP and aged 16 years and over, in Algeria during the period of 12 months of inclusion, by diagnosis stage.

	4/ Number of new cases 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 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 and comorbidities).
Patients selection criteria	Inclusion criteria: 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. Criteria for non-inclusion: 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. . Data will be collected on a case report form (CRF) during study period (from 1 st September 2017 to 31 st August 2018). Data will be collected during these routine patient visits at initial visits, 3 months, 6 months wich will occur during the study period. No data will be collected after the end of study period. • 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	**Department form:** 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 •
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. <u>Analysis of study endpoints</u> ▪ 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: April 2017 ▪ Study initiation in the hematology departments: September 2017 ▪ End of patient data collection: August 2018 ▪ Data analysis: March 2019 ▪ Final Study Report: September 2019 ▪ Date of publication: December 2019