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Title
Platelet-increasing strategies in patients with Immune Thrombocytopenia requiring long-term antithrombotic prophylaxis
Acronym: PLatelet ENhancers in patients with Immune Thrombocytopenia requiring Antithrombotic Drugs - PLENITAD Study

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Type of study: multicenter retrospective / prospective observational study

Background:
As in the general population, patients with immune thrombocytopenic purpura (ITP) can develop pathologies requiring long-term treatment with anticoagulant or antiplatelet agents. Challenging situations in this setting are primary or secondary antithrombotic prophylaxis in patients with atrial fibrillation (AF), artery stenosis, previous cardiac or vascular surgery, percutaneous transluminal coronary angioplasty (PTCA) with or without stenting, arterial or venous thrombosis. Concomitant use of platelet increasing treatment is mandatory for acceptable safety.

Objectives:

The primary objective of the study is to gain information about the incidence of major bleeding in patients with ITP and platelet count < 100 $x10^9$/L requiring antithrombotic treatment including vitamin K-antagonists (VKA), direct oral anticoagulants (DOACs), unfractionated (UFH) or low molecular weight heparin (LMWH), fondaparinux, antiplatelet agents.

The secondary objective is to gain information about safety and efficacy in different clinical scenarios according to:

- Type of clinical situation requiring antithrombotic prophylaxis or treatment (atrial fibrillation, arterial stenosis, cardiovascular surgery, major arterial thrombosis and TIA, major venous thromboembolism and superficial vein thrombosis)
- Type of antithrombotic treatment (VKA, DOACs, UFH, LMWH, fondaparinux, antiplatelet agents)
- Type of management strategy: prednisone (PDN), high-dose dexamethasone (DEX), high-dose immunoglobulins (HD-IG), rituximab, other immunosuppressive drugs, thrombopoietin receptor agonists (TPO-RA: eltrombopag ETP, romiplostim RPL). Patients treated with observation or with platelet transfusions will be included too. Patients undergoing splenectomy after the start of the antithrombotic prophylaxis will be censored at the time of the intervention in the case of no further need of platelet increasing treatment.
- Level of platelet count over time
- Dosage of the antithrombotic drugs above listed

Study design:
Observational retrospective (from January 1, 2000 to the official start date of the study) and prospective (from the official start date of the study for a period of 3 years) case-series study.
The duration of the observation time for each patient will be until cessation of the need of antithrombotic treatment and/or withdrawal of the antithrombotic treatment or until occurrence of the primary outcome (major bleeding).

Population:

Inclusion criteria:

All consecutive subjects that present to the centre and satisfy the inclusion criteria will be considered as potential candidates for enrolment. There is no age limit for including the patients in the study.

Potential subjects must satisfy all of the following criteria to be enrolled in the study:

- diagnosis of ITP independently of the phase of disease (acute, persistent, chronic)
- previous arterial or venous thrombosis and/or high risk condition (AF, artery stenosis, previous cardiac or vascular surgery)
- need of antithrombotic treatments as vitamin K-antagonists (VKA), direct oral anticoagulants (DOACs), unfractionated (UFH) or low molecular weight heparin (LMWH), fondaparinux, antiplatelet agents.
- platelet count $< 100 \times 10^9/L$ at the time of starting antithrombotic prophylaxis or treatment or
- platelet count $< 100 \times 10^9/L$ at the time of diagnosis of arterial or venous thromboembolism or at diagnosis of an high risk condition (AF, artery stenosis, previous cardiac or vascular surgery)

Cases will be recorded also if receiving antithrombotic agents without any platelet-increasing strategy such as prednisone (PDN), high-dose dexamethasone (DEX), high-dose immunoglobulins (HD-IG), rituximab, other immunosuppressive drugs, thrombopoietin receptor agonists (TPO-RA: eltrombopag ETP, romiplostim RPL).

Cases will be recorded also in the case of high-risk condition (i.e. previous arterial or venous thrombosis, AF, artery stenosis, previous cardiac or vascular surgery) treated by observation only, i.e. without either any platelet-increasing strategy nor antithrombotic treatment.

Cases will be recruited on an intention-to-treat basis, including also those receiving a platelet-increasing drug without reaching a platelet count safe enough to start antithrombotic treatment.

The subjects recruited in the prospective arm of the registry (or their legally-acceptable representatives) must have signed a signed written informed according to ICH/EU/GCP and national local laws.

Exclusion criteria:

There are no predefined exclusion criteria, being an observational study aimed to record all the treatment strategies delivered by the care physician.

Patients undergoing splenectomy after the start of the antithrombotic prophylaxis will be censored at the time of the intervention in the case of no further need of platelet increasing treatment.

End Points

Primary end point

- Major bleeding events according to the ISTH definition

Secondary end points

- Occurrence of major arterial or thrombotic events during the observation time
- Occurrence of minor arterial or thrombotic events (i.e. TIA, superficial vein thrombosis) during the observation time
- Duration of platelet count $> 100 \times 10^9/L$, $50 \times 10^9/L$, and $30 \times 10^9/L$
- Occurrence of the adverse events other than bleeding and related to the platelet increasing strategies or to the antithrombotic drugs
- The above primary and secondary end-points after stratification according to the type of platelet increasing strategy or observation

Sample Size

Target accrual was not defined, all eligible patients observed between January 2000 and until 3 years from the date of open to enrolment will be included.

Study duration:

The period of recruitment will be of 3 years.