SSC Subcommittee Project/Collaborative Project

NAME OF PROJECT: International Registry of Thrombotic APS patients Treated With Direct Oral Anticoagulants

(*In French:* OBServaToire INternational des patients AnTiphospholipidEs traités par anticoagulants oraux directs). The OBSTINATE study.

Subcommittee

Lupus Anticoagulant/Antiphospholipid Antibodies Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis

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Description Abstract

Direct oral anticoagulants (DOACs) are indicated for the prevention of recurrent venous thromboembolism (VTE). The management of APS patients is based on a long-term anticoagulation. The gold standard anticoagulant for these patients remains vitamin K antagonists (VKA) mainly warfarin. VKA could be difficult to manage due to several factors: young age population, prolonged treatment requiring regular INR monitoring, INR variations, and many drug interactions. DOACs were developed to offer patients an easy and efficient oral treatment without any laboratory monitoring.

In 2016, the RAPS trial evaluated the impact of rivaroxaban – an anti-Xa inhibitor – vs warfarin on thrombin generation parameters in fifty patients (1). At the end of the study, the absence of thrombotic as well as bleeding occurrence seemed reassuring, however, this study was not designed for comparing clinical outcomes. Instead, it showed that thrombin generation parameters were different among groups suggesting a drug effect in the presence of antiphospholipid antibodies (aPL).

In parallel, several case series suggested an increased risk of thrombosis in APS patients treated with DOACs. A meta-analysis which encompassed all the literature published so far included 447 APS patients treated with DOACs only to identify markers of recurrent thrombosis while on DOACs by comparing patients with and those without recurrent thrombotic event (2). A 16% rate of recurrent thrombosis was detected which was abnormally high in comparison with what we expect to record in APS patients treated with VKA. Furthermore markers of recurrent thrombosis were identified: triple positivity (presence of all three laboratory criteria for definite APS), a history of both arterial and small vessels thromboses, and a higher number of clinical criteria for APS classification.
Subsequently, the TRAPS randomized controlled trial which compared rivaroxaban to warfarin in APS patients was stopped prematurely due to an increased risk of thrombosis in the group of APS patients treated with DOACs (3).

Thus, DOACs does not seem to work efficiently in all APS patients, especially those with a high-risk laboratory profile i.e. the "triple positivity". In this context, the European Medicines Agency (EMA) has indicated the need for a cautious use of all DOACs in APS patients, especially those with triple positivity (4). This information was endorsed by the French Medicine Agency the same month in May 2019. However: a) the risk of recurrent thrombosis on DOACs has been well demonstrated by the TRAPS trial and the recent meta-analysis but no data support the fact that DOACs are dangerous in a subgroup of low-risk APS patients; b) besides rivaroxaban, no other data support that dabigatran, apixaban, and edoxaban are not preventing recurrent thrombosis in APS; c) a significant number of APS patients remain treated with DOACs especially in the following situations: firstly, when APS is diagnosed several months after the initiation of DOACs and no event occurred during follow-up; secondly, when INR is highly unstable inducing a risk of either recurrent thrombosis or bleeding; thirdly, when patients don't want to be treated with VKA due to INR monitoring or other drawbacks of this treatment. Indeed the due to many advantages of DOACs over AVK, patients are not always in favor of modifying their DOACs treatment, especially if it has been established for many years with a good tolerance. The European League Against Rheumatism (EULAR) advocates in its recommendations for management of APS published in May 2019 to contraindicate rivaroxaban (and not the other DOACs) in triple-positive APS patients only (5).

Based on the fact that it is assumed that many patients with APS are treated with DOACs and should be monitored and that some low-risk APS patients could benefit from DOACs treatments, we are convinced that further research is needed.

The flaws of the previous meta-analysis gathering 53 studies was the management of missing data. Therefore, we would like to perform an observational prospective registry of APS patients treated with DOACs to follow these patients (Phase IV design) and more precisely define a subgroup with low recurrent thrombosis while on DOACs. These results would make possible a better identification of the target population that could benefit from this type of treatment.

Design and methodology (Data expected to collect, sample size and statistical analysis):

Primary objective: To determine the frequency of thrombotic complications in APS patients treated with DOACs

Primary outcome: Recurrent thrombosis either venous, arterial, or small vessels confirmed by a reference exam:

- Pulmonary embolism: CT angiogram, V/Q scan
- Stroke: MRI, encephalic CT scan
- Deep vein thrombosis: Compression US echography, CT angiogram, magnetic resonance imaging

- Myocardial infarction: EKG, troponins, coronary angiogram, trans-thoracic echocardiography, magnetic resonance imaging
- Skin necrosis: skin biopsy
- Adrenal infarction with hemorrhage: CT angiography, magnetic resonance imaging

Secondary objectives:

- To identify markers associated with recurrent thrombosis (all thromboses, only arterial thromboses, only venous thromboses, only small vessels thromboses) during DOACs treatment (all, only anti-Xa inhibitors, only IIa inhibitor)
- To determine the frequency of non-criteria manifestations occurring during DOACs treatment
- To determine the frequency of bleeding occurring during DOACs treatment
- To estimate adherence to DOACs

Secondary outcomes:

- Recurrent thrombosis either venous, arterial or small vessels confirmed by a reference exam (more details in the primary outcome description)
- Non criteria manifestations: thrombocytopenia, hemolytic anemia, heart valve disease, livedo, APS-related nephropathy, superficial vein thrombosis, chorea.
- Bleeding according to the definition of the International Society on Thrombosis and Haemostasis
- Adherence to DOACs according to the Morisky score

DOACs use is defined by patients treated with either dabigatran, rivaroxaban, apixaban or edoxaban.

APS patients treated with DOACs will be recruited by specialists involved in the field of APS in expertise centers for autoimmune diseases: vascular medicine specialists, internists, rheumatologists (VTE), neurologists, specialists in haemostasis and thrombosis, cardiologists, pulmonologists. Patients will be enrolled during an hospitalization or an outpatient visit.

The investigator will check for eligibility inclusion criteria and give information about the study. Since it is not an interventional study, usually no consent form will have to be signed. However, if the patient is opposed to participate in this observational study, he will be able to sign an *opposition* form. After obtaining the agreement of the patient, the investigator will fill out a computerized inclusion form, available 24/7 over the Internet via the e-CRF (secure access previously granted to each pre-declared investigating centre).

All participating centers involved in this project will require a local IRB approval.

Data will be collected with respect to patient's demographic characteristics, APS type (primary or associated with other autoimmune diseases), APS-related clinical manifestations, treatments, as well as recurrent thrombosis, side effects and bleeding.

A limitation of the study may be selection bias, investigators might register cases they remember with new events, but will forget to enter patients that are stable on DOAC for many years. To avoid this

bias, consecutive patients will be included in this registry and reasons for a non-inclusion will be asked. Furthermore we will not include a control group since our main objectives are to follow APS patients treated with DOACs as a Phase IV study design (post marketing approval) and to identify factors associated with thrombotic recurrence while treated with DOACs.

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

The inclusion criteria will be:

- Patient receiving a comprehensive information about the study, and not opposed to participate
- Age ≥ 18 yo
- Classification of definite APS according to revised Sapporo-Sidney criteria
- DOACs treatment prescribed during at least 6 months or with the possibility of follow-up of at least 6 months
- Patient affiliated to the social security

Criteria for exclusion

- Incomplete revised Sapporo-Sydney criteria
- No data regarding the recurrent thrombosis
- Pregnant woman
- Age < 18 yo

Because it is a registry, there is no minimal number of included patients to achieve. The aim of this registry is to collect a maximum number of patients to analyze data worldwide. A number of 500 patients could be expected.

Expected timeline: Project stage/set up

Project stage/set up: Until fall 2019
Launch of the project: Winter 2019
Duration: 60 months
Finalization/statistical analysis: Each year an interim analysis will be done.
Reporting: research results and project milestones will be reported at the annual ISTH meeting and annual progress report made to the Executive Committee starting in 2020.

Expected outcomes

The results will be submitted as a Society publication, both SSC Communication and original research on behalf of the SSC. Depending on the outcome, also a Recommendation of the SSC could be proposed.

All publications resulting from the research will be published in ISTH journals.

The results of this longitudinal study will have important clinical consequences on the choice of treatments in APS.

Description of project set/up and management, needed infrastructure and resources:

The project will be led by the Lupus Anticoagulant/Antiphospholipid Antibodies SSC. A computerized register with an inclusion form, available 24/7 over the Internet via the e-CRF (secure access previously granted to each pre-declared investigating centre) is already created on CleanWeb®. Data will be collected at baseline and every 6 months by each investigator.

Nancy Academic Hospital funded the secure online database on CleanWeb®. No other expense is planned.

References

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