NAME OF PROJECT

ANTIPHOSPHOLIPID ANTIBODIES AND LYMPHOMA (NYMPHEA REGISTER)

Subcommittee

Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis

Person responsible (Chair / Principal Investigator): Pr K Devreese/ Dr C Belizna

Description Abstract

The application is included in the broad of ISTH/SSC supported research and is a proposal of creation of an international registry of lymphoma associated with antiphospholipid antibodies (aPL). Recent findings reported elevated levels of aPL in various malignancies. In addition, several studies suggested an increased prevalence of certain malignancies in aPL-positive patients. Nevertheless, it is suggested that aPL positivity and titers do not reflect their pathogenicity; therefore, their pathological significance in patients with solid cancer or hematological malignancy is still unclear and controversial (1, 2, 3). In breast cancer, it has been suggested that aPL promote the transition of indolent tumors to an angiogenic malignant state through a tissue-factor (TF) mediated pathogenic mechanism (4).

In patients with lymphoma, although for some authors the presence of aPL has been reported as associated with an increased risk of thrombosis (5), several data are contradictory (6, 7).

Data are also controversial regarding the eventual role of aPL as markers of disease activity and progression in hematological malignancies. Some authors suggested that aPL positivity could not predict disease prognosis and treatment response in lymphoma patients (5-8); however, these data were contradicted by other reports (9, 10). Therefore, some authors found a high prevalence of aPL in lymphoma patients (around 40%) and suggested that aPL are correlated with shortened event-free survival (9, 10).

Nowadays, based on these data, on the limited number of patients and of limited type of hematological malignancies analyzed, no formal conclusions could be drawn with respect to the potential role of aPL as markers of worse prognosis in lymphoma and of the increased risk of thrombosis in this population. Therefore, we propose an international register (5 years of follow up) in lymphoma patients with positive aPL. We have chosen to concentrate this study only in non-hodgkinian lymphoma patients for the homogeneity of the studied population.

The main aim of this register will be to characterize the clinico-biological features of non-hodgkinian lymphoma (NHL) patients with associated aPL.

Secondary aims will be:

• To estimate the prevalence of the IgG, IgM and IgA anticardiolipin and antiB2GP1 antibodies and of lupus anticoagulant in this population.
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- To evaluate whether the presence of antiphospholipid antibodies in different types of NHL lymphoma influences their response to treatment, their survival and their rate of thromboembolic complications,
- To establish correlations of aPL and circulating TF with the markers of unfavorable prognosis of lymphoma (such as score FLIPI, Bulky, International Prognostic Index (IPI) score, high LDH, high B2 microglobulin); with age, sex, lymphoma type, stage and grade, bone marrow involvement, presence of extranodal disease, presence of various lymphoma symptoms, performance status, type of treatment, response to treatment, number of relapses, number of un-programmed hospitalizations, number of transfusions.
- To establish if the treatments for NHL lymphoma could influence aPL titers.

This research focused on the association between the antiphospholipid antibodies and hematological malignancies has a major importance, as it has a potential impact on the identification of high risk population and would allow formal conclusions if aPL could be a potential marker of prognosis and survival in this population. These results will have potential clinical consequences with respect to the screening and therapeutic regimens in the high risk identified subgroups of patients.

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

We propose a prospective international multicenter 5 years register study. The study group population will include patients with all types of non-hodgkinian lymphoma (incident and prevalent cases).

Specialists from multidisciplinary teams (clinical hematologists and oncologists, biologists, immunologists, internists) from international centers from several countries (France, Belgium, Italy, Israel, The Netherlands, Germany, Spain, Turkey, Slovenia, Romania, Russia) agreed to participate to this register. Additional centers are welcome and expected. The investigator will check for eligibility inclusion criteria and give information about the study (orally and information letter). If agreement, patients will sign an informed consent. After informing the patient and obtaining his/her signature on the informed consent form, the investigator will fill in a computerized inclusion form, available 24/7 over the Internet via the e-CRF (secure access previously granted to each pre-declared investigating center). The specialists will progressively include in an electronic register form data with respect to lymphoma patients at inclusion and every 6 months during follow-up. Data will be collected with respect to patient's age, sex, disease type, disease stage, disease grade, bone marrow involvement, presence of extranodal disease, presence of various lymphoma symptoms, serum lactate dehydrogenase levels, serum beta2 microglobulin levels, International Prognostic Index (IPI) score, FLIPI score, Bulky score, performance status, type of treatment, response to treatment, number of relapses, number of un-programmed hospitalizations, number of transfusions.

The statistical analysis will be realized by means of the software Excel version 2010 of Microsoft (Redmond Washington the United States) and of the software IBM SPSS statistics version 23 (Chicago Illinois the United States). For the comparative analysis of the groups, the test t of Student will be used for the quantitative variables, having verified beforehand the equality of the variances for the studied parameters, and the test of Chi ² for the nominal qualitative variables.
Collected variables shall be described globally and per group. Qualitative variables are expressed in population size and percentage. Quantitative variables are expressed in terms of mean ± standard deviation with 95% confidence interval, along with the 5th and 95th percentiles. These are, however, expressed in terms of median, minimum, maximum and 5th and 95th percentiles when normality is rejected. The Kolmogorov-Smirnov test will be used to check parameter normality and the Levene test will be used to determine equality of variances. An alpha risk of error of 5% with a significance for p of 0.05 will be admitted. The analysis of one of the outcome measures shall consist in comparing the proportions of subjects with new thrombotic events, and with different prognostic profiles in the groups of patients with different types of lymphoma. This comparison shall be performed by means of a Chi-square test, or a Fisher exact test if the Chi-square application conditions are not met. If a difference between groups is demonstrated for at least one of the potential confounding variables, the main outcome measure shall be analyzed by means of multivariate logistic regression to consider the adjustment factors. Also, the number of events in each group will be compared, with a Poisson regression model and a negative binomial regression model. The search for correlation will use the calculation of the coefficient rho of Spearman in case of the low size of groups, the not parametric character and the not normal distribution of the data.

We will perform statistical comparative analysis based on type of antiphospholipid antibodies types and values (low, moderate and high). A survival analysis related to the risk of thrombosis and with the risk of relapse associated with aPL during follow-up shall be performed and estimate by calculating the hazard ratio (Cox model). Descriptions for time to adverse events including new morbidity events using Kaplan-Meier methods for evaluation will be used to support interpretation of results.

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

The inclusion criteria will be

- Patients with diagnosis of NHL lymphoma based on international criteria including confirmation by biopsy,
- Age > 18 years
- Patients are volunteers, informed and signed the consent form for participation in the register after receiving the information letter.

Criteria of exclusion

- None

Considering the number of centers having agreed to participate at date and the period of inclusion, a number of 4-5 patients per month and per center is expected. The expected total number to be included is of 900 patients.

**Expected timeline: Project stage/set up**

Finalization of the project and creation of register data base: September 2018
Launch of the project: January 2019
Duration: 60 months
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Finalization/statistical analysis: March 2024

Reporting: research results and project milestones will be reported at the Subcommittee’s annual SSC meeting and annual progress report made to the Executive Committee starting march 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 an ISTH journal.

The research on the association between the antiphospholipid antibodies and hematological malignancies has a major importance, as it has a potential impact on the identification of high risk population and would allow formal conclusions with respect to the role of aPL as a potential marker of prognosis and survival in this population. These results will have potential clinical consequences on the screening and therapeutic regimens in the high risk identified subgroups of patients.

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

The project will be leaded by the lupus anticoagulant SSC subcommittee. 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 center) will be created. Data will be recorded every 6 months by each investigator.

The valorization of the project results will be through communications in congress and international conferences and via different publications.

Funding will be needed for a part time data manager, methodologist/ biostatistician and a clinical research assistant. In total this is estimated on 20 000 USD.

References:


