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## **IDENTIFICATION OF PROGNOSTIC FACTORS FOR PATIENTS WITH ANCA ASSOCIATED VASCULITIS**

### **PROJECT DESCRIPTION**

**Background** European Vasculitis Society 'EUVAS' is a society founded in 1994 from the previous EC/BCR ANCA study which in turn was initiated to harmonize and improve quality in ANCA (Anti Neutrophil Cytoplasmic Antibody) testing as a tool for diagnosing small vessel vasculitis predominantly affecting the kidneys. After the introduction of ANCA testing diagnosis of Granulomatosis with polyangiitis (GPA) as well as Microscopic polyangiitis (MPA) has been dramatically improved and quicker. Thus, an increased interest was raised for these entities of vasculitis and a new group \*EUVAS' was established, with the aim to improve and harmonize diagnosis, clinical evaluation of vasculitis activity (BVAS scoring was established) and to improve outcome for these patients by improving therapy. Several randomized clinical trials, investigator initiated and driven, and without the impact of pharmaceutical companies, were launched. Thus, we have within EUVAS a unique cohort of European patients extremely well defined in their phenotypes at entry of trial, i.e. predominantly at time of diagnosis of the vasculitis. Patients have been stratified to predefined induction treatment and remission sustaining therapy and followed up 5-10-20 years from time of diagnosis. Presently, we have an ongoing 10-year follow-up study on patient and renal survival, cumulative incidence of cardiovascular disease and malignancies respectively.

Our group has already developed histological criteria that predict outcomes based on renal biopsies (the Berden Classification), and has supported the development of rituximab (now licensed for AAV) and avacopan (anti-C5a receptor), both targeted therapies for AAV. Despite similarities in presentation and treatment, outcomes remain variable and with an increasing range of interventions it is now becoming important to consider factors that aid treatment selection or personalization of therapy.

In parallel with the long-term follow-up of patients recruited between 1995 and 2005, we intend to use the PEXIVAS cohort to validate prognostic marker discovery and to assess changes in outcomes over time. In conjunction with the European Vasculitis Genetics Consortium and the PEXIVAS project we plan to support further genomic studies identifying genetic polymorphisms predictive of outcome in vasculitis.

Aim for identifying prognostic factors present at time of diagnosis regarding relapses, patient and renal survival, risk for cardiovascular disease and malignancy.

Secondary aims include the validation of prognostic factors and the development of a cohort with long term outcomes to permit a genomic approach to prognosis. Integration of predictive factors to develop prognostic tools that might also aid treatment selection.



Material Patients who have participated in EUVAS randomized clinical trials during the period 1995-2013. The cohort comprises the 535 patients, who participated in NORAM, CYCAZARE, MEPEX and CYCLOPS) and who have been followed-up in the 5-year study published in 2011 together with 156 patients within the IMPROVE and another 44 in the RITUXVAS and those within the MYCYC study. All together these studies rendering a possible cohort comprising 875 patients which have been followed up for 5-20 years after diagnosis and inclusion in the initial RCT. Furthermore, patients participating in the PEXIVAS trial (704 patients followed for an average of 3 years, recruited 2010-2016), The study will be performed in accordance with the principles laid down in the 1964 Declaration of Helsinki and subsequent amendments, and ethical approval will be obtained by local and national ethics committees in accordance with national legislation, prior to sending out questionnaires.

**Methods:** Data on outcome variables of patients are retrieved from questionnaires which have been sent to the participating centers. During 2018 a research physician is assisting in retrieving the follow up data electronically to a central database in Oxford UK. Data retrieval will be finalized within 2019.

Descriptive and comparative statistics on outcome data will be done after the collected information has been transferred as a data set to Lund University, Sweden. A list of which statistical analyses to be done have been settled, for example patient survival, renal survival, number of relapses, duration and type of immunosuppression. Comparisons regarding gender, type of induction therapy and outcome data.

Prognostic factors for good outcome, for example no relapses during follow up, cumulative incidence of malignancies, severe cardiovascular events, patient- and renal survival will be analysed from data obtained from the questionnaires and the trial datasets. The specific aims are to analyse specific proteins and other analytes in frozen and stored sera and plasma drawn at entry of the original studies, and also in renal tissue specimens when available.

For this task we need a full time research fellow to arrange these analyses, including co-operation with other research groups as European vasculitis Genetics Consortium, EURECA-m and Descartes and potentially industrial companies, if methods are not developed at the University Labs.. Serum samples are stored in Sweden and UK, and kidney biopsies in the Netherlands. However, all samples and analyses should be restricted to be kept within Europe as this is stated in the original ethical approvals. All material and results from analyses should stay within / belong to EUVAS and the PEXIVAS consortium. Besides, retrieving samples and arranging for analyses the research fellow should also participate in analyzing data and writing manuscripts on results and outcome.

**Importance:** If we could identify markers for risk for relapse, risk for end stage renal disease, risk for severe cardiovascular events we also could improve outcome by better understanding pathogenesis and to better find a therapy or more accurately a cure. If we could define patients with a good outcome, with low risk for relapse, death or end stage renal disease we could offer these patients a less toxic therapy with less risk for severe side effects.

**Participating researchers:** Members of the Scientific Council of EUVAS, [www.vasculitis.org](http://www.vasculitis.org). Depending on the results obtained in the long term follow-up regarding clinical outcomes we will aim for collaboration with the European Vasculitis Genetics Consortium, Descartes and EURECA-m.



## DETAILS RELATED TO THE FELLOWSHIP

1. **Duration:** 12 months

to analyse and describe patient outcome, including statistical analyses, and also to start and plan analyses to be done on spared sera and tissues re. specific proteins and analytes.

2. **Location of the hosting centre:**

Department of Nephrology, Lund University /Skane University Hospital Malmö-Lund, Sweden

3. **Principal Investigator(s) of the project:**

Assoc. Prof. Kerstin Westman ([kerstin.westman@med.lu.se](mailto:kerstin.westman@med.lu.se))

**Supervisor** Prof Peter Höglund (for the statistical analyses of the follow-up) and Assoc. Prof. Sophie Ohlsson, director for the Euvass Serum Bank for the laboratory analyses to be done.

4. **Start of the fellowship:** January 2020.

5. **Essential requirements to be involved in the project:**

A young research fellow with some experience from clinical research and with skills in English and preferably also in French, German and or Italian/Spanish. As the project includes both epidemiological and statistical work up as well as experimental/laboratory research, it may be of some value if the fellowship could be split into two segments (6 months each): one for the statistical task and another for the experimental-laboratory one.