

IMPACT OF LONG TERM-STEROID TREATMENT PRESCRIBED FOR SYSTEMIC AND AUTOIMMUNE DISEASES ON THE DEVELOPMENT OF ATHEROSCLEROSIS. A NETWORK ORGANIZED BY THE EUROPEAN FEDERATION OF INTERNAL MEDICINE

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Participating centers: to be completed

- Loïc Guillevin France
- Alain Simon, France
- Christian Jorgensen
- Stefan Fava, Malta
- Poland
- Czsec republic
- Pr Merino Spain
- Davidson (UK) au moins, demander à Bacon, Hugues, Cruz etc...
- Qui en Allemagne ? voir Haussinger
- Yehuda Shoenfeld
- Stefano Bombardieri
- Vasconcelos Porto
- So en suisse ?
- Belgique plusieurs centres.

DOSAGES : Shoenfeld, Peter USA

I - INTRODUCTION

Atherosclerosis is the most prevalent disease responsible for death from myocardial infarction, cerebrovascular disease and renal failure. For years the traditional factors such as high lipid levels, diabetes, hypertension, smoking, family history... were believed to be the major factors playing in the pathogenicity of atherosclerosis.

In the last decade, it has been understood that atherosclerosis, an inflammatory process may have infectious, iatrogenic and autoimmune components. Among them, prolonged steroid treatment could be of major importance in the occurrence of accelerated atherosclerosis observed in autoimmune diseases. If the majority of long-term side effects of steroids are well known, comprising hypercorticism and its metabolic consequences, osteoporosis and infections, it is not the case for atherosclerosis which has been poorly studied.

The efficacy of steroids and immunosuppressants has dramatically reduced the risk of death in patients with autoimmune diseases like systemic lupus or vasculitis and now steroid treatment could be one of the first cause of death. The evaluation of atherosclerosis and its impact on morbidity and mortality is not easy to make, and markers of atherosclerotic process need to be carefully measured and their respective weight compared before considering a panel of surrogate markers able to predict the occurrence of atherosclerosis and its consequences.

Such study needs the participation of a large number of physicians and patients and should be organized at a European level.

One of the objectives of the European Federation of Internal Medicine (EFIM) is to foster clinical research in Europe and to involve the national Internal Medicine scientific societies in large scale studies on topics of major interest for public health and clinical practice.

SCIENTIFIC PROJECT

Objectives

- The first objective of the study is to measure the frequency of atherosclerosis in a large population of patients with autoimmune and systemic diseases.
- The second objective is to measure the impact of steroids on the occurrence of atherosclerosis.
- The third objective is to determine surrogate markers able to evaluate the presence of atherosclerosis in the patients with autoimmune and systemic diseases.

Study design

a) Inclusion criteria

- A cross sectional study will be undertaken in patients with autoimmune and systemic diseases: systemic lupus erythematosus, rheumatoid arthritis and systemic vasculitides have been selected because all the patients receive usually different therapeutic schemes but long term steroid treatments.
 - *Systemic lupus* requires usually a high dose steroid treatment for several months then a maintenance treatment for several years. Treatment is prescribed alone or in combination with other drugs, hydroxychloroquine, immunosuppressants. The patients will satisfy to the ACR criteria.
 - *Rheumatoid arthritis* patients receive low dose steroids (5 to 10 mg//day) for many years and sometimes during all life. Additional treatments are considered in every case: DMARDS like methotrexate, non steroids anti-inflammatory drugs, and more recently anti TNF antibodies. The patients will satisfy to the ACR criteria.

- *Vasculitides* are treated with high dose steroids for a few months or years (rarely more than 2 years) alone or in addition to immunosuppressants (cyclophosphamide, azathioprine, methotrexate). The patients will satisfy to the ACR criteria and the Chapel Hill nomenclature.

The heterogeneity of diseases and treatments is an advantage for the study: For each disease, treatment is well codified and practices are very similar from a country to another. On the contrary, pathogenesis of diseases and treatment schemes are different from a disease to another. A large scale study would facilitate the understanding of the responsibility of steroid treatment in the occurrence of atherosclerosis; We expect differences on one or several surrogate markers measured in each patients and make hypothesis on the factors responsible for such differences.

Patients with the same disease but who did not necessitate a steroid treatment will be included and serve as a control group.

Non inclusion criteria

- Other systemic or autoimmune diseases
- Localized vasculitis
- Patients will be excluded if they have a well-known risk factor for atherosclerosis: diabetes, statin-treated hypercholesterolemia, arterial hypertension, known history of ischemic heart disease or stroke.
- Patients who do not accept to participate in the protocol
- Patients with malignancies or affected with a life threatening disease that could reduce life expectancy

Protocol

- All the patients presenting one of the autoimmune and systemic diseases will be included consecutively in each center, whatever the treatment will

be. The patients not receiving steroids will serve as control group (case control study)

- The following investigations will be performed:

▪ *Common to each disease*

- A questionnaire asking for risk factors for atherosclerosis will be filled (smoking, diabetes, overweight, lipids...). Treatments prescribed for the autoimmune disease and all the other treatments will be recorded.
- Blood samples for biological investigation will be stored because some surrogate markers will be measured in one or several reference laboratories (Yehuda Shoenfeld, Tel Aviv; Peters, Los Angeles, Hantz, Bobigny).

A carotid echography measurement will be performed in each patient and a precise measurement of the wall will be noted on the report form. Atherosclerotic plaques will be detected. Assessment of intima media thickness of the common carotid artery will be used using a high resolution B mode ultrasound echography type ULTRAMARK 9, the vascular image will be numerized on Apple personal computer. The software IOTEC system (Société IODP, Paris, France) will be used to evaluate automatically the intima media thickness.

- A similar investigation will be performed 3 years after inclusion or in case of event related to atherosclerosis.

Specific to each disease

-Information specific to each studied disease will be recorded

Duration of the study

A three-year period will be sufficient to establish the cohort of patients and to make the first study on atherosclerotic markers and to register the clinical manifestations related to atherosclerosis occurring during this period of time.

We plan also to follow the patients participating in the study in the years following inclusion and to register clinical events and to renew the atherosclerosis evaluation.

Ethical consideration. All information remains anonymous, and obtained after informed consent of the patients. All tests are non invasive investigation justified by the prevention of cardiovascular risk in this exposed population.

The impact of the European contribution

- Facilitate the organisation of the network throughout Europe and facilitate the dissemination of protocols and scientific information through the European scientific societies
- The ability to organize scientific meetings
- Facilitate transport of samples
- Prepare uniform requirements for inclusion of patients and follow-up
- Facilitate the comparison of data from country to country taking into account the therapeutic regimen, the nutritional status and behaviour, the specificities of each country
- Facilitate the participation to eastern Europe and small countries to studies of major importance
- Transfer of medical knowledge
- Individualisation of a cohort of patients at risk who could benefit of treatment or prophylactic recommendations (diet)
- Analyse the respective part of the disease, steroids treatments, other drugs (estrogens, statins..), infections on the development of atherosclerosis