THE MEMBERS OF THE SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS (SLICC) GROUP

SLICC INTERNATIONAL INCEPTION COHORT STUDY OF SLE PARTICIPANT NEWSLETTER

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BACKGROUND

The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) is an international group of rheumatologists and lupologists who have been working together on lupus research since 1987. They have collaborated to develop standardized outcome measures so that physician-researchers can better measure and describe the course of lupus and its response to new therapies. These outcome measures are now widely used by lupus researchers throughout the world and allow comparisons of patient populations among centers.

REGISTRY FOR ATHEROSCLEROSIS

It is known that women with SLE develop CAD (atherosclerosis of the coronary arteries) at a higher rate and at an earlier age than the general population. In addition, women with SLE develop clinical manifestations such as heart attack and angina up to five times more often than the general population.

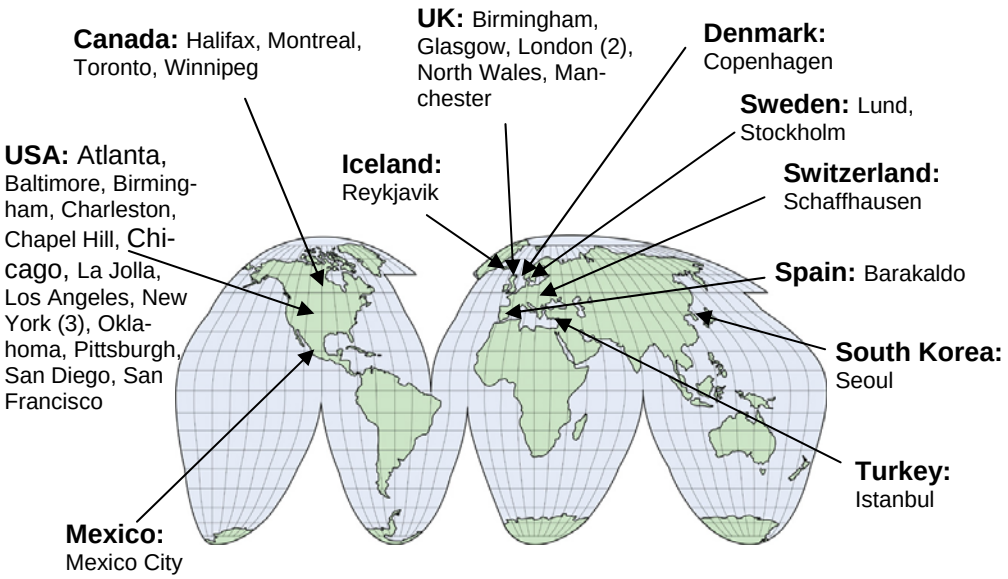
The SLICC group has developed the Registry for Atherosclerosis with the goals to:

- Determine the prevalence and nature of early atherosclerotic coronary artery disease (CAD) in SLE
- To identify associated risk factors and to discern the contribution of disease and therapy to the occurrences of these risk factors
- Develop intervention studies to modify risk factors for the development of CAD including educational programs and potential drug therapies.

INSIDE THIS ISSUE:

SLICC REGISTRY FOR ATHEROSCLERIS – PARTICIPATING SITES

AS A PARTICIPANT IN THIS STUDY, YOU JOIN 1408 OTHER LUPUS PATIENTS FROM 12 COUNTRIES AROUND THE WORLD. EACH PARTICIPANT BRINGS US CLOSER TO ANSWERING IMPORTANT RESEARCH QUESTIONS SO THANK YOU FOR YOUR PARTICIPATION!



ACTIVITIES TO DATE

We are pleased to report that we are now close to our **new** recruitment goal of 1650 participants. As of May 2009, **1408 participants** have been enrolled in the Registry. This constitutes the largest cohort of newly diagnosis SLE patients assembled to date!

Achieving our goal of 1650 patients will mark the end of the beginning as we plan to follow our cohort for 10 years so that we will be able to accurately document this complication of SLE.

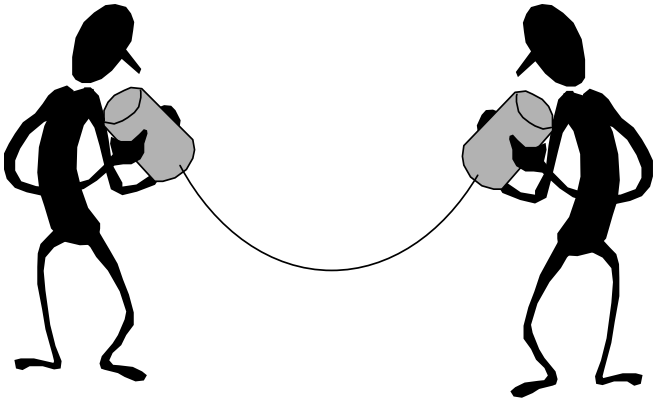
The following table provides some descriptive features of the SLICC cohort based on data from 1356 participants.

Total Number of Participants	1356
Female	1209 (89 %)
Race (%) Caucasian / Black / Asian / Hispanic / Other	48 / 15 / 17 / 16 / 4
Average age at SLE diagnosis	34 years
Average time from diagnosis of SLE to enrolment	5.5 months
Married or Common-Law	613 (45 %)
Education – College or University	788 (59 %)

CURRENTLY PARTICIPATING?

PLEASE STAY IN TOUCH...

The SLICC study is designed to follow participants for up to 10 years, and a lot can change over that time period! Please be sure to provide your participating rheumatologist with updates if you move or change your phone number so you can be reached when it is time for your annual follow up visit. If you have moved too far away to attend your annual follow up visit at your recruitment site, we would still appreciate being able to contact you by telephone to collect information.



WHAT'S NEW?

For your next SLICC follow up visit, your doctor may request that you do not to eat or drink anything but water for up to 12 hours before your visit.

This is necessary (where possible!) because we need to collect specific laboratory tests as part of the study including fasting glucose, triglyceride and cholesterol. These tests help us study a very important metabolic abnormality that a significant number of SLE patients demonstrate which predisposes them to atherosclerosis.

So if possible, please try to schedule your appointment on a day and at a time it is convenient for you not to eat or drink anything but water before your visit!

WHAT WE HAVE LEARNED SO FAR

SLICC Members have already started answering relevant research questions using the information collected in the SLICC Registry and 5 manuscripts have been published or accepted for publication in Scientific Journals. We have included a summary below of some of the findings presented at National Scientific Meetings of the American College of Rheumatology (ACR) and International Lupus Meetings over the past two years.

Description of Coronary Artery Disease Outcomes

Now that further follow-up information is available on this diverse group of SLE patients, we are able to begin looking at heart disease outcomes and associated risk factors. A presentation at the ACR meeting described the occurrence of coronary artery disease (CAD) events such as heart attack, angina, stroke, etc. In the first 1078 patients, 47 patients have gone on to have a CAD event. Detailed information was collected regarding each of these events, and it was determined that 17 were attributable to atherosclerotic changes. When we looked at the difference between patients who had an event and those who didn't, we found that those patients with an event were more likely to be older at the time of diagnosis of SLE and were more likely to have high blood pressure. There was also a slight increased risk for development of CAD in patients who were diabetic, overweight or had a family history of heart disease. This study tells us that even early in the course of SLE, patients are at an increased risk for development of coronary heart disease. With continued follow-up, we will be able to explore the nature of these outcomes and risk factors in more detail.

SLE Features Over Time

In addition to learning more about the specific complication of coronary artery disease, the SLICC Registry is allowing us to learn more about the course of SLE in general. Another presentation that was given at the ACR meeting in November was a general description of disease outcomes in the first four years after diagnosis. We showed that while disease activity is high at diagnosis, it does generally improve over the first four years. Quality of life as measured by the SF-36 Quality of Life Questionnaire, which is completed by the patient, improves over the first four years. However, even though disease activity and quality of life improves, it appears that damage (or permanent changes resulting from lupus) does continue to occur.

Differences in Risk Factor Development Between Patient Groups

A further study was presented at the ACR that compared the development of classic risk factors CAD between different ethnic groups. Over the three-year period of available follow-up on these patients, there were some differences between ethnic groups: Caucasians were more likely to be smokers and had a higher frequency of family history for coronary artery disease, but the lupus disease activity tended to be lower than that in the other groups, requiring less drug treatment. Asians and Hispanics had higher disease activity, and Black patients had more damage as a result of their disease than the other groups. There were no consistent differences in other classic risk factors for coronary artery disease among the ethnic groups. As it is still early in the follow-up of these patients, it is difficult to draw any major conclusions from this study, but continuing to look at differences between the various groups may allow researchers and treating physicians to be more aware of potential risk for their individual patients and to tailor preventive therapies accordingly.

Metabolic Syndrome - It's role in Development of Heart Disease

Dr. Murray Urowitz gave a presentation to the attendees of the Lupus International Conference held in Shanghai China in May 2007 on the occurrence of metabolic syndrome in the SLICC cohort. Metabolic syndrome is the name for a group of risk factors linked to development of conditions such as diabetes and heart disease in the general population. These risk factors include increased body mass index, high triglycerides, reduced HDL (or good) cholesterol, raised blood pressure and increased blood sugar levels. It is suspected that steroid treatment or inflammation (both features of lupus) may play a role in the development of metabolic syndrome. Using the data from the SLICC Registry, we set out to determine if patients with SLE do in fact have an increased presence of metabolic syndrome and to try to determine if any specific features of lupus are associated with this condition. We found that metabolic syndrome occurred in 28% of patients within the first three years since diagnosis. Factors associated with the presence of this syndrome included use of immunosuppressive drugs, higher accumulation of damage from SLE and a family history of coronary artery disease. This would lead to the impression that those patients with more aggressive SLE that requires more drug therapy are at an increased risk for the development of metabolic syndrome. The role of metabolic syndrome in the development of coronary artery disease, the interplay between the inflammation and the possible contribution of steroid therapy to the development of metabolic syndrome are areas that we definitely plan to pursue further.

Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) Study

As many of our participants know, involvement of the nervous system is one of the biggest concerns for patients with SLE. Although NP-SLE has been recognized for many years, there continue to be several unanswered questions. For example, how frequent are nervous system events in SLE patients, how many of them are due to SLE, how do they change over time, what is the cause of these events and how are they best treated? One of the initiatives arising from the SLICC registry is the NP-SLE SLICC study, which is coordinated by Dr. John Hanly and his research team at Capital Health and Dalhousie University in Halifax, Nova Scotia. Since 2002 this study has received funding from the Canadian Institutes of Health Research. It has the following objectives:

- To determine the frequency of overall NP events in SLE patients and determine which ones are due to lupus or to other causes.
- To determine the short and long-term impact of NP-SLE as assessed by its effects on patients' quality of life, outcome of events, overall damage to the nervous system, and patients' survival.
- To determine if various antibodies produced by the immune system in lupus patients (eg. those which react against brain tissue or cause blood clots within the brain) are associated with specific NP events.

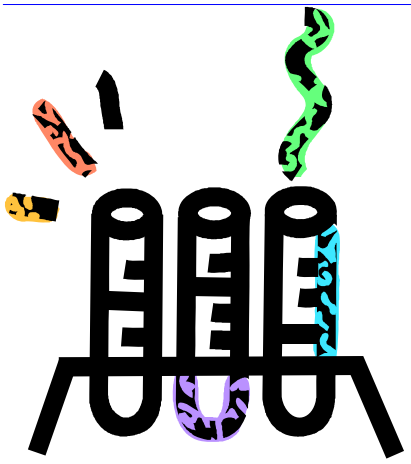
FINDINGS SO FAR FOR THE NP-SLE STUDY

To date 1404 patients have been enrolled in the NP-SLE study. Although still in the early stages, a number of important observations have already been made which have been reported at international scientific meetings and in scientific journals.

Frequency and Impact of NP Events Around the Time of Diagnosis of SLE

In a study of the first 572 patients, it was determined that 28% of patients had at least one of 19 NP syndromes around the time of diagnosis of SLE. Using different rules to determine the cause of events, it appeared that 19-38% of the NP events were due to SLE and affected 6-12% of patients. Of significance was the observation that regardless of the cause of the NP events, their presence was always associated with a significant reduction in self-reported quality of life. This emphasizes the importance of all NP events in the daily lives of our patients.

The Association Between Lupus Autoantibodies and NP Events

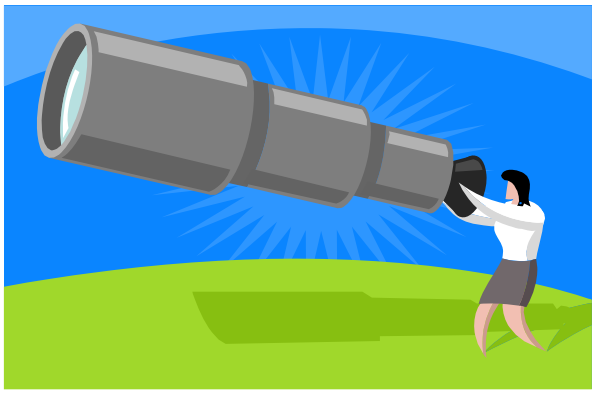


In a study of 412 patients enrolled in the SLICC registry, a panel of lupus antibodies was measured by Dr. Joan Merrill (a SLICC member) in her research laboratory at the Oklahoma Medical Research Foundation. We found that NP events which were due to SLE were more likely to be associated with certain lupus antibodies. Specifically, the presence of antibodies which increase the risk of blood clot formation were associated with the occurrence of stroke and antiribosomal-P antibodies were associated with lupus psychosis, a relatively rare NP manifestation of SLE.

The Outcome of NP Events in SLE Patients

Two studies have now been completed in the assessment of how NP events evolve over time in our patients. The first study in 890 patients, who were followed for around four months, found that the outcome of NP events due to SLE was better than the outcome of events due to non-SLE causes. In a subsequent study of 1206 patients who were followed for two years it was again found that those NP events which were caused by SLE were associated with a better outcome. As before, regardless of the cause of the NP events, their occurrence significantly lowered patients' perception of both their mental and physical health over time.

FUTURE PLANS



As with the Atherosclerosis Study, the intent of the NP-SLE SLICC study is to follow patients for ten years. This is now underway and will provide a unique opportunity to further evaluate not only the overall outcome of NP events in our patients, but how specific NP events such as strokes, seizures, mood disorders and others change over time. The study will continue to investigate how lupus antibodies and other immune system abnormalities may cause nervous system disease is SLE patients. The net result of our findings should provide information on how to best treat this important but poorly understood manifestation of lupus.

Other Studies Emerging from the SLICC Registry

A Study of Metabolic Syndrome in Patients with Systemic Lupus Erythematosus (SLE)

The Canadian Institutes of Health Research recently awarded funding for a study examining Metabolic Syndrome in patients with SLE which will use data from the SLICC Registry. Premature heart disease is a significant problem in patients with lupus. We have found that a pre-diabetic state (the metabolic syndrome) is more common in SLE but the causes are unclear. This pre-diabetic state is itself an important risk factor for the development of future heart disease. We suspect that steroid therapy and inflammation related to the condition together cause this problem to develop. This study will examine what factors in SLE over time increase the risk of developing the metabolic syndrome. In particular, we wish to study whether certain SLE patients inherit a greater sensitivity to steroids that increase their risk of developing this pre-diabetic state. This study will allow us to understand better the risks associated with steroid therapy in SLE and to help us better target steroid doses on an individual basis. It will also help us suggest ways to reduce the risk of future heart disease in SLE. As noted above this study requires that we get fasting samples from patients. For this reason your doctor may ask you to fast for 12 hours before coming for your clinic visit.

Even More Studies Underway...

In addition to the NP-SLE and Metabolic Syndrome Study, several other exciting studies are underway using clinical data and biological materials collected as part of the SLICC Registry. We look forward to reporting the findings from the studies listed below in upcoming newsletters!

- QTc Prolongation in Anti-Ro/SSA Positive SLE Patients submitted by Dr Christian Pineau and Dr Ann Clarke, Montreal, Canada
- Reproductive Health Issues in Women with Systemic Lupus Erythematosus submitted by Dr Sasha Bernatsky and Dr Ann Clarke, Montreal, Canada
- Serum vitamin D levels and cardiovascular disease in systemic lupus erythematosus submitted by Dr Peggy Wu and Dr Rosalind Ramsey-Goldman, Chicago, USA
- Genetic Risk for Atherosclerosis in SLE submitted by Joan Merrill, Oklahoma City, USA
- SNP Array of SLE Risk Genes submitted by Dr John Harley, Oklahoma City, USA
- Autoimmune Peripheral Nerve Injury in SLE by Dr John Hanly, Halifax, Canada

PARTICIPATING SLICC RECRUITMENT SITES

Do you have a question or do you want to reach the research staff at your SLICC Recruitment site to stay in touch? See below for the names of participating rheumatologists and their contact numbers.

Dr. Graciela Alarcon, University of Alabama, Birmingham, **USA** (205) 934-4084

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Dr. Sang-Cheol Bae, Hanyang University College of Medicine, Seoul, **Korea** (2) 290-9203

Dr. Ian Bruce, Manchester Royal Infirmary, Manchester, **England** (161) 276-6841

Dr. Ann Clarke, Montreal General Hospital, Montreal, **Canada** (514) 934-1934 x 44251

Dr. Mary Ann Dooley, University of North Carolina, Chapel Hill, **USA** (919) 966-4191

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Dr. Caroline Gordon, University of Birmingham, Birmingham, **England** (121) 414-6778

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Dr. Jorge Sanchez-Guerrero, National Institute of Nutricion, Mexico City, **Mexico** (525) 655-5954

Dr. Kirstjan Steinsson, Landspitalinn University, Reykjavik, **Iceland** (354) 525-1000

Dr. Thomas Stoll, Chefarzt Rheumatologie und Rehabilitation, Schafthausen, **Switzerland** (52) 634-2570

Dr. Ronald van Vollenhoven, Karolinska Hospital, Stockholm, **Sweden** (468) 5177-6077

Dr. Daniel Wallace, Cedars-Sinai Medical Center, West Hollywood, **USA** (310) 360-9197

Dr. Asad Zoma, Stonehouse Hospital, Glasgow, **Scotland** (135) 558-5222

FUNDING OF THE SLICC REGISTRY FOR ATHEROSCLEROSIS: A TRULY COLLABORATIVE EFFORT

The SLICC Registry has been partially funded by an operating grant from the Canadian Institutes of Health Research. However, the Registry would not exist without the generous support of several patient groups, including:

Lupus Foundation of Ontario

New Jersey Chapter of the Lupus Foundation of America

Lupus UK

The Tolfo Family – Dance for the Cure Fundraiser

Western New York Chapter of the Lupus Foundation of America

Nashville Chapter, Lupus Foundation of America

Long Island-Queens Chapter, Lupus Foundation of America

Hudson Valley Chapter, Lupus Foundation of America

Lupus Ontario

The SLICC Registry has also been supported by donations from the Conn Smythe Foundation and the Lupus Flare Foundation.

THE SLICC GROUP WOULD LIKE TO GRATEFULLY ACKNOWLEDGE THE SUPPORT OF THESE PATIENT GROUPS.

The SLICC group continues to apply for funding from traditional granting agencies for specific research projects. However, the core-operating costs of data and specimen collection activities are not normally funded through these operating grants. SLICC will therefore continue to rely on their patient-partners for their support of this important work.