



SLICC INTERNATIONAL INCEPTION COHORT STUDY OF SLE

A YEARLY NEWSLETTER FROM YOUR PARTNERS IN LUPUS RESEARCH

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 1991. They have partnered to develop outcome measures so that physician-researchers can better measure and describe your course of lupus and its response to new treatments. These outcome measures are now widely used by lupus researchers throughout the world and allow comparisons of patient groups among centres.

REGISTRY FOR ATHEROSCLEROSIS

Atherosclerosis is a potentially serious condition where your arteries become clogged by fatty substances known as plaques or atheroma. Plaques can cause affected arteries, such as the main arteries that supply blood to your heart, to harden and narrow, which can be dangerous. It is known that women with lupus develop heart disease at a higher rate and at an earlier age than the general public. In addition, women with lupus develop health problems such as heart attack and angina (chest pain caused by reduced blood flow the heart muscle) up to five times more often than the general public.

The SLICC group has developed the Registry for Atherosclerosis (SLICC-RAS) with the goals to:

- Study the occurrence and nature of early atherosclerotic heart disease in lupus
- To find related risk factors and to look at the role of disease and therapy in the presentation of these risk factors
- Develop studies to change risk factors for the development of heart disease including educational programs and possible medications.

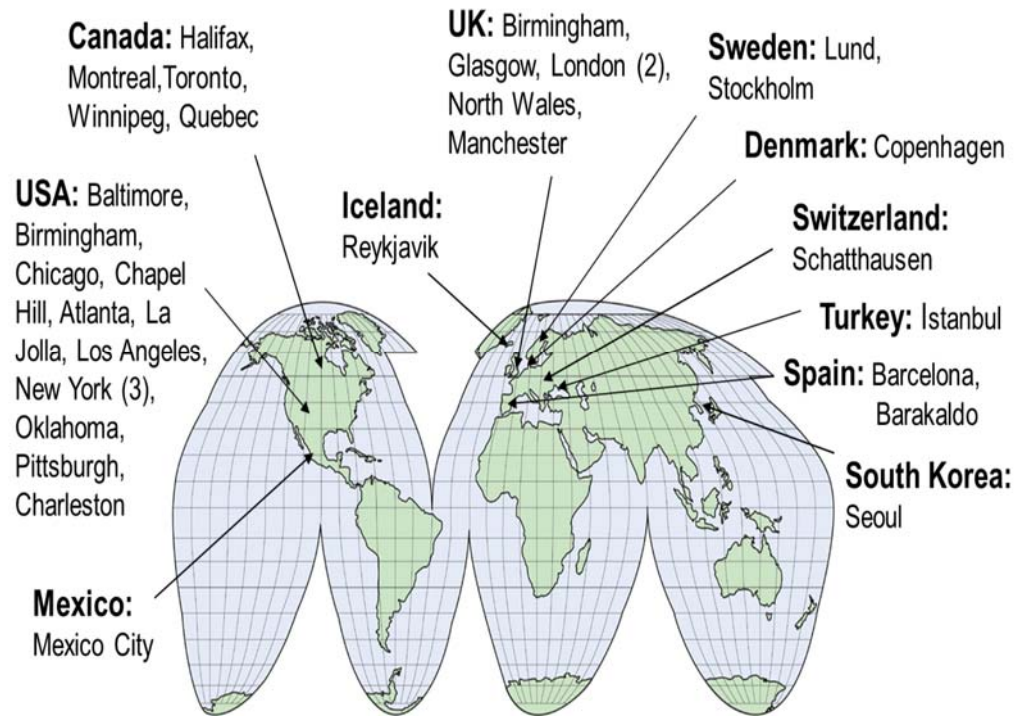
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SLICC RECRUITMENT SITES FROM AROUND THE WORLD

The SLICC Registry is a multinational study with sites all over the world. As a participant in this study, you join 1836 other lupus patients from 11 countries and 33 centres around the world.

We are very thankful to you and the time you have contributed to participate in this study. We are one step closer to answering important research questions regarding lupus and CAD.



ACTIVITIES TO DATE

Longterm Follow-up

We are happy to report that many of our participants have been followed for more than 10 years. It is hard to believe this registry began in 2000. Our very first enrolled patient is now at 15 years of follow-up.

Achieving our goal of 1800 participants has allowed us to study the long term effects of living with lupus. One of the main goals of our research is to look at the risk factors associate with heart disease in lupus. Previous studies have indicated that long term complications such as heart failure are more likely to present themselves 8-10 years after diagnosis. As a result of these findings it is very important to follow each of you to better understand lupus and prevent these long term complications.

The following table provides a breakdown of the final recruitment numbers by country:

COUNTRY	NUMBER OF PATIENTS
CANADA	422
DENMARK	7
ICELAND	28
KOREA	169
MEXICO	223
SPAIN	31
SWEDEN	45
SWITZERLAND	3
TURKEY	16
UNITED KINGDOM	350
UNITED STATES	542

CHANGES TO YOUR PARTICIPATION !



We believe the SLICC Registry for Atherosclerosis in Lupus is an extremely important resource to aid in the understanding of lupus and heart disease. We also recognize the tremendous cost of your healthcare to both yourself and our healthcare system.

We would like to take a closer look at the medical costs associated with managing lupus and its associated risk factors. Our aim is to look at both direct costs such as hospital visits, inpatient stays and specialist appointments in addition to indirect costs such as your time off work for sick days or medical appointments.

PATIENT REMINDERS

KEEP
CALM
AND
STAY IN
TOUCH

Please stay in touch...

The SLICC study is designed to follow participants for their entire lifetime, and a lot can change in a lifetime! 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 WE HAVE LEARNED SO FAR

SLICC Members have been working hard to answer many research questions using the information collected in the first 10 years of follow-up. To date we have published 20 manuscripts in Scientific Journals. We have included a summary below of some of the new research findings that were published in journals and presented at the National Scientific Meeting of the American College of Rheumatology (ACR) and International Lupus Meetings that took place in 2014.

Quality of Life After Your Diagnosis

A diagnosis of lupus can have a large impact on your quality of life; this includes activities you may do throughout your day, in addition to your ability to work. As a part of your participation in the SLICC Registry for Atherosclerosis in Lupus you may recall filling out a questionnaire called the SF-36 Health Survey. This survey is used to study the physical, psychological and social impacts of having a chronic disease such as lupus. We looked at patient responses to this survey in order to determine if your quality of life changes over time in the first 5 years after your diagnosis.

We were happy to find that quality of life improved over time, most notably in the part of the survey that addressed your physical health. Most of the improvement occurred within the first 2 years after diagnosis.

We also looked at what other factors, such as sex, race, disease activity and age may be linked with the changes we saw in survey responses. We found that men tended to have larger improvements in vitality, social function and physical activity responses. Older age at diagnosis of lupus was linked to slower improvements in physical, social and emotional function and Asians showed more improvement in survey responses than Whites. We also noted, that having active lupus while completing the survey showed lower improvement rates in bodily pain and physical, social and emotional function.

This study demonstrates that in early lupus, the SF-36 Health Survey is a good quality questionnaire that can be used to test for changes in your quality of life. It also highlights disease activity, especially at diagnosis, is related to the changes in your quality of life in early disease. This is most likely due to the fact that many patients start with active lupus at diagnosis and then receive proper treatment. Once your lupus is controlled at years 2-5 your quality of life stabilizes or remains unchanged.

This study also highlights the importance of receiving regular healthcare regarding your lupus, instead of seeking help only when symptoms worsen. By maintaining regular medical exams your doctor can note changes to your health and identify and treat your flares early. Proper management of your health can avoid active disease and hopefully improve or maintain a higher quality of life throughout your disease.



How to Better Predict Heart Disease Risk in Lupus Patients

Premature heart disease is a major problem in patients with lupus. It is known that women with lupus are more likely to experience vascular events such as heart attack and angina (chest pain) up to five times more often than the general public. This study looks at how to better predict which patients may go onto develop atherosclerotic vascular events over 10 years of follow up in the SLICC Registry for Atherosclerosis.

We looked at a number of factors known to be related to increased risk of atherosclerotic vascular events; these included:

- your age at diagnosis;
- whether you were male or female;
- if you were a diabetic;
- a current smoker or had a history of smoking;
- if you were overweight;
- or have high blood pressure and/or high cholesterol

When we examined all of the risk factors listed above we found that older age at diagnosis and male sex significantly affects your risk for atherosclerotic vascular events. This study confirms the importance of regular follow up with your doctor in order to better understand your prognosis and delay or prevent the onset of heart disease.

Cardiovascular Events Prior to or Early After Diagnosis of Lupus

Previous studies have shown a history of cardiovascular events, such as a heart attack, can be experienced prior to the diagnosis of lupus and rheumatoid arthritis. This study describes the number of heart attacks (myocardial infarction) prior to the diagnosis of lupus and within the first two years of follow-up.

We found that a small number of patients (1.6%) had a heart attack prior to or early after diagnosis. Of those, 23 patients had a heart attack prior to their lupus diagnosis. We looked at the race, sex and typical heart disease risk factors such as lupus disease activity, use of medications to treat lupus, blood chemistries, blood pressure and family history of patients that had a heart attack prior to or early after diagnosis of lupus and compared them to patients that did not have an early heart attack. We found similar results to the study listed above, only male sex and older age at diagnosis contributed to the increased likelihood of having a heart attack prior to or early after lupus diagnosis.

This study suggests that having a heart attack prior to or early after the diagnosis of lupus may indicate either an early or low grade disease activity that goes undiagnosed or an alternative explanation is some patients may have a predisposition to heart disease and lupus. This study illustrates that if you are an older male that was diagnosed with lupus you should be intensely screened for atherosclerosis at diagnosis.



Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) SLICC Study



The nervous system consists of the brain, spinal cord and peripheral nerves which carry information to muscles and other structures. Although it has been known for a long time that lupus can target the nervous system there are many unanswered questions about this aspect of SLE. For example, how common are nervous system events and how many of them are due to SLE? Do they become more frequent over time and how do they impact on quality of life? Can they be predicted and what is the best treatment? These and other questions are being studied within the NPSLE 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 core funding from the Canadian Institutes of Health Research (CIHR).

The study has the following objectives:

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

FINDINGS SO FAR FROM THE SLICC NPSLE STUDY

Enrollment into the SLICC NPSLE study was completed in December 2011 at 1,826 patients. The average follow-up is 6.13 years and 397 patients have been followed for at least 10 years. Patients lost to follow-up due to geographic relocation or withdrawal from the study varies between SLICC sites. However, the average percentage of patients lost per site (17%) and the average absolute number of patients lost per site (10) are small. This is a unique group of patients which will provide the means of answering many important questions in NPSLE.



Mood Disorders in SLE

Mood disorders (e.g. depression and anxiety) are frequent in patients with SLE. In 2015 an article will be published in the prestigious medical journal Arthritis and Rheumatology that reports the findings of a study of mood disorders in the SLICC inception cohort.

As part of the SLICC inception cohort registry, patients are assessed annually for mood disorders and other neuropsychiatric (NP) events. Of the 1827 enrolled patients, 47.2% were found to have had at least one NP event over an average of 4.7 years. Mood disorders occurred in 12.7% of the total study patients and 38.3% of these mood disorders were attributed to SLE.

Points of interest were the fact that patients of Asian race/ethnicity and those patients taking immunosuppressant drugs were found to have a lower risk of a mood disorder and that there was a greater risk of a mood disorder in those patients who had a concurrent NP event.

The study also found that mood disorders were associated with a lower self-reported Health Related Quality of Life (HRQoL) but not with active lupus or specific lupus antibodies. Antidepressants were used in 72.4% patients with depression which resolved in 50.4% patients and improved in additional patients over the period of follow-up.

The study demonstrates that mood disorders, the second most frequent NP event in SLE patients, have a negative impact on HRQoL but improve over time in the majority of cases. The lack of association with active lupus and lupus autoantibodies emphasize that multiple factors contribute to depression in SLE patients and that there is a role for non-lupus specific therapies.

Recent Findings In Lupus and Kidney Disease

Outcome of Lupus Nephritis: Results from an International, Prospective, Inception Cohort Study



Kidney disease is common in SLE patients. When it is caused by the patient's SLE, it is called Lupus Nephritis (inflammation of the kidney due to lupus). Using all of the previously collected information in the SLICC inception cohort, we examined the outcomes of lupus nephritis over the past ten years as therapies and clinical care have improved. This study is currently in press with the Journal of Rheumatology.

This is what was found in a study of 1,827 lupus patients who were followed for an average of 4.6 years:

- Lupus nephritis occurred in 38.3% of SLE patients over the period of study but 80.9% of these patients developed nephritis within a year of the diagnosis of SLE.
- Patients with lupus nephritis were younger overall and more frequently men
- They were also more frequently of African, Asian and Hispanic race/ethnicity
- Poor kidney function resulted in a lower Health Related Quality of Life score
- Patients with nephritis had a 10.1% risk of developing kidney failure over 10 years following the diagnosis of nephritis and had a 3-fold increased risk of dying compared to patients without nephritis

The results of this study suggest that despite current standard of care, patients with lupus nephritis have a reduced quality of life and a substantial risk of kidney failure. Further advances are required for the optimal treatment of lupus nephritis.

SLICC Sub-Studies



Cancer Risk in Systemic Lupus

The SLICC research network has strongly supported the mandate to further understand cancer risk in SLE, and cancer outcome information is currently collected. Members of the SLICC group, led by Drs. Sasha Bernatsky, Ann Clarke, and Rosalind Ramsey-Goldman, are proposing work to further advance the work of SLICC on cancer risk in SLE. In previous landmark studies, the SLICC investigators have documented a lower breast cancer risk in SLE versus the general population. This does not seem to be fully explained by genetic factors, reproductive issues, or drug exposures. Auto-antibodies (antibodies to self) are a characteristic feature of SLE. Novel data suggest that some auto-antibodies may affect cancer risk and prognosis, representing new targets for cancer treatment and/or surveillance. These future analyses within the SLICC registry will thus allow us to better understand cancer risk in SLE, which would could translate into optimal care. For now, patients with SLE should continue to have age appropriate cancer screening (including pap tests, mammogram, and other routine cancer screening according to guidelines) as recommended for the general population.

International Registry for Biologics in SLE (IRBIS)

IRBIS is an international collaboration with a focus on patients with SLE. In IRBIS, patient data is collected at baseline and thereafter at yearly intervals for a number of years providing a comprehensive record of patient's treatment history and disease progression over a long period of time.

The use of registries, where data is collected systematically is an important source of information and has the advantage of reflecting the real world environment for patients. Because registries provide data on various aspects of treatment and goals (efficacy, safety, epidemiology, genetics, and more), registries contribute in crucial ways to make optimal therapy choices and guide future research.

In IRBIS data is collected on patients treated with any biologic therapy and recently the registry is also collecting data on patients treated with immunosuppressives. The type of data collected in IRBIS, together with the yearly follow-ups, will enable us to perform analysis to determine treatment efficacy and treatment safety.

As part of the larger efficacy and safety goals for IRBIS, we aim to compare the clinical response of patient treated with biologics to patients treated with immunosuppressives (controls) and similarly, compare adverse events such as serious infections between the two patient groups. As part of smaller objectives, IRBIS aims to characterize patients receiving biologics, and the impact of biologic dosing and frequency, and concomitant medications.

FUTURE PLANS



Lupus and Metabolic Syndrome

Premature heart disease is a significant problem in patients with lupus. We have found that a prediabetic state (metabolic syndrome) is more common in lupus patients. Metabolic syndrome (MetS) is itself an important risk factor for the development of heart disease.

The Canadian Institutes of Health Research previously awarded funding for a study examining MetS in patients with lupus that used data from the SLICC Registry. From our previous research, we found that steroid therapy seems to be a major factor in the development of MetS. Higher daily steroid dose was linked with MetS and early steroid exposure may have a long lasting effect on MetS. We also noted that Korean, Hispanic and Black ethnicity patients are more likely to develop MetS, with Hispanics having the highest likelihood of having MetS over time. We plan to extend this study by looking at genetic factors, such as ethnicity and non-genetic factors, such as steroid exposure and inflammation and how they influence MetS in early SLE and how the relationship between these factors changes over time. This study will help us better understand how ethnicity, inflammation and steroids may exert a long lasting effect on MetS and heart disease risk in lupus patients.



NP-Manifestation Studies

Due to the large number of patients enrolled in the cohort, and the increasing length of follow-up, we have been able to start examining these individual NP manifestations. Additional studies in the future will allow us to determine the outcome of other specific types of nervous system disease and subsequently improve the ways in which these are monitored and treated. The results of the studies to date have already

provided valuable insight into this important aspect of lupus. Additional studies over the next few years will improve our understanding and treatment of this condition which will be to the benefit of all patients with SLE.



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

The SLICC Registry have been partially funded by a grant from the Canadian Institutes of Health Research. However, the registry could not continue its operation without the generous support of the following patient groups:

Lupus Foundation of Ontario

Lupus UK

Conn Smyth Foundation

The Tolfo Family/Lupus Ontario —Dance for the Cure Fundraiser



The SLICC Registry would like to give a special thanks to Tiziana Tolfo who has supported the registry for 11 years. Mrs. Tolfo has worked extensively in organizing the Dance for the Cure fundraiser to help support lupus research. We extend our sincere gratitude for her continued support of this important research.

Dance for the Cure Committee Member Tina Sarta, Dr. Dafna Gladman, Dance for the Cure Director Tiziana Tolfo and Dr. Murray Urowitz.

THE SLICC MEMBERS WOULD LIKE TO THANK THESE PATIENT GROUPS FOR THEIR EXTENSIVE SUPPORT.

The SLICC group continues to apply for funding from granting agencies for specific research projects, but our core operating costs for data and specimen collection are not normally funded through these grants. SLICC will continue to rely on the generous donations from our patient partners in support of this important work.

PARTICIPATING SLICC CENTRES

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. Barri Fessler, University of Alabama, **Birmingham, USA** (205) 934-4084

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