THE SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS (SLICC) GROUP

SLICC

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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 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 groups among centres.

REGISTRY FOR ATHEROSCLEROSIS

It is known that women with lupus develop coronary artery disease (atherosclerosis of the coronary arteries) at a higher rate and at an earlier age than the general public. In addition, women with SLE develop clinical conditions such as heart attack and angina 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 prevalence and nature of early atherosclerotic coronary artery disease (CAD) in lupus
- To identify related risk factors and to look at the contribution of disease and therapy to the presentation of these risk factors
- Develop intervention studies to change risk factors for the development of CAD including educational programs and possible drug therapies.

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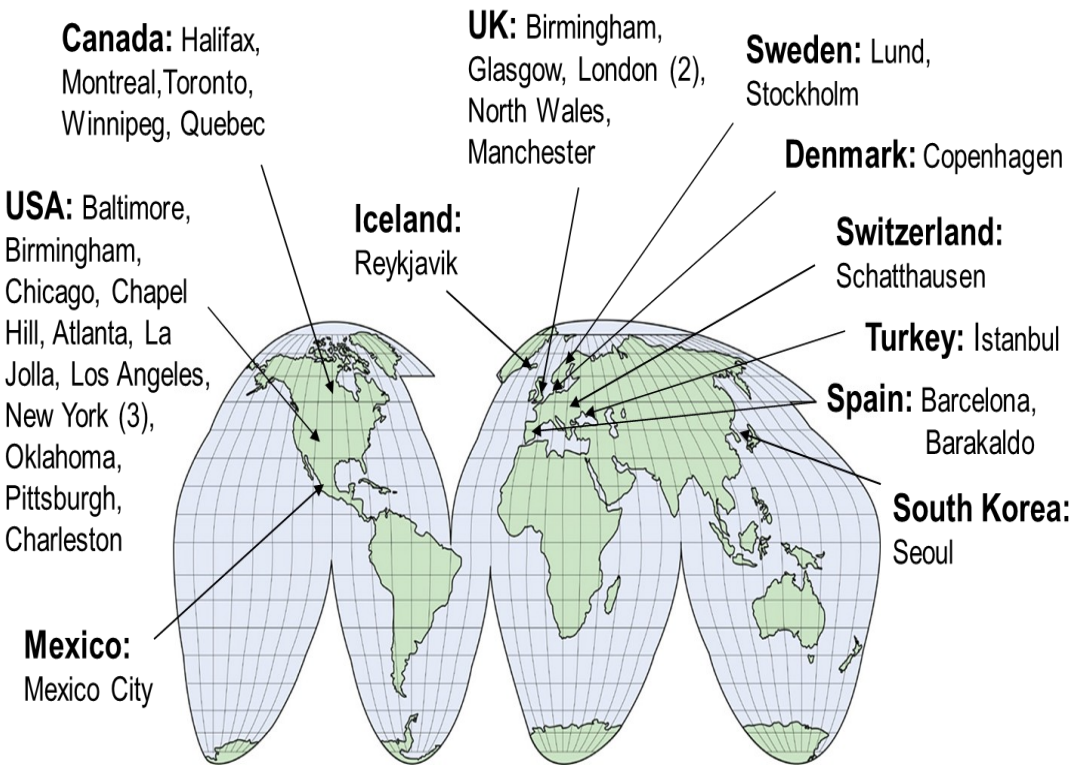
SLICC RECRUITMENT SITES FROM AROUND THE WORLD

The SLICC Registry is a multinational study with sites all over the world. As a participant in this study, you join 1837 other lupus patients from 12 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

Recruitment Closure

We are happy to report we have reached our recruitment target of 1800 patients. This constitutes the world's largest cohort of newly diagnosed SLE patients assembled to date!

Achieving our goal of 1800 patients has marked the end of the beginning as we are now in the long term follow phase of the study. This will allow us to accurately document the many complications associated with SLE.

The following table illustrates the descriptive features of the SLICC cohort based on data from all participants.

Total Number of Participants	1837
Female	1629 (88.3%)
Race (%) Caucasian / Black / Asian / Hispanic / Other	922 (50.4%), 308 (16.8%), 254 (13.8%), 282 (15.4%), 65 (3.6%)
Average age at SLE diagnosis (years)	34.7
Average time from diagnosis of SLE to enrolment (months)	5.6
Married or Common-law	842 (45.7%)
Education—College or University	1071

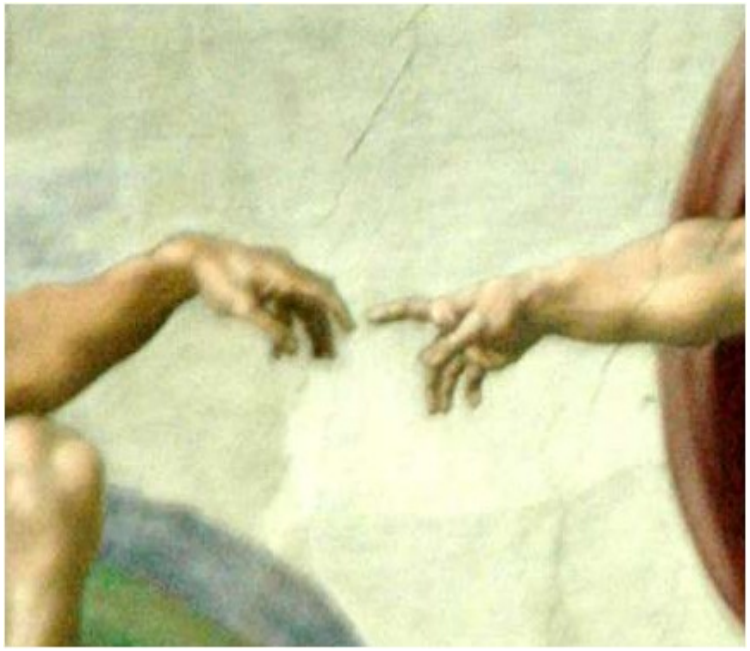
The following table provides a breakdown of the final recruitment numbers by country:

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	543

PATIENT REMINDERS

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 17 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 2012.

Lupus Disease Burden in the First 5 Years After Diagnosis

Lupus is a chronic autoimmune disease in which the body's immune system, switches from its normal protective function to forming antibodies that attack healthy tissues and organs. Many people with lupus may have a mild disease affecting only a few body organs; for others, it may cause serious life threatening problems. This study looks at varying disease burden, which was determined both by the degree and severity of disease inflammation and the resulting organ damage in patients. We examined disease activity, damage and the increase in autoantibodies in SLICC patients.

A total of 298 newly diagnosed lupus patients were followed for 5 years. We demonstrated that the average disease activity in newly diagnosed patients decreased and remains low over the first 5 years. However, despite this early disease control, disease damage increased over this time.

We also examined disease activity and damage among different races. It was found that disease activity was lower in whites as compared to nonwhites and overall disease activity decreased over the first 5 years. When disease activity was further studied in nonwhite patients, it was found that Asians and Hispanics influenced the difference in disease activity the most.

Disease damage can accumulate from both lupus itself and from treatment such as steroid therapy. Steroid therapy is among the most effective anti-inflammatory drugs for lupus patients. Although they can cause some undesirable side effects, their use can substantially reduce the symptoms associated with inflammation. In our study we found that damage due to steroid therapy increased over the first 5 years of follow up, while damage independent of steroid therapy remained constant throughout the 5 year period.

We also examined the occurrence of auto-antibodies in lupus patients. Over the 5-year period, there was a progressive increase in the number of patients that tested positive for auto-antibodies. These findings may help physicians better manage steroid therapy and avoid increased disease damage throughout the first 5 years after diagnosis.

The Metabolic Syndrome Study

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 future heart disease. We suspect that both steroid therapy and inflammation related to the condition together cause this problem to develop. This study looked at the presence of, and the factors associated with metabolic syndrome in SLICC patients at enrollment.

At enrollment approximately 16% of SLICC patients had MetS and 24% of patients had MetS on at least one occasion in the first 2 year follow up period. MetS was more common in men than women and those with MetS were older than those without. We also found that Hispanic and Korean patients had the highest prevalence of MetS compared to Caucasians.

This study also showed an association between steroid exposure and MetS. Patients who had MetS had a higher daily dose of steroid and therefore, had a history of increased exposure to steroids as compared to patients that did not have metabolic syndrome.

The results from this study will aid physicians in treating recently diagnosed SLE patients. By highlighting which ethnicities may have a higher risk for the development of MetS and therefore increased risk for heart disease, physicians can better tailor treatment plans for these patients. This study may also helps physicians balance disease control while minimizing steroid exposure.

The Incidence of Atherosclerotic Vascular Events Over a 10 Year Period

A large number of SLICC participants have now reached the 10 year follow up mark. This has allowed us to begin to look at long term outcomes associated with heart disease. It is known that women with lupus are more likely to experience vascular events such as heart attack and angina up to five times more often than the general public. The purpose of this study was to determine the occurrence of vascular events during a 10 year follow up of SLICC patients, and establish their association with heart disease.

Since 2000 we have enrolled 1837 patients into the SLICC RAS study. A total of 157 vascular events were reported in 115 patients. These events included: heart attack, angina, heart failure, stroke, pacemaker insertion and peripheral vascular disease (condition of the blood vessels that leads to narrowing and hardening of the arteries that supply the legs and feet). Approximately 40% of these events were due to active lupus, while 30 % were due to atherosclerosis and the remainder were due to other causes.

Our analysis indicated that over the first 10 years, vascular events that occurred in patients and were attributable to heart disease, increased by 0.5% per year reaching a total of 4.4% at the 10 year mark. This study reaffirms the necessity of long-term outcome studies to track the increased risk of vascular events in SLE patients. The information gained from this research will help physicians better manage and follow heart disease risk factors in SLE patients.

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 know 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 are all areas requiring further research? 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 funding from the Canadian Institutes of Health Research (CIHR) and has recently received a third 5-year CIHR grant up to provide core funding up to 2018. 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.

Enrollment into the SLICC NPSLE study was completed in December 2011 at 1,826 patients. The average follow-up is 4.87 years and 220 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 (10.4%) and the average absolute number of patients lost per site (7.6) are small. This is a unique group of patients which will provide the means of answering many important questions in NPSLE.

FINDINGS SO FAR FROM THE SLICC NPSLE STUDY

Enrollment into the study is currently at 1,826 patients. The results of the studies so far have provided important information related to the diagnosis and outcome of NPSLE. These results have been reported at international scientific meetings and in high quality scientific medical journals.

Seizures and Lupus

August of 2012, an article was published in the medical journal *Annals of the Rheumatic Diseases* that reported our findings to date about seizures in SLE patients. In this study we reported how many lupus patients had seizures, how often they had them, why they occurred and what happened afterwards. By studying this information we also hoped to find similarities so that we might be able to predict what type of SLE patient might be at a higher risk of seizure. This is what we found:

- 4.6% of patients had at least one seizure, most of which occurred around the time of their SLE diagnosis.
- Seizures due to SLE frequently got better without long-term seizure medication and without decreasing quality of life.
- There was some indication that the regular use of antimalarial drugs (such as Plaquenil) reduced the risk of seizures.
- A higher risk of seizure was seen within three groups;
  - Patients with lower education status
  - Patients with more organ damage since the diagnosis of SLE
  - Lupus patients with African race/ethnicity

Headaches and Lupus

We have recently completed a study of headaches in people with SLE. We studied what types of headaches people had, and how often they had them, to better understand how SLE and headaches are related. This is what we found:

- Headaches are common in SLE patients but probably not more frequent than in the general population of similar age and gender.
- The occurrence of headache is not related to overall SLE disease activity and is not associated with changes in lupus medications.
- The majority of headaches in SLE patients are probably not due to a direct effect of lupus affecting the nervous system
- Regardless of the cause, SLE patients with headaches report a lower quality of life.
- Most headaches in SLE patients get better and resolve over time.

SLICC Sub-Studies

AROSE Study:
Revision and Validation of the American College of Rheumatology (ACR) Diagnostic Criteria for Lupus

SLICC sites were involved in a 7 year study to develop and validate new classification criteria for SLE. The new criteria emphasize advancement in both clinical knowledge about lupus-- such as subtypes of neurological involvement and subtypes of cutaneous lupus -- but also immunologic testing such as low complement. Over 1400 patients helped with this effort and deserve our sincere thanks!

Lymphoma Risk in Systemic Lupus: Effects of Disease Activity Versus Treatment

Treatment In this study, we examined the effects of medications and disease activity as they relate to lymphoma risk in SLE. This was based on a very large sample of patients from all over the world, including most centres that participate in the SLICC inception cohort. At the 2012 ACR meeting, the SLICC group, represented by Dr. Sasha Bernatsky, presented information on 75 lymphoma cases and almost 5000 cancer free controls. In this study, which is the largest of its kind ever performed, we did not show clearly increased lymphoma risk for any medications. There is much interest in this kind of research, and the SLICC co-investigators (lead by Drs. Ann E. Clarke and Rosalind Ramsey-Goldman) are very grateful for the patients who participate in our clinical research programs, and for the opportunity to conduct this work. Further work will focus on cancers other than lymphoma, such as breast cancer, a malignancy for which SLE patients seem to have an decreased risk.

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.

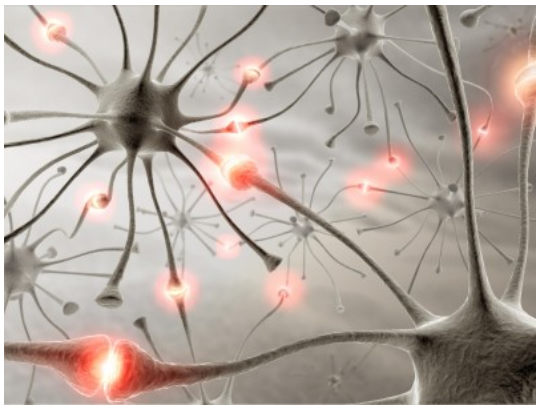
In IRBIS data is collected on patients treated with any biologic therapy and recently the registry is also collecting data on patients treated with immunosuppressives. The type of data collected in IRBIS, together with the yearly follow-ups, will enable us to perform analysis to determine treatment efficacy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

As part of the larger efficacy and safety goals for IRBIS, we aim to compare the clinical response of patients 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

SLICC-RAS and Metabolic Syndrome Study

The Canadian Institutes of Health Research previously awarded funding for a study examining metabolic syndrome in patients with SLE that used data from the SLICC Registry. From our previous study of SLE we found that steroid therapy seems to be a significant factor in the development of metabolic syndrome (MetS). Higher daily steroid dose was associated with MetS and early steroid exposure may have a persistent influence on MetS. We also noted that Korean and Hispanic ethnicity patients are more prone to MetS, with Hispanics having the highest prevalence 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 prolonged influence on MetS and heart disease risk in high risk populations.



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.

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

Dr. Cynthia Aranow, Feinstein Institute for Medical Research**, Manhasset, USA** (516) 562-2401

Dr. Anca Askanase, NYU Hospital for Joint Disease, **New York, USA** (646) 356-9400

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 & Dr. Sasha Bernatsky, Montreal General Hospital**, Montreal, Canada** (514) 934-1934 x 44251

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

Dr. D. Gladman, Dr. M. B. Urowitz, Dr. J. Sanchez-Guerrero, Dr. Paul Fortin* Toronto Western Hospital, **Toronto, Canada** (416) 603-5800 x 2481

Dr. Ellen Ginzler, SUNY Health Science Centre, **Brooklyn, USA** (718) 270-1662

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

Dr. John Hanly, Dalhousie University and Capital Health , **Halifax, Nova Scotia, Canada** (902) 473-3818

Dr Murat Inanc, Istanbul University, **Istanbul, Turkey** (90) 212-161-8699

Dr. David Isenberg and Dr Anisur Rahman, University College, **London, England** (20) 7380-9219

Dr. Soren Jacobsen, Copenhagen University Hospital, **Copenhagen, Denmark** (45) 3545-7560

Dr. Diane Kamen, Medical University of South Carolina, **Charleston, USA** (843) 792-1991

Dr. Kenneth Kalunian, UCSD, **San Diego, USA** (858) 657-7076

Dr. Munther Khamashta, St. Thomas Hospital, **London, England** (20) 7620-2567

Dr. S. Sam Lim, Emory University, **Atlanta, USA** (404) 616-5602

Dr. Susan Manzi, Allegheny General Hospital, **Pittsburgh, USA** (412) 641-7633

Dr. Joan Merrill, Oklahoma Medical Research Foundation, **Oklahoma, USA** (405) 271-7805

Dr. Ola Nived & Dr. Gunnar Sturfelt, University Hospital Lund, **Lund, Sweden** (46) 172-451

Dr. Christine Peschken, University of Manitoba, **Winnipeg, Canada** (204) 787-1969

Dr. Michelle Petri, Johns Hopkins University, **Baltimore, USA** (410) 614-1839

Dr. Manel Ramos-Casals, Unidad de Enfermedades, Barcelona, Spain (34) 93 227 57 74

Dr. Rosalind Ramsey-Goldman, Northwestern University, **Chicago, USA** (312) 503-0251

Dr. Guillermo Ruiz-Irastorza, Universidad del Pais Vasco, **Barakaldo, Spain** (34) 94-600-6348

Dr. Juanita Romero Diaz, National Institute of Nutricion, **Mexico City, Mexico** (525) 655-5954

Dr. Kirstjan Steinsson, Landspitalinn University, **Reykjavik, Iceland** (354) 543-1000

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

*Currently at Université de Laval, **Quebec, Canada**

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 it's 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

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

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.

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.