ASIG

AUSTRALIAN SCLERODERMA INTEREST GROUP

SCLERODERMA connections:

EDITION 8: MAY 2015

SSC SCREENING CENTRE UPDATE

greetings,

Welcome to the 2015 edition of Scleroderma Connections. More than 1500 patients from around Australia have now enrolled in the Australian Scleroderma Cohort Study, through 15 Australian Scleroderma Interest Group (ASIG) centres, some for up 9 years. This longitudinal observational cohort has provided the framework for an expanding body of research work that has led to collaborations with other Australian researchers and internationally, some of which are listed in the Research Update section of this newsletter. Internationally, a collaboration with the Canadian Scleroderma Research group (Drs Marie Hudson and Murray Baron) is proving very fruitful with several projects underway under the general umbrella of Burden of Disease, including a report of outcomes in Australian, Canadian and Spanish patients (Dr Patricia Carreira) and establishment of the INSYNC inception cohort (with these collaborators and Dr Tracy Frech, Utah, USA). A large body of work is underway to develop a Damage Index with Delphi rounds involving nearly 100 international scleroderma experts. In the last 12 months, ASIG has contributed data to international research efforts concerning scleroderma renal crisis and calcinosis and individual ASIG members participate in other international research groups including the Scleroderma Clinical Trials Consortium Gastrointestinal working group and the OMERACT CTD-ILD and CRISS disease activity working groups.

We would like to thank our patients who have participated in the ASIG study and generously contributed their data. ASIG is also indebted to the hardworking nurses, doctors and the researchers in devoting their time and energy for caring for and finding better ways to treat scleroderma.

While these projects are very exciting, one of the most rewarding outcomes of ASIG's activities has been the improvement in the quality of care the ASIG centres can deliver for people living with scleroderma. Most centres have expanded the service they offer with specialist nurses and have become centres of excellence. This growth in patient numbers and experience has led to a number of centres being invited to participate in industry-funded clinical trials, allowing patients to have access to new therapies for the first time in many years.

In this issue, learn about new appointments to ASIG and our "newest" centre at the Fiona Stanley Hospital in Perth. The patient version includes an article about the importance of exercise for scleroderma from physiotherapist, Carolyn Page.

Susanna

Susanna Proudman
ASIG Chair

watch this space!

In addition to those already cited, below is a selection of the studies currently in the pipeline to watch out for in the coming year:

VCAM1 as a therapeutic target in scleroderma
Matt Brown, Tony Kenna, Susanna Proudman, Wendy Stevens, Mandy Nikpour

Incidence and prevalence of muscle disease in systemic sclerosis
Susanna Proudman, Vidya Limaye, Adam Maundrell

The efficacy of Mycophenolate and Azathioprine in Scleroderma Interstitial Lung Disease
Jo Sahhar, Claire Owen

Genetics of Scleroderma
Matt Brown and Katie Cremin

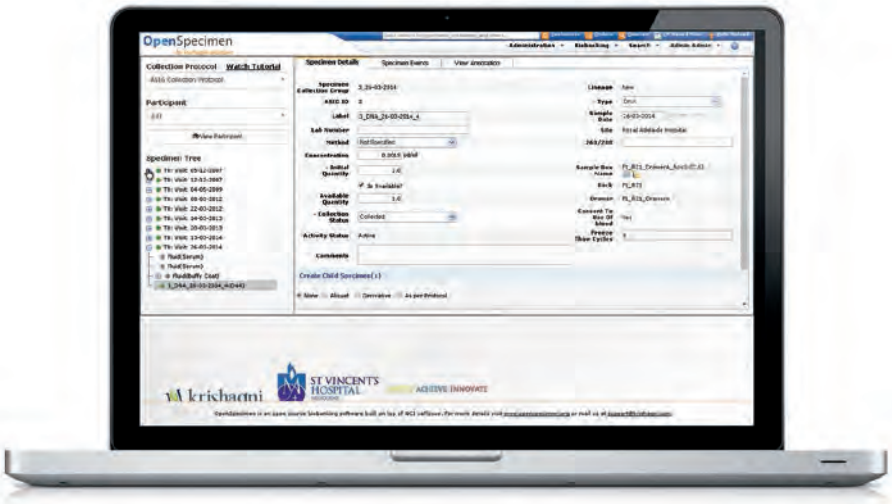
Measuring CXCL4 as a biomarker in the Australian systemic sclerosis cohort
Peter Youssef, Stephen Adelstein, MaiAnh Nguyen

Molla Huq

It is our great pleasure to announce the appointment of our new ASIG Research Biostatistician. Mr Molla Huq, who joins us from Monash University, has more than seven years of work experience in public health and preventive medicine and three years as an Econometrician and Health Economist. He has a BSc (Hons) and Masters in Applied Statistics and is in the final stages of finishing his PhD in Biostatistics (Monash). He is also working as a Lecturer of Biostatistics at Monash University (part time) as well as working for ASIG. His research interest includes risk prediction modelling, model validation, systematic review, cost-effectiveness analysis, etc. Currently he is working on the SSc-DI development and its validation for the ASIG database.

launch.

conferences.



The ASIG Open Specimen

We are excited to announce the release of our very own ASIG Open Specimen (previously known as caTissue).

Open Specimen is a powerful software package that is capable of tracking the samples, generously contributed by the participants of the Australian Scleroderma Screening Program. In particular these samples are buffy coat, sera and DNA. By tracking, we mean Open Specimen can efficiently retrieve any type of information about a single tube at any point in time; eg. quantity left, quality, whether it has travelled to other laboratories and so on.

Open Specimen is a National Cancer Institute (NCI in the US) initiative, which is primarily used to manage complicated cancer biobanks. With the help of Krishagni Institute and Dr Susan Lester who kindly established the ASIG biobank, we were able to adapt the Open Specimen to our own sample storage.

At the moment we store all this information in an Access database. Albeit being very efficient in its early days, it is now showing signs of difficulty coping with the fast-growing number of samples (we have about 10,000 tubes in our freezers!) and bigger demands for the use of these samples as our interesting research grows.

Open Specimen is linked to the ASIG database and is updated overnight. St Vincent's IT has kindly agreed to host Open Specimen whilst continually supporting the ASIG DB. As such, Open Specimen can only be accessed through the citrix token.

Ultimately, Open Specimen will save us a lot of time and will help us to more efficiently manage our precious samples.

What does this mean for doctors and nurses? Open Specimen can be used as a tool to find out whether a patient has good quality DNA and enough sera so that they can make a decision on whether to collect more research blood at a particular visit. You have to know the ASIG ID of your patient in order to search for their samples in Open Specimen. There are no names or UR numbers stored in the database. If you create a new patient number in the ASIG database this will only be active in Open Specimen the next day and a record will appear once samples have been collected and processed.

What does this mean for researchers? Researchers can now perform simple searches in the database without asking for Dr Lester to search for available samples. However, you need to define your selection criteria first so that eligible patients can be selected from the ASIG database.

Where to from here? For centres that collect blood, you should be able to see an icon in your remote access page that says Open Specimen. Your username and password should be the same as your ASIG DB username and password.

Mark your calendar

Members are reminded of the following scientific meetings:

EULAR Annual European Congress of Rheumatology
10th to 13th of June, 2015, Rome, Italy

2015 American College of Rheumatology Annual Meeting
6th to 11th of November, 2015

ACR/ARHP 79th Annual Scientific Meeting 2015
San Francisco, CA, United States

14th International workshop on Scleroderma Research
1st to 5th of August, 2015
St. John's College, Cambridge, UK

4th Systemic Sclerosis World Congress
18th to 20th of February, 2016, Lisbon, Portugal

Abstracts accepted for the Australian Rheumatology Association Annual Scientific Meeting, Adelaide May 2015:

Podium

The Association of hypocomplementemia with disease activity in systemic sclerosis
Esposito J, Stevens W, Rabusa C, Sahhar J, Walker J, Thakkar V, Major G, Roddy J, Zochling J, Proudman S, Nikpour M

Posters

Mycophenolate mofetil in the treatment of scleroderma-associated diffuse skin disease: Results from the Australian Scleroderma Cohort Study
Rajadurai A, Ngian GS, Elford K, Stevens W, Proudman SM, Roddy J, Nikpour M, Youssef P, Hill C, Sahhar J

Changes in rheumatologists' screening practices for pulmonary arterial hypertension and interstitial lung disease.
Proudman SM, Nikpour M, Stevens W

Measures of disease status in systemic sclerosis: Systematic review
Tay T, Ferdowsi N, Stevens W, Hudson M, Baron M, Rabusa C, Prior D, Proudman S, Nikpour M

Validation of the 2013 ACR/EULAR classification criteria for systemic sclerosis in Australian patients
Murthy S, Lester S, Limaye V, Goldblatt F, McWilliams L, Nikpour M, Stevens W, Zochling J, Proudman S

Development of a disease damage index in systemic sclerosis: survey of experts and item reduction using Rasch modelling
Ferdowsi N, Tay T, Baron M, Stevens W, Hudson M, Sundararajan V, Mancuso S, Burchell J, Rabusa C, Prior D, Proudman S, Nikpour M

Differential pattern of microRNA expression in Limited and Diffuse Cutaneous variants of Systemic Sclerosis - A possible mechanism to explain the unique clinical phenotypes.
Hissaria P, Bert A, Proudman S, Goodall G, Khew-Goodall

Dr Janet Roddy

Dr Krista Makin

Fiona Stanley Hospital

I am very pleased to have the opportunity to contribute to this issue of the newsletter, as this has been a time of great change for health care in Western Australia. Many of you will know the Royal Perth Hospital (RPH) WA scleroderma clinic has been relocated to the new Fiona Stanley Hospital (FSH) and is now held on a Wednesday morning. This change has resulted in some confusion, but all patients who have been seen at RPH will continue to be seen at FSH.

As FSH is a new site, there has been some delay in obtaining ethics approval for the Australian Scleroderma Interest Group (ASIG) database at this site. This is now in place, so we are able to contribute patient data to the Australia Scleroderma Cohort Study (ASCS) from FSH. I am grateful to all those who have expressed a willingness to continue to contribute their data to the database.

The FSH scleroderma clinic welcomes any new scleroderma patients. All that is required is a referral from your GP or rheumatologist. I am pleased to say respiratory physician Dr Melanie Lavender continues to bring her expertise in cardiorespiratory disease to help with the care of scleroderma patients seen in our clinic.

Our new rheumatology trainee, Dr Lauren Host has a special interest in scleroderma and is using the WA database to look at better ways of assessing the progression of scleroderma. Many of you will now have met Dr Krista Makin, who has been working in the clinic with me. Helen Marsden, our clinic nurse, is due to return to the scleroderma clinic shortly, after a well deserved holiday.

The data collected through ASCS, combined with the hard work of many members of ASIG, has resulted in publications, many of which have received international attention and raised the profile of scleroderma in Australia. As a result, WA, along with other sites in Australia, has been selected to participate in randomised controlled treatment studies, which may result in new treatment options.

Overall, the future holds promise for WA scleroderma patients, with a new facility, improved understanding of the disease and the opportunity to participate in clinical trials.

Katie Morrisroe

We are delighted to welcome our new ASIG-Scleroderma Australia research fellow, Dr. Katie Morrisroe. She is in her third and final year of advanced training in rheumatology at St Vincent's Hospital Melbourne. Her training has been shared between the Royal Melbourne Hospital and St Vincent's Hospital Melbourne. She will be working alongside Dr Wendy Stevens as a clinician in the scleroderma specialist clinic once a week. Clinical research will form the foundations of her PhD which will be supervised by Dr Mandy Nikpour. Her research will focus on quantifying the burden of disease of systemic sclerosis to the Australian community and affected individuals through data linkage with key hospital and ambulatory care data and the Australian cancer database. The true 'burden' of scleroderma in Australia remains unquantified, including its health service utilisation and impact on physical function, health-related quality of life, employment and work ability. This research is particularly exciting as it a novel project in Australia, allowing interstate collaboration between scleroderma experts and is of particular relevance to patients living with systemic sclerosis. The study will inform allocation of resources, with the ultimate goal of improving patient outcomes and reducing the financial and human costs of this disease.

Validation of the 2013 ACR/EULAR classification criteria for SSc in the Australian population

Dr Suman Murthy, Rheumatology Registrar,
Repatriation General Hospital, Daw Park, South Australia

Systemic sclerosis (SSc) is a heterogeneous multi-organ disease of obscure etiology that causes significant morbidity and mortality. The clinical manifestations and prognosis of SSc are highly variable, particularly in the early stages and hence it has been challenging to develop and validate classification criteria which are sufficiently sensitive but still able to distinguish SSc from other autoimmune diseases with similar clinical features. The 1980 ACR classification criteria lack sensitivity especially for patients with early and limited disease. To tackle this issue, in 2013, a joint ACR and EULAR committee was established to develop a new set of classification criteria for SSc that has improved sensitivity and specificity compared to 1980 criteria.

Recently, we sought to validate 2013 criteria in a large Australian cohort with SSc and controls with a range of autoimmune diseases. The sensitivity and specificity of the new criteria were determined in patients with SSc (1318) and mixed connective tissue disease (MCTD) (69) from the Australian Scleroderma Cohort Study (ASCS), patients with idiopathic Raynaud's phenomenon (RP) (105) from the Menzies Institute and SLE (16) and idiopathic inflammatory myopathy (IIM) (26) from the Royal Adelaide Hospital.

A higher proportion of SSc patients fulfilled the new SSc criteria compared to the ACR criteria (Table 1). This difference was attributed to an increased positive rate in limited SSc patients. Specificities for the differentiation of SSc from SLE/Myositis were high for both criteria. However, specificities were lower for differentiation of SSc from either RP or MCTD, with the ACR criteria being superior.

Lower specificity for SSc from MCTD compared with published results may be due to a selection bias in the ASCS towards MCTD patients with more "SSc-like" disease.

Table 1: Sensitivity and Specificity of 2013 and 1980 ACR criteria

	SSc *vs* MCTD		
Measure	New Criteria	ACR Criteria	p-value
Sensitivity	0.96 (0.95, 0.97)	0.85 (0.83, 0.87)	< 0.001
Specificity	0.23 (0.13, 0.33)	0.41 (0.29, 0.52)	0.004
	SSc *vs* SLE/Myositis		
Measure	New Criteria	ACR Criteria	p-value
Sensitivity	0.96 (0.95, 0.97)	0.85 (0.83, 0.87)	< 0.001
Specificity	0.90 (0.82, 0.99)	0.95 (0.90, 1.00)	0.50
	SSc *vs* Raynauds		
Measure	New Criteria	ACR Criteria	p-value
Sensitivity	0.96 (0.95, 0.97)	0.85 (0.83, 0.87)	< 0.001
Specificity	0.76 (0.68, 0.84)	0.88 (0.81, 0.94)	< 0.001

Recent ASIG Research Publications

Morrisoe KB, Nikpour M, Proudman SM. **Musculoskeletal Manifestations of Systemic Sclerosis. Invited review.** *Clinics in Rheum Dis* (in press)

Thakkar V, Nikpour M, Stevens W, Proudman SM. **Prospects for improved screening and outcomes for patients with scleroderma-related pulmonary hypertension. Invited review.** *Intern Med J* (in press)

Moore O, Proudman SM, Goh N, Corte T, Rouse H, Hennessy O, Morrisroe K, Thakkar V, Sahhar J, Roddy J, Gabbay E, Youssef P, Nash N, Zochling J, Stevens W, Nikpour M. **Quantifying Change in Pulmonary Function as a Prognostic Marker in Systemic Sclerosis-Related Interstitial Lung Disease.** *Clin Exp Rheumatol* (in press)

Hao Y, Thakkar V, Stevens W, Morrisroe K, Prior D, Rabusa C, Youssef P, Gabbay E, Roddy J, Walker JG, Zochling J, Sahhar J, Nash N, Lester S, Rischmueller M, Proudman SM, Nikpour M. **A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis.** *Arthritis Res Ther.* 2015;17(1):7.

Osthoff M, Ngian G-S, Dean M, Nikpour M, Stevens W, Proudman S, Eisen D, Sahhar J. **The Lectin Pathway of Complement - a Potential Role in the Pathogenesis and Disease Manifestations of Systemic Sclerosis.** *Arthritis Rheum* 2015;66:S751-S751.

Zochling J, Newell F, Charlesworth JC, Leo P, Stankovich J, Cortes A, Zhou Y, Stevens W, Sahhar J, Roddy J, Nash P, Tymms K, Rischmueller M, Lester S, Proudman S, Brown MA. **An Immunochip based interrogation of scleroderma susceptibility variants identifies a novel association at DNASE1L3**. *Arthritis Res Ther.* 2014;16:438.

Vacca A, Meune C, Gordon J, Chung L, Proudman S, Assassi S, Nikpour M, Rodriguez-Reyna TS, Khanna D, Lafyatis R, Matucci-Cerinic M, Distler O, Allanore Y; on behalf of the Scleroderma Clinical Trial Consortium (SCTC) Cardiac Subcommittee. **Cardiac arrhythmias and conduction defects in systemic sclerosis.** *Rheumatol* (Oxford). 2014;53(7):1172-7.

Morrisroe KB, Stevens W, Nandurkar H, Prior D, Thakkar V, Roddy J, Zochling J, Sahhar J, Tymms K, Sturgess A, Major G, Kermeen F, Hill C, Walker J, Nash P, Gabbay E, Youssef P, Proudman S, Nikpour M. **The association of antiphospholipid antibodies with cardiopulmonary manifestations of systemic sclerosis.** *Clin Exp Rheumatol* 2014;32(6):S133-S137 .

Ngian GS, Sahhar J, Proudman SM, , Wicks IP, Van Doornum S. **Arterial stiffness is increased in systemic sclerosis: a cross-sectional comparison with matched controls.** *Clin Exp Rheumatol* 2014;32:S-161-6.

Collaborative study of outcomes in Australian, Canadian and Spanish Scleroderma Patients

Dr Jenny Hao, Peking University First Hospital, Beijing, China

Systemic sclerosis (SSc) is one of the most common type of connective tissue diseases in Caucasian and remains the highest case-based mortality. A number of mortality studies in patients with SSc have been reported since 1970s. However, most reports were based on 'prevalent' cohorts where no limits were placed on disease duration at study entry, survival may be underestimated as patients with more severe disease may die before being recruited. 'Incident' cohorts wherein patients are recruited soon after disease onset, may overcome this potential source of bias. Recently, we combined the data from three national Scleroderma cohorts (Australian Scleroderma Cohort Study, Canadian Scleroderma Research Group and Spanish national scleroderma group) in order to quantify mortality in patients with SSc and to compare patients with prevalent and incident disease.

We quantified mortality as Standardised Mortality Ratio (SMR) and Years of Life Lost (YLL), and percentage survival in the first decade of disease in a) the whole combined 'prevalent' cohort and b) in a subset of patients recruited within 4 years of disease onset (the combined 'incident' cohort).

Our results showed that in the whole combined prevalent cohort of 3218 patients, 55.5% of the primary causes of 440 deaths recorded were SSc related; the most common cause of SSc-related death was heart-lung disease. Malignancy, atherosclerotic disease and sepsis were the most common non-SSc related causes. Male sex, older age at disease onset, diffuse subtype and presence of PAH and ILD were identified to be independent predictors of mortality. The SMR and YLL were higher in the Australian and Canadian incident cohorts compared with the respective prevalent cohorts. The pooled SMR for the three incident cohorts was also higher than the three prevalent cohorts (4.148 versus 3.418). The survival was lower in the combined incident cohort than the prevalent cohort, particularly in male and diffuse disease.

> "...prevalent cohorts underestimate mortality in SSc by failing to capture early deaths, particularly in male and diffuse disease. These findings provide a compelling rationale for establishing a large multi-national inception cohort of patients with SSc to more accurately quantify early mortality in this disease."

In conclusion, prevalent cohorts underestimate mortality in SSc by failing to capture early deaths, particularly in male and diffuse disease. These findings provide a compelling rationale for establishing a large multi-national inception cohort of patients with SSc to more accurately quantify early mortality in this disease.

Table 1: Measures of mortality (SMR,YLL and survival) in each of the Australian, Canadian and Spanish prevalent and incident cohorts.

	Australian Patients 01/2007-12/2012		Canadian Patients 01/2005-12/2012		Spanish Patients 01/2000-12/2012	
	'Prevalent' cohort n=1252	'Incident' cohort n=339	'Prevalent' cohort n=1325	'Incident' cohort n=420	'Prevalent' cohort n=342	'Incident' cohort n=183
Number of deaths	110	27	182	58	58	30
SMR(95%CI)						
Women	2.6(2.1–3.1)	2.4(1.2–3.5)	3.4 (2.9–4.0)	4.4 (3.1–5.7)	3.8(2.7–4.9)	2.8(1.7–3.9)
Men	4.2(2.4–5.9)	9.1(3.7–14.5)	5.9 (4.1–7.8)	8.6 (4.4–12.9)	7.9(3.0–12.8)	9.3(1.9–16.8)
Overall	2.8(2.4–3.3)	3.4(2.3–4.5)	3.8 (3.3–4.2)	5.1 (4.0–6.2)	4.2 (3.3–5.0)	3.2(2.3–4.2)
YLL (years)						
Women	11.9	11.3	19.4	22.4	20.9	15.2
Men	17.2	25.8	16.7	19.2	23.9	26.0
% survival in the first decade of disease						
Women	97%	87%	96%	85%	88%	80%
Men	88%	74%	88%	65%	75%	50%
Overall	95%	84%	94%	80%	86%	77%

Further information about ASIG can be found at:
http://rheumatology.org.au/rheumatologists/asig-public.asp

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