ASIG

AUSTRALIAN SCLERODERMA INTEREST GROUP

SCLERODERMA connections.

EDITION 9: APRIL 2016

greetings,

Welcome to the 2016 edition of Scleroderma Connections. The ASIG centres around Australia continue to actively screen patients with scleroderma, often referred by other rheumatologists, for the heart and lung complications of this disease. Various research projects ranging from studies of risk factors for pulmonary hypertension to work ability in scleroderma continue, with presentations at international conferences and publications featuring ASIG research.

Although improvements in therapy and care for patients with scleroderma cannot come fast enough, it is an exciting time in scleroderma research with the prospect of effective therapies on the horizon, arising from the efforts of both clinician-researchers and pharmaceutical companies.

In this issue, we hope you enjoy reading Dr Mandy Nikpour's piece about how ASIG research is leading to tangible benefits for Australian patients with scleroderma, and twin articles from two of our ASIG Fellows, Katie Morrirsoe and Nava Ferdowsi concerning their work on understanding the burden of disease through linkage with large datasets and the Damage Index. In this issue, we welcome the new ASIG project Officer, Michelle Wilson, who comes to us with a broad range of skills in epidemiology and project management.

Susanna

Susanna Proudman
ASIG Chair

Recent ASIG Research Publications

The role of asymmetric dimethylarginine alone and in combination with N-terminal pro-B-type natriuretic peptide as a screening biomarker for systemic sclerosis-related pulmonary arterial hypertension: a case control study. Thakkar V, Stevens W, Prior D, Rabusa C, Sahhar J, Walker JG, Roddy J, Lester S, Rischmueller M, Zochling J, Nash P, Gabbay E, Youssef P, Proudman SM, Nikpour M. *(in press Clin and Exp Rheum)*

Mycophenolate mofetil is an effective and safe option for the management of systemic sclerosis –associated interstitial lung disease: results from the Australian Scleroderma Cohort Study. Owen C, Ngian G-S, Moore O, Stevens W, Nikpour M, Rabusa C, Proudman S, Roddy J, Zochling J, Hill C, Sturgess A, Tymms K, Youssef P, Sahhar J. *(in press Clin and Exp Rheum)*

Systemic sclerosis: has the time come for structured care? Morrisroe K, Frech T, Schniering J, Maurer B, Nikpour M. *Best Practice & Research Clinical Rheumatology* April 2016.

Monospecific anti-Ro52/TRIM21 antibodies in a tri-nation cohort of 1574 systemic sclerosis subjects: evidence of an association with interstitial lung disease and worse survival. Wodkowski M, Hudson M, Proudman S, Walker J, Stevens W, Nikpour M, Assassi S, Mayes MD7, Wang M, Baron M, Fritzler MJ; Canadian Scleroderma Research Group (CSRG); Australian Scleroderma Cohort Study (ASCS); Genetics versus Environment in Scleroderma Outcome Study (GENISOS). *Autoimmunity.* 2015;48:542-51.

Clinical correlates of monospecific anti-PM75 and anti-PM100 antibodies in a tri-nation cohort of 1574 systemic sclerosis subjects. Wodkowski M, Hudson M1, Proudman S, Walker J, Stevens W, Nikpour M, Assassi S, Mayes MD, Tatibouet S, Wang M; Canadian Scleroderma Research Group (CSRG); Australian Scleroderma Interest Group (ASIG), Genetics versus Environment in Scleroderma Outcome Study (GENISOS), Baron M, Fritzler MJ. *Clin Exp Rheumatol.* 2015;33(4 Suppl 91):S131-5.

Cost Savings with a New Screening Algorithm for Pulmonary Arterial Hypertension in Systemic Sclerosis. Quinlivan A, Thakkar V, Stevens W, Morrisroe K, Prior D, Rabusa C, Youssef P, Gabbay E, Roddy J, Walker JG, Zochling J, Sahhar J, Nash P, Lester S, Rischmueller M, Proudman SM, and Nikpour M. *Intern Med J.* 2015;45:1134-40.

A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis. Hao Y, Thakkar V, Stevens W, Morrisroe K, Prior D, Rabusa C, Youssef P, Gabbay E, Roddy J, Walker J, Zochling J, Sahhar J, Nash P, Lester S, Rischmueller M, Proudman SM, Nikpour M. *Arthritis Res Ther.* 2015 Jan 18;17:7

Interpretation of an Extended Autoantibody Profile in a Well-Characterized Australian Systemic Sclerosis (Scleroderma) Cohort Using Principal Components Analysis. Patterson KA, Roberts-Thomson PJ, Lester S, Tan JA, Hakendorf P, Rischmueller M, Zochling J, Sahhar J, Nash P, Roddy J, Hill C, Nikpour M, Stevens W, Proudman SM, Walker JG. *Arthritis Rheumatol.* 2015;67:3234-44.

This paper has attracted considerable interest:

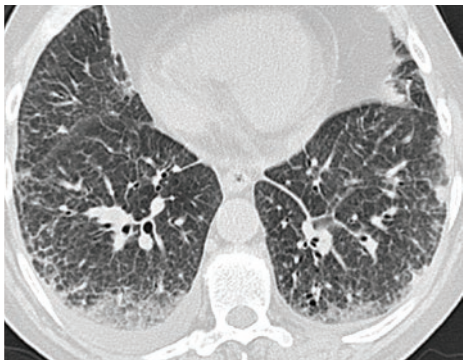
- Editorial Comment: Ligon CB, Wigley FM. Editorial: Scleroderma: Bringing a Disease From Black-and-White Into Technicolor. *Arthritis Rheumatol.* 2015 Dec;67(12):3101-3.
- Award for Best Research Higher Degree Student Publication 2015 (Flinders University)
- ABC news Report Sunday 6 March 2016 South Australia: http://www.abc.net.au/news/2016-03-06/phd-student-unearths-scleroderma-clusters/7222216

World Systemic Sclerosis Congress — Lisbon Portugal

What's new? New treatment options for sclerodema

The World Systemic Sclerosis Congress was held in Lisbon Portugal in February 2016. Experts from around the world joined together for three days to hear about the latest updates in systemic sclerosis research and treatment and to present their research findings.

It is reassuring to know that there is a lot of research going on in systemic sclerosis with over 400 posters being displayed in the poster hall and three days worth of back-to-back lectures.



New trials in systemic sclerosis that were presented include the *Scleroderma Lung Study II* which looked at treating interstitial lung disease with cyclophosphamide for one year or mycophenolate mofetil for two years. Both groups of patients were followed for two years. At the end of the two-year trial, both treatment groups had an improvement in their lung function, which was measured by respiratory function tests and an improvement in their symptoms of breathlessness. In addition, there was a slight improvement in patients' skin scores which measure skin thickness. This is an important study, which may change medical practice in Australia with more patients with interstitial lung disease being treated initially with mycophenolate mofetil.

Another study that was presented was the *AMBITION trial*, which looked at systemic sclerosis patients with pulmonary arterial hypertension, treated initially with two specific pulmonary arterial hypertension drugs (combination therapy) rather than one (monotherapy). In Australia, the government only funds treatment with one specific pulmonary arterial hypertension drug, with combination therapy being accessible from some hospitals, drug companies or patient funded. This trial demonstrated that patients treated initially with combination therapy had an improved survival compared with those patients on monotherapy. This trial may pave the way for more than one drug to be funded upfront to enable access to all patients.

Tocilizumab is an immunosuppressive drug used primarily for the treatment of rheumatoid arthritis. It inhibits the function of interleukin-6, which plays an important role in inflammation, and the development of systemic sclerosis. In early phase studies, tocilizumab was compared with placebo in a group of 48 patients with active diffuse systemic sclerosis of less than 5 years' duration and elevated inflammatory markers on blood testing. Over two years, outcomes such as skin thickness, lung function tests and patient reported quality of life were measured with tocilizumab showing promise. Even though no statistical difference was shown, the patients receiving tocilizumab had a greater improvement skin thickness scores compared with patients receiving placebo, had a better quality of life and showed a trend towards an improvement in lung function. The use of tocilizumab was also shown to be safe in systemic sclerosis patients.

This study is suggestive of possible benefit in systemic sclerosis and supports the further evaluation of tocilizumab in the treatment of scleroderma in the near future.

Drs Nava Ferdowsi and Katie Morrisroe
Scleroderma Australia ASIG, St Vincent's Hospital Melbourne

Pulmonary Hypertension Society ANZ – Sydney, October 2015

Podium

Predictors of pulmonary arterial hypertension in Australian scleroderma patients: results from a large multicentre cohort study
Morrisroe K, Huq M, Rabusa C, Sahhar J, Zochling J, Roddy J, Strickland G, Thakkar V, Proudman S, Stevens S, Nikpour M.

American College of Rheumatology ASM – San Francisco, November 2015

Posters

Development of a Disease Damage Index in Systemic Sclerosis: survey of experts, item reduction and item weighting using consensus and data driven methods.
Ferdowsi N, Huq M, Burchell JL, Mancuso S, Tay T, Stevens W, Rabusa C, Hudson M, Sundararajan V, Prior D, Proudman S, Baron M, Nikpour M. Arthritis Rheumatol. 2015; 67 (suppl 10).

Health-Related Quality of Life in Early Systemic Sclerosis.
Hudson M, Baron M, Wang M, Canadian Scleroderma Research Group, Australian Scleroderma Cohort Study, Proudman S, Nikpour M, Rabusa C, Stevens W. Arthritis Rheumatol. 2015; 67 (suppl 10).

World Systemic Sclerosis Congress – Portugal, February 2016

Podium

Determinants of unemployment amongst Australian Scleroderma patients: results from large multicentre cohort study[2].
Morrisroe K, Huq M, Rabusa C, Zochling J, Sahhar J, Roddy J, Strickland G, Thakkar V, Proudman S, Stevens W, Nikpour M.

Development of a disease damage index in systemic sclerosis using consensus and data driven methods[1].
Ferdowsi N, Huq M, Burchell J, Mancuso S, Tay T, Stevens W, Rabusa C, Hudson M, Sundararajan V, Prior D, Proudman S, Baron M, Nikpour M.

Posters

Survival in scleroderma pulmonary arterial hypertension in the modern treatment era: results from large multicentre cohort study[1].
Morrisroe K, Huq M, Rabusa C, Zochling J, Sahhar J, Roddy J, Proudman S, Stevens W, Nikpour M.

Risk factors for the development of pulmonary arterial hypertension in Australian scleroderma patients: results from a large multicentre cohort study[2].
Morrisroe K, Huq M, Rabusa C, Sahhar J, Zochling J, Roddy J, Strickland G, Thakkar V, Proudman S, Stevens W, Nikpour M.

Also accepted for podium[1] or poster[2] presentation at the Australian Rheumatology Association Annual Scientific Meeting, Darwin May 2016

research fellowship.

Call for expressions of interest ASIG-Scleroderma Australia Research Fellow 2017

Expressions of interest are sought from MBBS graduates with an interest in research in systemic sclerosis (SSc).

The Australian Scleroderma Cohort Study is a valuable resource for a range of research projects, often with a strong clinical focus. Currently ASIG is undertaking studies in interstitial lung disease and pulmonary hypertension and developing disease-specific and organ-specific outcome measures.

Expressions of interest for this fellowship are invited from physicians and advance trainees.

Eligibility:

- Australian resident who will be residing in Melbourne for the duration of the fellowship
- Enrolled or planning to enrol in a fulltime graduate research degree, preferably a PhD.
- Apply for a scholarship through sources such as RACP, Arthritis Australia and NHMRC (with ASIG's assistance)

The successful candidate would commence in February 2017 and receive supervision and support from experienced clinicians and researchers.

Queries should be addressed to:

Dr Mandy Nikpour:
m.nikpour@unimelb.edu.au

Or Chair of ASIG, Susanna Proudman:
sproudman@internode.on.net

Or Secretary of ASIG, Wendy Stevens:
wendy@svhrheum.com

Submissions should include a cover letter outlining why you want this Fellowship and a CV and be emailed to: michelle.e.wilson@svha.org.au

new project officer.

Michelle Wilson

We are pleased to introduce Dr. Michelle Wilson who will be our ASIG Project Officer while Candice Rabusa is away on maternity leave. Michelle completed her Science degree majoring in Physiology in New Zealand before moving to Australia to do an honours year and her PhD in reproductive biology at The University of Melbourne. She has since spent the past three years teaching at The University of Melbourne and working as an environmental consultant. Through her work in both research and consulting she has developed expertise in data management and project administration. Her research interests include epidemiology and the development of non-invasive monitoring techniques. In her spare time, she enjoys horse riding, scuba diving, cycling and hiking.

Research Award

Fc gamma receptor IIIB gene copy number variation in systemic sclerosis.
Nguyen L, Lester S, Proudman S, Hill C, Rischmueller M and Australian Scleroderma Interest Group (ASIG) study investigators.

Oral presentation at the SA Branch of the Rheumatology Association's annual meeting 23rd October 2015. Won the Philip Alpers Award for the Best Scientific Presentation.

Mark your calendar

Members are reminded of the following scientific meetings:

EULAR Annual European Congress of Rheumatology
8th to 11th June, 2016, London, UK

2015 American College of Rheumatology/ Association of Rheumatology Health Professionals Annual Meeting
11th to 16th November, 2016, Washington DC, USA

ASIG Research: tangible benefits for patients

Dr Mandana (Mandy) Nikpour, NHMRC Research Fellow, The University of Melbourne
Rheumatologist, St. Vincent's Hospital Melbourne

Since its inception in 2007, the prime research objective of the Australian Scleroderma Interest Group (ASIG) has been to undertake studies of risk and prognostic factors for important outcomes in scleroderma. Risk factors are disease features that confer a greater likelihood of developing a certain complication, while prognostic factors are variables that affect the course of disease. 'Important outcomes' are those that matter to patients and their doctors, for example quality of life, physical function, the ability to work, and life expectancy. By focusing on important outcomes, ASIG research leads to near-term benefits to patients. Below are some examples of how ASIG research over the past seven years has resulted in, or holds prospects for improved outcomes for patients.

One in ten patients with scleroderma develops pulmonary arterial hypertension (PAH), a condition of increased resistance to blood flow in the lungs that places strain on the heart and in so doing, reduces life expectancy. ASIG has developed a new algorithm to screen scleroderma patients for the earliest signs of developing PAH. This algorithm combines a blood test for the level of a biomarker named NT-proBNP, which goes up with heart strain, and lung function tests, which measure lung volumes and the capacity for transfer of gases across alveolar membranes. This new algorithm is simpler, more accessible, equally accurate and more cost-effective than its counterparts, and allows early detection and initiation of life-saving treatment in PAH. ASIG is now pursuing the listing of NT-proBNP blood level testing on the medical benefits scheme for reimbursed use in this setting.

> "This new algorithm is simpler, more accessible, equally accurate and more cost-effective than its counterparts, and allows early detection and initiation of life-saving treatment in PAH."

With project grant support from the National Health and Medical Research Council of Australia (NHMRC), several ASIG investigators are now undertaking a multi-centre clinical trial (the SPHInX study) to evaluate the role of blood thinning treatment with the drug apixaban as add-on therapy for reducing rates of clinical worsening and prolonging survival in scleroderma PAH.

Interstitial lung disease (ILD) is also a major cause of disability and reduced life expectancy in scleroderma. However, not all patients with ILD have the type which progresses to cause breathing problems. ASIG research has shown that those who have greater than 20% of their lungs affected on high-resolution CT scanning and those in whom there is a 10% or more decline in lung volumes and gas transfer in the early stages of disease, are those that require more aggressive therapy early on to save lung function.

ASIG research has also enabled identification of important 'auto-antibodies' measured in patients' blood that are associated with higher risk of certain organ complications. For example, anti-RNA polymerase antibodies are found in 15% of Australian patients and one in 4 of these patients develops kidney crisis. Therefore, patients with these antibodies need careful monitoring of blood pressure and kidney function.

These are only a few examples of discoveries made by ASIG researchers that are intended to improve outcomes that matter to patients. These discoveries are made possible through an Australia-wide interdisciplinary collaboration of like-minded physician-researchers from the specialties of rheumatology, cardiology and pulmonary medicine, and through the participation of scleroderma patients in research projects. By working toward a common goal of improving outcomes in scleroderma, we can ensure a brighter future for those affected by scleroderma.

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:

Early Mortality in Australian, Canadian and Spanish Scleroderma Patients: a comparison of survival and causes of death in incident and prevalent systemic sclerosis cohorts. Hao Y, Hudson M, Baron M, Carreira P, Stevens S, Rabusa C, Tatibouet S, Carmona L, Joven B, Huq M, Proudman S, Nikpour M,

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.

A multi-centre randomised placebo-controlled trial of oral anticoagulation with apixaban in systemic sclerosis-related pulmonary arterial hypertension: the SPHInX study protocol. Calderone A, Stevens W, Prior D, Nandurkar H, Gabbay E, Proudman SM, Williams T, Celermajer D, Sahhar J, Rischmueller M, Won P, Thakkar V, Dwyer N, Wrobel J, Chin W, Staples M, Buchbinder R and Nikpour M.

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

Genetics of Scleroderma. Matt Brown and Katie Cremin

The utility of biomarkers of interstitial lung disease in systemic sclerosis. Peter Youssef, Jo Sahhar, Stephen Adelstein, MaiAnh Nguyen

Predicting fibrosis progression in Scleroderma. Jacob George, Nick Manolios, Eslam Mohammed

The clinical relevance of ANCA in systemic sclerosis. Mandy Nikpour, Jayne Moxey

FCGR3B Genetic Copy Number Variation in Systemic Sclerosis. Susan Lester, Leanne Nguyen

Anti-Fibrillarin Autoantibodies in Systemic Sclerosis. Jenny Walker, Shervin Assasi, Carolina Mejia Otero

Validation of modified Rodnan skin score, a measure of skin thickness, as an enrichment criterion for clinical trials in systemic sclerosis. Susanna Proudman, Wendy Stevens, Mandy Nikpour, Dinesh Khanna

Assessing the burden of Scleroderma

Assessing the burden of Scleroderma through data linkage

Dr Katie Morrisroe,Scleroderma Australia ASIG
St Vincent's Hospital Melbourne

Australia has one of the highest frequencies of systemic sclerosis (scleroderma). Scleroderma is a chronic incurable autoimmune disease that can affect multiple organ systems including skin, joints, blood vessels causing Raynaud's phenomenon and digital ulceration, gastrointestinal tract, kidneys, heart and lungs.

We currently have no cure for scleroderma and the scleroderma community is working hard to discover effective treatments. Given the many different clinical features, which occur over time, scleroderma has the potential to damage multiple organ systems causing signification burden to the patients with scleroderma, their caregivers and the community.

The true 'burden' of scleroderma in Australia remains unquantified, including hospital use, impact on physical function, employment, and quality of life (QoL). We are currently trying to quantify the healthcare burden by means of a nationwide 'data linkage' project. We will combine the Australia Scleroderma Cohort Study (ASCS) database with a number of key institutional databases to determine healthcare use. This data linkage project will ensure the privacy of all information is maintained at every step. Participants are free to withdraw from the study at any time.

This linkage project has been under planning for the last 16 months. We have almost received ethical approval from all sites involved and we hope to have some results to share with you by the beginning of 2017.

Assessing the burden of Scleroderma through measurement of damage: the Systemic Sclerosis Damage Index

Dr Nava Ferdowsi, Scleroderma Australia ASIG
St Vincent's Hospital Melbourne

For the last 2 years, ASIG has been working towards developing a research tool designed to measure organ damage in scleroderma patients. A potential use of such a tool includes measurement of overall damage in a scleroderma patients participating in a clinical drug trial. No such tool currently exists, and we are in the final stages of its development.

The Systemic Sclerosis Damage Index (SSc DI) has been developed through the combined efforts of scleroderma experts internationally, specialists outside of rheumatology such as cardiology and gastroenterology and scleroderma patients. The use of data from the Australian Scleroderma Cohort Study has been vital with the final SSc DI containing 22 items from 6 organ systems.

Initially, through review of already existing scleroderma research, an initial 83 items were presented in survey form to over 300 scleroderma experts internationally. They were asked to rate each item on how appropriate they felt they were for inclusion in a damage index, with items such as interstitial lung disease and scleroderma renal crisis represented. Items rated highly by the experts and shown to be reflective of mortality and morbidity using statistical analysis were retained in the final product.

We are very excited that the SSc DI is almost finalised and has come about from an international collaboration between ASIG and the Canadian Scleroderma Research Group. The index was also presented at the recent Systemic Sclerosis World Congress held in Lisbon and was received with very positive feedback.

Journal of Scleroderma and Related Disorders (JSRD)

JSRD is an international, multi-disciplinary, peer-reviewed publication targeted to scientists and clinicians interested in systemic sclerosis, scleroderma, and other related autoimmune and fibrotic diseases. The journal publishes high quality, original research articles on the epidemiology, natural history, pathophysiology, diagnosis, treatment and outcome of these diseases as well as reviews and thought-provoking editorials and commentaries, with the aim of becoming the leading worldwide reference journal in the field of scleroderma and related diseases. It is the official journal of the World Scleroderma Foundation and the European Scleroderma Trials and Research Group.

Visit www.sclerodermajournal.com for more information

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

ASIG
AUSTRALIAN SCLERODERMA INTEREST GROUP

contact.

RESEARCH QUERIES

Michelle Wilson, Project Officer
Ph: 03 9231 3986
Email: michelle.e.wilson@svha.org.au

AUSTRALIAN SCLERODERMA SCREENING CENTRES

Western Australia

FIONA STANLEY HOSPITAL
Janet Roddy
Ph: 08 9224 1310

South Australia

ROYAL ADELAIDE
Susanna Proudman
Ph: 08 8222 5190

QUEEN ELIZABETH
Catherine Hill
Ph: 08 8222 6688

Queensland

SUNSHINE COAST RHEUMATOLOGY, MAROOCHYDORE
Peter Nash & Louisa Voight
Ph: 07 5443 1033

GOLD COAST UNIVERSITY HOSPITAL
Julien de Jager
Ph: 07 5687 6501

Australian Capital Territory

CANBERRA RHEUMATOLOGY
Kathie Tymms
Ph: 0437 595 334

Victoria

ST VINCENT'S
Wendy Stevens &
Mandana Nikpour
Ph: 03 9231 3983

MONASH MEDICAL CENTRE
Joanne Sahhar
Ph: 03 9594 3566

BARWON RHEUMATOLOGY SERVICES
Gemma Strickland
Ph: 03 5222 4491

Tasmania

MENZIES RESEARCH INSTITUTE
Jane Zochling

Ph: 03 6226 7776

New South Wales

JOHN HUNTER, NEWCASTLE
Gabor Major &
Glenn Reeves
Ph: 02 4921 3000

ROYAL NORTH SHORE
Rodger Laurent
Ph: 02 9926 7351

ST GEORGE SYDNEY
Allan Sturgess
Ph: 02 9113 2670

ROYAL PRINCE ALFRED
Peter Youssef
Ph: 02 9515 9337

LIVERPOOL HOSPITAL
Vivek Thakkar
Ph: 02 8738 4088

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