OPTIMISING OUTCOMES IN SYSTEMIC SCLEROSIS – COMBATING MORBIDITY AND MORTALITY

CCIB | BARCELONA, SPAIN | 5 – 6 FEBRUARY 2011
Systemic sclerosis (SSc) is a connective tissue disease that is characterised by chronic and recurrent inflammation, vasculopathy and excessive fibrosis. These pathophysiological processes manifest as a diverse range of tissue and organ-specific complications that cause considerable morbidity and mortality. The heterogeneous nature of SSc, combined with its relatively poor prognosis in comparison with other autoimmune diseases, presents physicians with many challenges. Nevertheless, recent years have seen improvements in the diagnosis and treatment of the organ-based pathologies associated with SSc, which have translated into better outcomes for patients.

Early diagnosis is of vital importance to managing SSc as it allows patients to be monitored frequently for development of organ-based complications. The launch of the EULAR 4-year orphan disease programme for SSc has given rise to important research initiatives such as the very early diagnosis of SSc programme, which aims to identify criteria that enable very early diagnosis. Progress has also been made in identifying organ-based complications earlier; for example, screening of SSc patients for pulmonary arterial hypertension (PAH) permits earlier detection of this life-threatening complication. Early diagnosis of SSc promises to benefit patients by allowing prompt therapeutic intervention once complications are found.

Improved understanding of SSc pathogenesis has facilitated research into therapies that target molecular mediators of the underlying pathological processes. With some therapies already on the market, and others holding promise for the future, physicians can expect an increasing number of treatment options. In particular, the armamentarium against SSc has benefited from therapies that target vascular dysfunction, a hallmark of many SSc complications including PAH, scleroderma renal crisis and digital ulceration. The increased number of therapies, combined with the availability of the EULAR treatment recommendations, has undoubtedly improved the outlook for SSc patients.

The 4th International SSc Forum will bring together renowned experts in the field of SSc from across the globe. Participants will receive an in-depth update on recent progress in SSc and challenges that remain for the future. The aim of the meeting is to be as clinically relevant as possible with an emphasis on day-to-day patient management. The “Meet the Professor” sessions and the breakout presentations will allow participants to focus on specific topics of particular interest to their clinical practice. The meeting will also provide an excellent opportunity to exchange ideas and knowledge with other physicians who are involved in caring for SSc patients.

It is with great pleasure that we welcome you to the 4th International SSc Forum, and we look forward to a stimulating and educational meeting.

Prof. Dame Carol Black  Prof. Christopher Denton  Prof. Loïc Guillevin
### SATURDAY | 5 FEBRUARY 2011

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<td><strong>What progress have we made in the classification of SSc?</strong></td>
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<td>Plenary 2: Pulmonary arterial hypertension associated with SSc (PAH-SSc) – Appropriate responses to a devastating disease</td>
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### Parallel breakout sessions: Practical approaches to managing SSc and its manifestations

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### SUNDAY | 6 FEBRUARY 2011

#### 09:00 – 10:45 Plenary 3: The reality of managing SSc – An interactive patient case

**Co-Chairs: A Herrick, J Pope**

- A patient with SSc – Part 1 - D Khanna 38
- Digital ulcers – A huge burden from a small manifestation - L Mouthon
- A patient with SSc – Part 2 - D Khanna
- Dyspnoea – A symptom to look out for - V Steen
- A patient with SSc – Part 3 - D Khanna
- Quality of life – Addressing the patient’s perspective - G Riemekasten

**10:45 – 11:15 Coffee break with poster exhibition**

#### 11:15 – 12:15 Plenary 4: New developments in SSc – Driving tomorrow’s care?

**Co-Chairs: C Black, A Tyndall**

- Moving forward in SSc - M Clozel 40
- Highlights of the year - R Moots 42
- Highlights of the 4th SSc Forum - C Black

**12:15 – 13:30 Lunch**

**Compendium: A collection of key publications** 44
SYMPOSIUM FACULTY

**Yannick Allanore** | Cochin Hospital, Paris, France

Professor Yannick Allanore is Professor of Rheumatology in the Department of Rheumatology A at the Cochin Hospital, Paris, which is affiliated to Paris Descartes University. He is also head of a research group on the pathogenesis of systemic sclerosis at the Cochin Institute (INSERM U1016). Professor Allanore’s research interests include inflammatory rheumatic disorders and systemic diseases. Professor Allanore is Counsellor of EUSTAR (the EULAR Scleroderma Trials and Research group) and a member of the Scleroderma Clinical Trials Consortium. Professor Allanore speaks regularly at international congresses and is an advisory editor for *Arthritis and Rheumatism*. He has authored and co-authored a number of books and book chapters, and has published over 150 papers in peer-reviewed journals.

**Carol Black** | Royal Free Hospital & University College Medical School, London, UK

Professor Dame Carol Black is the UK National Director for Health and Work, Chairman of the Nuffield Trust, Chairman of the Governance Board of the new Centre for Workforce Intelligence, President of the British Lung Foundation, and Pro-Chancellor of the University of Bristol. She is a past-President of the Royal College of Physicians, and has recently stepped down as Chairman of the Academy of Medical Royal Colleges. The centre she established at the Royal Free Hospital, London, is internationally renowned in the field of connective tissue diseases. Since the early 1990s, she has worked at board level in a number of organisations, and recently chaired the UK Health Honours Committee. She is on several national committees aiming to improve healthcare and has been awarded many honorary degrees and fellowships.

**Maya Buch** | University of Leeds, Leeds, UK

Dr. Maya H. Buch, MBChB, PhD, MRCP, is an NIHR Clinician Scientist, Senior Lecturer and Honorary Consultant in Rheumatology at the Section of Musculoskeletal Disease, University of Leeds, UK. Her doctoral thesis focused on TNF inhibitors in rheumatoid arthritis, and her current work revolves around response prediction to targeted agents and the development of effective treatment algorithms. Dr. Buch also undertook a Clinical Research Fellowship at the University of Michigan Hospitals Scleroderma Program, Ann Arbor, USA, and is now developing the clinical scleroderma research programme in Leeds. She is increasingly involved in European activities including the formation of EMEUNET (EMerging EULAR NETwork), an initiative aimed at promoting education, collaboration and excellence in research by emerging young rheumatologists in Europe.

**Rolf Buettemeyer** | Charité University Hospital Medical School, Berlin, Germany

Rolf Buettemeyer, MD, PhD, received his medical degree from RWTH Aachen, Germany, in 1978. From 1978 to 1986 he undertook his training in General Surgery. His specialisation in the field of plastic surgery began with residencies at the University Hospital Aachen and Hospital am Urban, Berlin. This was followed by an appointment as the Head of Staff, Plastic Surgery and Burn Unit, Hospital am Urban, Berlin. Professor Buettemeyer then undertook two fellowships in plastic surgery in the United States, first at the University of Pittsburgh and then at the University of California Los Angeles. Upon his return to Germany, he became Head of Staff at the Department of Plastic Surgery, University of Bochum, and he is currently Professor of Plastic and Aesthetic Surgery and Hand Surgery, at the Charité University Hospital Medical School, Berlin.
Patrick Carpentier | Grenoble University Hospital, Grenoble, France
Professor Patrick Carpentier is the Chairman of the Department of Medicine at Grenoble University Hospital, and the Chief of the Division of Vascular Medicine. The division specialises in the diagnosis and treatment of peripheral vascular diseases, with particular expertise in diseases of the microcirculation, such as scleroderma. Professor Carpentier also teaches vascular medicine at the Joseph Fourier University, Grenoble. Professor Carpentier is former President of the European Society for Microcirculation and Secretary General of the International Union of Angiology. He has published numerous peer-reviewed articles, mainly on the subjects of chronic venous disorders, peripheral arterial disease and Raynaud’s phenomenon.

Patricia Carreira | University Hospital 12 de Octubre, Madrid, Spain
Dr. Patricia E. Carreira works as a rheumatologist at the University Hospital 12 de Octubre in Madrid. She previously worked in the Rheumatology Division of the Medical University of South Carolina, under the direction of Dr. Carville E. LeRoy, and since then she has been especially interested in scleroderma and pulmonary hypertension. She follows a large group of scleroderma patients and works in close collaboration with the Pulmonary Hypertension Unit in her hospital. She has been actively collaborating with EUSTAR (the EULAR Scleroderma Trials and Research group) since its formation in 2002.

Richard Channick | Harvard University, Boston, USA
Richard N. Channick, MD, is Associate Professor of Medicine in the Pulmonary and Critical Care Division at Harvard Medical School and Director of the Pulmonary Hypertension Program at Massachusetts General Hospital. He completed his fellowship training and was previously a faculty member at the University of California, San Diego Medical Center. He has been a member of the American Thoracic Society since 1991 and has served on the Pulmonary Circulation Program Committee. Professor Channick’s major focus is on the pathophysiology and clinical aspects of pulmonary hypertension. He has published over 100 peer-reviewed papers, book chapters and invited reviews, and has been involved in numerous clinical trials studying new therapies for pulmonary hypertension. He is Editor-in-Chief of Advances in Pulmonary Hypertension, and is a reviewer for numerous other journals.

Andrew Clarke | Poole Hospital, Dorset, UK
Mr. Andrew D. Clarke, MD, FRCS, is Consultant General and Colorectal Surgeon at Poole Hospital in Dorset, UK. He trained in the North West of England and was awarded a fellowship to work for a brief period in the USA, prior to being appointed Consultant and Honorary Senior Lecturer at Manchester Royal Infirmary for three years. He has a sub-specialty interest in pelvic floor and keyhole surgery, and he was the first in the North West of England to use sacral neuromodulation for the treatment of faecal incontinence. He moved to Poole in 2004 to develop these interests locally. He is a founding member of the Southern Pelvic Floor Society, the first of its kind in the UK, which brings surgeons with similar interests together.
Christopher Denton, PhD, FRCP, is Professor of Experimental Rheumatology at University College and Consultant Rheumatologist at the Centre for Rheumatology, Royal Free Hospital, London. He graduated in medicine from Guy’s Hospital, and later obtained a PhD from University College London. Following a postdoctoral research fellowship in molecular genetics at M.D. Anderson Cancer Center in Houston, USA, he was appointed as a consultant in rheumatology at the Royal Free Hospital in 2000. Professor Denton’s laboratory research has focused on mediators of vasculopathy and fibrosis in connective tissue diseases and preclinical models. He leads the large clinical programme in scleroderma at the Royal Free Hospital and co-ordinates multidisciplinary care for more than 1300 patients. He is Treasurer of EUSTAR and immediate past-President of the Scleroderma Clinical Trials Consortium (SCTC) and has published extensively on laboratory and clinical aspects of connective tissue disease.

Maurizio Cutolo is Professor of Rheumatology and Director of the Research Laboratories and Academic Unit of Clinical Rheumatology at the University of Genoa. Professor Cutolo is also Chairman of the EULAR Standing Committee on Education and Training, a member of the Scientific Board of the American Autoimmune Related Diseases Association and past-Vice President of the Italian Society for Rheumatology. Furthermore, he is Founder and Chairman of the Neuroendocrine Immunology and Capillaroscopy Study Groups at the American College of Rheumatology. Professor Cutolo is an associate/advisory editor or board member of several international journals, including Arthritis and Rheumatism, Annals of the Rheumatic Diseases and Clinical and Experimental Rheumatology.

Martine Clozel, a paediatrician specialised in neonatal intensive care, obtained her MD degree at Nancy University, France, and received further training in physiology and pharmacology at McGill University, Montreal, and the University of California, San Francisco. During her 11 years at F. Hoffmann-La Roche Ltd, she initiated the research project on endothelin and endothelin receptor antagonists (ERAs) which led to the discovery and clinical development of bosentan (Tracleer®), tezosentan, clazosentan and other molecules. Her group has published over 130 peer-reviewed papers in the fields of endothelial function, endothelin and ERAs. In 1997 she was awarded the Hoffmann-La Roche Research Prize for her achievements in the field of endothelin research. In 1997 she co-founded Actelion Pharmaceuticals Ltd, where she is Senior Vice President and Co-Head of Drug Discovery. She was nominated in 2009 by the Board of Directors to take on the role of Chief Scientific Officer. Martine Clozel is a member of the Scientific Editorial Board of Science Translational Medicine.

Gerry Coghlan, MD, FRCP, studied cardiology at Harefield Hospital from 1988 to 1994, where he also completed his MD thesis (in association with Brunel University) on “Free Radicals in Ischaemic Heart Disease”. He became Consultant Interventional Cardiologist at the Royal Free Hospital in 1997, where he has developed, together with Professor Dame Carol Black, a specialist pulmonary hypertension service for patients with connective tissue disease. Dr. Coghlan is a founder member of the Pulmonary Hypertension Physicians’ Group, which has standardised care for pulmonary arterial hypertension (PAH) in the UK, and has worked with government organisations (NSCAG) to secure funding for PAH as a recognised supraregional speciality.

Gerry Coghlan | Royal Free Hospital & University College Medical School, London, UK

Maurizio Cutolo | University of Genoa, Genoa, Italy

Martine Clozel | Actelion Pharmaceuticals Ltd, Allschwil, Switzerland

Christopher Denton | Royal Free Hospital & University College Medical School, London, UK
Oliver Distler | University Hospital Zurich, Zurich, Switzerland
Oliver Distler, MD, is Privatdozent, Assistant Medical Director of Rheumatology, Director of the Connective Tissue Disease Programme at the Department of Rheumatology, as well as Research Group Leader at the Center of Experimental Rheumatology, University of Zurich. His main research interests in systemic sclerosis (SSc) are the molecular mechanisms leading to microvascular lesions, the biological action of profibrotic mediators and design of proof of concept trials. Dr. Distler served as Associate Editor of Arthritis and Rheumatism and is an editorial board member of several scientific websites and journals, including Rheumatology and Clinical and Experimental Rheumatology. He serves as a scientific secretary of EPOSS (Expert Panel on Outcome Measures in PAH related to SSc), is Counsellor of EUSTAR (the EULAR Scleroderma Trials and Research group) and is President elect of SCTC (Scleroderma Clinical Trial and Research Consortium).

Roberto Giacomelli | University of L’Aquila, L’Aquila, Italy
Roberto Giacomelli graduated from the School of Medicine at the University of Rome “La Sapienza”, where he also trained in internal medicine and clinical immunology and received a PhD in experimental immunology. Presently, he is Professor of Rheumatology and Director of the Rheumatology Clinical Unit at the University of L’Aquila School of Medicine. Professor Giacomelli is involved in several international scientific groups, including the European Scleroderma Study Group, the Scleroderma Clinical Trial Consortium and EUSTAR (the EULAR Scleroderma Trials and Research group). His research focuses on the pathogenesis of scleroderma, activation of the immune system in autoimmune diseases and the possible role of stem cells in the field of regenerative medicine. He is a referee for several journals and has authored over 200 published scientific articles, reviews and book chapters.

Loïc Guillevin | Cochin Hospital, Paris, France
Loïc Guillevin received his MD from the University of Paris, France, where he is currently Professor of Medicine and Head of the Department of Internal Medicine and Immunopathology in the Cochin Hospital, Paris. He is also Director of the referral centre for rare autoimmune and systemic disease, vasculitis and scleroderma. Professor Guillevin is a member of several international scientific societies, and the author of over 600 scientific papers and 300 teaching papers, books and book chapters. He is co-ordinator of several scientific groups, national and international, and of several prospective trials.

Eric Hachulla | Hospital Claude Huriez, Lille, France
Eric Hachulla has been Professor of Internal Medicine at the Hospital Claude Huriez, University of Lille, since 1995. He is the Head of the Scleroderma National Centre in France. He has published many papers and carried out clinical research into a variety of topics, mainly in connective tissue diseases. He is a member of several professional bodies, including the French Society of Internal Medicine, the American College of Rheumatology and EULAR. He is a member of the educational committee of EUSTAR (the EULAR Scleroderma Trials and Research Group) and of the EULAR online course on rheumatic diseases.
Masataka Kuwana | Keio University, Tokyo, Japan
Masataka Kuwana, MD, PhD, is Associate Professor of Rheumatology at Keio University School of Medicine. He obtained his MD and PhD at Keio University, Tokyo, Japan, and completed a fellowship programme at the University of Pittsburgh, USA, under the supervision of Professor Thomas A. Medsger, Jr. He is currently an active member of the Scleroderma Research Group sponsored by the Japanese Ministry of Health, Labour and Welfare. Dr. Kuwana has served on the editorial boards of Modern Rheumatology, The Journal of Infectious Diseases and Drugs. His major research interests include vascular and immune aspects of scleroderma.

Ariane Herrick | University of Manchester, Manchester, UK
Ariane Herrick, MD, is Reader in Rheumatology/Consultant Rheumatologist at the University of Manchester/Salford Royal NHS Foundation Trust. She qualified from the University of Aberdeen, trained in general medicine in Glasgow, and in rheumatology in Salford. Her major clinical and research interests are Raynaud’s phenomenon and systemic sclerosis, with a particular emphasis on measurement of microvascular structure and function.

Dinesh Khanna | University of California, Los Angeles, USA
Dinesh Khanna, MD, MSc, is Assistant Professor of Medicine in Residence at the University of California, Los Angeles (UCLA). He is also Clinical Director of the UCLA Scleroderma Program and concentrates his research efforts in this area. Dr. Khanna has published nearly 200 abstracts, peer-reviewed articles and book chapters. He has served as a reviewer for several professional journals, society committees and training programs, and grant applications. In addition, Dr. Khanna conducts grand rounds and lectures at domestic and international conferences on management of systemic sclerosis, including gastrointestinal disease and pulmonary hypertension, and standards of care for this condition. Dr. Khanna is a member of the American College of Rheumatology, where he serves on two steering committees.

Thomas Krieg | University of Cologne, Cologne, Germany
Professor Thomas Krieg is Director and Chairman in the Department of Dermatology at the University of Cologne, in addition to being the Vice President for Research at the University of Cologne. He has extensive experience in the field of dermatology, as well as serving for several years as Director of the Center for Molecular Medicine in Cologne. He is a Fellow of the Royal College of Physicians, London, and was awarded honorary membership of the Polish and Hungarian Dermatological Societies. Professor Krieg has an extensive publication record and has co-written many papers on systemic sclerosis, particularly with regards to the molecular mechanisms involved in pathogenesis.
Isabelle Marie | Rouen University Hospital, Rouen, France
Isabelle Marie, MD, PhD, is Professor of Internal Medicine at Rouen University Hospital, France. She is a member of several national and international scientific societies. Professor Marie’s research interests include clinical management, in particular digestive manifestations of patients with systemic sclerosis. She is the author of more than 130 scientific publications, including several book chapters.

Marco Matucci Cerinic | University of Florence, Florence, Italy
Marco Matucci Cerinic, MD, PhD, is Professor of Rheumatology and Medicine, and Director of the Department of Rheumatology and the Division of Rheumatology at the Azienda Ospedaliera Universitaria Careggi in Florence, Italy. Professor Matucci Cerinic has published widely in the field of rheumatology, particularly on the pathogenesis, clinical features and treatment of scleroderma, and has served as General Secretary of EULAR, as Vice President of the Scleroderma Clinical Trial Consortium and as Chairman of EUCLIPSE (the EULAR Scleroderma Trials and Research group). He is Associate Editor of *Rheumatology* and *Clinical and Experimental Rheumatology* and serves on various international and national committees. He is currently chairman of the World Scleroderma Association.

Robert Moots | University of Liverpool, Liverpool, UK
Robert J. Moots is Professor of Rheumatology at the University of Liverpool. After qualifying in medicine in London, he trained in immunology at the University of Oxford, earning his PhD, and continued his research on immunology of autoimmune diseases at Harvard Medical School, returning to Liverpool in 1997. In 2002 he became Professor of Rheumatology in Liverpool, the youngest appointment to such a post in the UK. His research interests lie in clinical and basic science aspects of inflammatory rheumatic diseases, particularly innate cellular immunity in rheumatoid arthritis and systemic sclerosis. He runs a drug discovery programme, has published extensively in both clinical and laboratory science, and is Editor of *Rheumatology*. He has won national and international prizes for research, is active in many medical and scientific societies, and is an active international speaker.

Luc Mouthon | Cochin Hospital, Paris, France
Luc Mouthon, MD, works in the National Centre of Reference for Vasculopathy and Systemic Sclerosis, Internal Medicine Department, Cochin Hospital, Paris. Professor Mouthon’s primary interest is in managing patients with scleroderma. As an immunologist, he is also the Co-Director of an INSERM research team at the Cochin Institute, entitled “neutrophils and vasculitis”. His focus in the laboratory is the identification of new immunological markers in vascular diseases, including idiopathic pulmonary arterial hypertension and systemic sclerosis.
Oliver Sander | Heinrich-Heine University Duesseldorf, Duesseldorf, Germany
Oliver Sander, MD, works as a clinical, scientific and teaching rheumatologist at the Department of Endocrinology, Diabetes and Rheumatology at the Heinrich-Heine University Duesseldorf. His interests include the role of imaging in rheumatological diseases, with a particular focus on capillaroscopy. He organises training courses, scientific interdisciplinary workgroups and consensus publications on capillaroscopy throughout Germany, to improve standards of capillaroscopic imaging. In addition, he has authored a pocket atlas of capillaroscopy, which has been translated into several languages.

Gabriela Riemekasten | Humboldt-University, Berlin, Germany
Professor Gabriela Riemekasten, MD, is a consultant at the Department of Rheumatology and Clinical Immunology, Charité Medical School, Humboldt-University, Berlin, where she is also an Associate Professor and head of the daily rheumatology clinic. Professor Riemekasten is a member of the German Network for Systemic Sclerosis (DNSS) and an elected board member of EUSTAR (the European Scleroderma Trials and Research group). She has been the principal investigator on a number of clinical studies in the field of rheumatology. Her primary research interests focus on systemic autoimmune diseases, and include study of their pathogenesis, identification of biomarkers, immunotherapy and treatment strategies in systemic sclerosis as well as in lupus.

Janet Pope | St. Joseph’s Health Care London, London, Canada
Janet Pope is Professor of Medicine in the Divisions of Rheumatology and Epidemiology and Biostatistics at the University of Western Ontario (UWO), Schulich School of Medicine & Dentistry. She is also Head of the Division of Rheumatology at St. Joseph’s Hospital. Following her MD at UWO, Professor Pope completed a fellowship in rheumatology and a Master of Public Health (Epidemiology) at Boston University, before returning to Ontario to complete a fellowship in scleroderma clinical research. She is co-founder of the Canadian Scleroderma Research Group (CSRG), Vice President of CaNIOS (Canadian Network for Improved Outcomes in SLE), Director of the Canadian Rheumatology Association Clinical and Research Summer Studentships, and is on the executive of the Canadian Rheumatology Research Consortium (CRRC). Her research includes clinical trials and epidemiological studies in scleroderma, lupus and rheumatoid arthritis, and she has published over 100 peer-reviewed articles.

Ulf Mueller-Ladner | Justus Liebig University Giessen, Giessen, Germany
Ulf Mueller-Ladner, MD, is Professor for Internal Medicine and Rheumatology at the Justus Liebig University Giessen, Germany, and Medical Director of the Department of Rheumatology and Clinical Immunology at the Kerckhoff-Clinic in Bad Nauheim. Professor Mueller-Ladner is a certified rheumatologist and immunologist. He is spokesman of the Rheumatology Centre Giessen-Bad Nauheim and chairs the Clinical Study Programme Panel of the German Research Foundation/ German Ministry of Education and Research. Professor Mueller-Ladner has been acting chairman of EUSTAR (the EULAR Scleroderma Trials and Research group) since 2010.
Jonathan Shaffer | Salford Royal Hospital, Salford, UK
Dr. Jonathan Shaffer is Lead Clinician for the Intestinal Failure Unit, and Honorary Consultant Physician and Gastroenterologist at Salford Royal Hospital. Dr. Shaffer is a Senior Lecturer at the Medical School of the University of Manchester and has a major role in undergraduate education. Dr. Shaffer’s interests include inflammatory bowel disease and clinical nutrition, particularly artificial nutrition support. He has been involved in establishing one of the largest units for home parenteral nutrition in the world. He sits on the council of the British Association for Parenteral and Enteral Nutrition (BAPEN) and of the European Society for Clinical Nutrition and Metabolism (ESPEN).

Cord Sunderkoetter | University of Muenster, Muenster, Germany
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Optimising Outcomes in Systemic Sclerosis – Combating Morbidity and Mortality
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Gabriele Valentini is Full Professor of Rheumatology and Chief of the Rheumatology Unit at the Second University of Naples, Italy. Following his medical degree, Professor Valentini specialised in Internal Medicine and Rheumatology. He went on to become a clinical investigator and then Associate Professor of Rheumatology. He has devoted his career to a number of inflammatory rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis and, in particular, systemic sclerosis. In the latter, he has made significant contributions to knowledge on pathophysiological, immunological, clinical and therapeutic aspects of the disease. These include identification of preclinical organ involvement in patients with early disease, studying the response of the pulmonary vasculature to exercise and identifying that fibroblast apoptosis is induced by co-culture with CD4+ T cells.

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Notes
Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease, typified by the excessive deposition of collagen in skin and various internal organs. Although not yet fully understood, the underlying pathogenesis of SSc involves a complex interplay of vasculopathy, inflammation/immunological activation and progressive fibrosis. In contrast to other fibrotic disorders, vasculopathy and autoimmunity occur prior to tissue fibrosis in SSc.

Vasculopathy, characterised by endothelial cell activation and altered vascular tone, is one of the earliest pathological events in SSc, and morphological changes in capillaries can be detected before or at disease onset using nailfold capillaroscopy. Endothelial cell activation commonly results from a vascular injury, and activation alters the production of the vasodilators prostacyclin and nitric oxide (NO) and the vasoconstrictor peptide endothelin (ET). The consequences of diminished NO and prostacyclin production coupled with an increased expression of ET are vascular hypertrophy, inflammation, mitogenic effects on fibroblasts, stimulation of collagen synthesis and inhibition of collagenase production. All of these processes contribute to vascular remodelling and fibrosis.

Destructive vasculopathy affects small vessels in the early course of SSc and causes progressive loss of capillaries and insufficient angiogenesis. The clinical manifestations of destructive vasculopathy are Raynaud’s phenomenon and digital ulcers (DU). Proliferative vasculopathy, which is characterised by the proliferation of vascular cells and obstruction of the lumen, manifests later in the course of SSc and affects larger vessels such as the pulmonary arteries, causing pulmonary arterial hypertension (PAH).

The differentiation of fibroblasts into contractile collagen-secreting myofibroblasts is initiated by a cascade of events involving the release of soluble mediators from surrounding cells. This leads to the replacement of smooth muscle and epithelial cells with a collagen-rich extracellular matrix, and the subsequent contraction of affected tissues and functional impairment of affected organs.

Progressive occlusive fibrotic vasculopathy is the hallmark of SSc and is thought to be the underlying mechanism of three of the major clinical manifestations of SSc: DU, PAH and scleroderma renal crisis (SRC). Studies suggest that DU are caused by fibro-proliferative lesions in the digital arteries that narrow the lumen, reducing blood flow and tissue oxygenation. Similarly, vascular remodelling in the pulmonary arterial tree, interlobular arteries and cortical blood vessels, is thought to cause PAH and SRC, respectively.

The vasoconstrictive and pro-proliferative effects of ET are known to contribute to the vasculopathy of SSc, and clinical trials have demonstrated the benefits of the dual ET receptor antagonist bosentan in PAH, as well as in reducing the number of new DU in patients with SSc.

Although the precise mechanisms of SSc pathophysiology remain unknown, immunological activity is thought to play a role and highly specific antibodies have been associated with SSc. Though the mechanisms still elude us, there is evidence to suggest that autoantibodies specific to receptors on fibroblasts and endothelial cells can activate both cell types and cause tissue damage.

The complex pathogenesis of SSc still requires further understanding, and the use of animal models such as transgenic and knockout models are essential to provide further insights into the underlying mechanisms of this debilitating disease.
References


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WHAT PROGRESS HAVE WE MADE IN THE CLASSIFICATION OF SSc?

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Systemic sclerosis (SSc) is a heterogeneous disease with a varied clinical course, and criteria for its classification continue to evolve. Accurate classification criteria and sub-setting of disease within the SSc spectrum are essential for predicting prognosis and survival, developing treatment guidelines and for understanding disease pathogenesis. They are also necessary to ensure that patients recruited for studies have comparable disease features, so that further advances can be made.

The Preliminary Criteria for the Classification of SSc, published in 1980 by the American College of Rheumatology (ACR), aimed to distinguish SSc from non-SSc. The ACR criteria involved one major criterion, sclerosis of the skin proximal to the metacarpophalangeal joints, and three minor criteria, sclerodactyly, digital pitting scars and bilateral basal pulmonary fibrosis. These criteria, however, are limited, primarily because they do not take into account the developments of the past 30 years, such as autoantibodies and use of nailfold capillaroscopy, and because they do not deal fully with the heterogeneity of SSc. Additionally, in current practice, use of the ACR criteria alone would exclude a number of individuals that experts consider to have SSc. For example, 20% of limited cutaneous SSc patients and some patients with early SSc would not be diagnosed using the ACR criteria alone.

In 1988, LeRoy proposed new criteria subdividing SSc into limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc), which is widely accepted in clinical practice. In lcSSc, skin thickening is distal to the elbows or knees, usually involving the fingers and possibly the hands. Skin thickening may also involve the face and neck, but not the trunk; lcSSc patients have less organ involvement than dcSSc patients. In dcSSc, patients have extensive skin changes which often develop rapidly, with earlier and more serious complications, such as heart, kidney and lung involvement. In addition, dcSSc patients have a shorter life expectancy. Whether lcSSc and dcSSc are different diseases or different phenotypes of the same disease remains uncertain. Since transitions from one to the other seldom occur, the former seems more likely.

Further SSc classification criteria were proposed in 2001, due to the shortcomings of the 1980 criteria and increased experience with nailfold capillaroscopy and autoantibody detection. Although not yet validated, LeRoy and Medsger proposed criteria for an early or limited form of SSc. These criteria include Raynaud’s phenomenon, abnormal nailfold capillaroscopy and the detection of SSc-specific autoantibodies.

Abnormal microvasculature, as seen in early SSc, can be easily detected in clinical practice using capillaroscopy, a simple and non-invasive technique which magnifies the nailfold vascular bed. Nailfold video-capillaroscopy can also be used to quantify microvasculature abnormalities. These features allow differentiation between lcSSc and dcSSc, and the detection of progression or regression of microvascular changes, but this is usually reserved for clinical studies.

The detection of autoantibodies in SSc patients may be related to and used to define disease course and progression. Antinuclear antibodies (ANA) can be found in 90% of SSc patients, and although their definitive role in pathogenesis is not yet understood, a number of specific antibodies are indicative of clinical features, disease course and overall severity, making them a useful diagnostic and prognostic tool. The detection of two specific ANAs enables the distinction between lcSSc and dcSSc, as the former is associated with anticentromere antibodies and the latter with antitopoisomerase antibodies. This difference in antibody expression may enable clarification of the pathogenesis of both subsets of SSc.

SSc classification is important, and in view of the fact that there are still uncertainties, initiatives have been set up to improve this, including a reclassification programme that has been launched by the EULAR/ACR task force.

Accurate classification criteria are essential for predicting prognosis, developing treatment guidelines and understanding pathogenesis.

A reclassification programme has been launched by the EULAR/ACR task force.
Systemic sclerosis (SSc) is inherently difficult to diagnose due to its complex pathology, which involves a complicated relationship between the vasculature, immune system and elements of connective tissue. Diagnosis is often obscured because SSc shares clinical and pathological manifestations with various other connective tissue disorders, and patients frequently exhibit the features of more than one disease. As a consequence, SSc is often well established at the time of diagnosis, at which time it has already evolved into an irreversible obliterative vasculopathy, with fibrosis and considerable organ damage.

Although the American College of Rheumatology criteria for the classification of SSc are often used for diagnostic purposes, they were not intended to aid diagnosis, but rather to establish a standard for definite disease. It is not surprising, therefore, that these criteria have been shown to perform poorly when attempting to make an early diagnosis. In 2001, LeRoy and Medsger proposed criteria for the early diagnosis (and classification) of SSc, reflecting the vascular and serological advances of the previous twenty years. Considerable improvements in detection methods, such as the widespread use of nailfold capillaroscopy and a more accurate immunofluorescence assay for the detection of autoantibodies, have enabled increased identification of individuals with features of SSc who do not fulfil the previous preliminary criteria. Since SSc is an aggressive disease with considerable mortality, early diagnosis may improve treatment efficacy and induce durable remission.

Nailfold capillaroscopy is a non-invasive and inexpensive microscopy technique used to identify morphological changes in capillaries prior to or at SSc disease onset. For the past decade, the morphological abnormalities seen in SSc have been classified as early (enlarged capillaries), active (capillary loss) and late (capillary telangiectasias). Raynaud’s phenomenon (RP) is the hallmark of microvascular involvement in SSc and is defined by the presence of giant capillaries, disorganised vasculature or bushy capillaries. Since RP is often the first sign of SSc, the use of capillaroscopy to distinguish primary from secondary RP is a useful tool to aid earlier diagnosis of SSc.

To address diagnosis of SSc at an early stage, EUSTAR (the EULAR Scleroderma Trials and Research group) has begun a multinational initiative: VEDOSS (Very Early Diagnosis of SSc; further information available at www.eustar.org). Within this programme, SSc experts have proposed and selected criteria to facilitate very early diagnosis of SSc. The following criteria with inherently high clinical relevance were selected: RP, puffy swollen digits turning into sclerodactyly, anticentromere antibodies, antitopoisomerase-1 antibodies and abnormal capillaroscopy with SSc pattern. Validation of these criteria to determine their discriminatory and predictive value is now ongoing in a prospective observational cohort. RP, puffy fingers and antinuclear antibodies have been identified as “red flags” that should arouse suspicion of very early SSc, and physicians are encouraged to send all patients exhibiting these symptoms to a rheumatologist for further investigation.

The diagnosis of SSc invariably occurs late during the course of the disease, and there has been little improvement over the past three decades. The establishment of a definition and new criteria for early diagnosis of SSc may enable treatment to commence before irreversible organ damage occurs, improving the long-term outcomes for patients with SSc.
Optimising Outcomes in Systemic Sclerosis – Combating Morbidity and Mortality

**References**

Pulmonary arterial hypertension (PAH), a severe clinical condition characterised by a progressive increase in pulmonary vascular resistance, is a frequent complication of systemic sclerosis (PAH-SSc). PAH-SSc patients have a particularly poor prognosis compared with idiopathic PAH patients, and PAH is one of the leading causes of SSC-related deaths. The malignant nature of PAH-SSc and the proven benefit of initiating PAH therapy at an early stage of disease provide a strong rationale for active screening programmes in SSC patients, as implemented at the Royal Free Hospital in London.

As PAH symptoms are generally non-specific, early identification of PAH-SSc presents a significant challenge, illustrated by the fact that the majority of PAH-SSc patients are in WHO functional class III or IV at diagnosis. As such, strategies that drive early diagnosis of PAH-SSc are an essential component of disease management. Diagnosis may be expedited by utilising the diagnostic algorithm in the ESC/ERS Guidelines, and by the availability of improved diagnostic techniques. Initiatives such as promoting awareness of the signs and symptoms of PAH amongst patients and physicians can also help to reduce the frequency of delayed diagnoses.

Screening SSC patients is an effective way of ensuring early diagnosis of PAH-SSc. Transthoracic echocardiography (TTE) is a commonly used and non-invasive screening tool that estimates right ventricular systolic pressure as an approximation of pulmonary arterial systolic pressure. Notably, the optimal thresholds for TTE are still under investigation, especially for patients with early pulmonary hypertension, and this technique may yield a significant number of false-positives and a currently unknown number of false-negatives. As with other forms of PAH, right heart catheterisation must be performed to confirm the diagnosis of PAH-SSc. Despite the known limitations of TTE, it is the recommended screening tool for PAH-SSc in the ESC/ERS Guidelines echocardiographic screening is recommended in symptomatic patients and may be considered in asymptomatic patients. As additional evidence emerges on the optimal parameters and thresholds to employ during TTE, it is crucial that established screening programmes are adapted accordingly. In addition, novel non-invasive screening tools with greater specificity for PAH must be investigated.

In the search for new screening tools, factors that are predictive of PAH development and simple to detect, such as decreased diffusing capacity for carbon monoxide (DL\textsubscript{CO}) and elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, represent attractive options. The ongoing DETECT study is evaluating the role of various non-invasive methods of screening for PAH, including whether NT-proBNP, DL\textsubscript{CO}, and electrocardiography can be used to determine which patients should undergo echocardiographic screening. The study represents an important step towards identifying novel screening tools that could facilitate early detection of PAH-SSc.

Early diagnosis of PAH-SSc has become an achievable prospect as a result of increased PAH awareness, improved diagnostic tools and implementation of screening programmes. As research continues and screening algorithms evolve to include ever more specific diagnostic tests, early identification of PAH can become a reality for all SSC patients who develop this devastating complication.
References

Improved outcomes are being sought for pulmonary arterial hypertension (PAH) patients by employing a treat-to-target approach to therapy. Goal-oriented treatment has been proven to effectively improve patient outcomes, and is recommended in the ESC/ERS Guidelines. In patients with PAH associated with systemic sclerosis (PAH-SSc), who have a particularly poor prognosis, optimal management using a treat-to-target approach is essential.

A central component of goal-oriented therapy is selecting appropriate treatment goals. It is important to choose a number of specific and measurable goals that will provide a clear picture of the overall clinical status of the patient. Several goals that incorporate parameters with prognostic significance, such as WHO functional class (FC), 6-minute walk distance (6-MWD) and a number of haemodynamic and echocardiographic variables, are suggested in the ESC/ERS Guidelines. An important requirement during goal-oriented therapy is tailoring treatment goals to account for the presence of SSc, along with additional patient-specific factors such as age and body mass index. For example, in SSc patients a 6-MWD goal must be adapted to consider co-morbidities that reduce exercise capacity, such as musculoskeletal involvement. Uniquely, FC II is a treatment goal that is broadly applicable to all patients, including those with PAH-SSc.

Treatment goals should aim to improve symptoms, quality of life and long-term outcomes, and FC II is an important treatment goal that fulfills these criteria. FC II patients have only a slight limitation of physical activity, are mildly symptomatic and have a better prognosis than those in FC III/IV, although without treatment PAH still progresses rapidly in FC II patients. Importantly, improvement from FC III/IV to FC II during treatment is associated with a better prognosis in idiopathic PAH and also PAH-SSc. For PAH-SSc patients treated with first-line bosentan, 3-year Kaplan-Meier survival estimates were significantly better for patients in FC II after 4 months of therapy, compared with those in FC III/IV. Notably, assessment of FC status showed that after 4 months of bosentan monotherapy, 16 patients (36%) were in FC II compared with 6 patients (14%) at baseline. Due to this improved prognosis, FC II is a vital target of PAH therapy, as reflected by its inclusion as a recommended goal in current expert guidance for PAH.

Following initiation of PAH therapy, careful and periodic patient re-assessment is crucial to determine if pre-defined treatment goals have been met. The ESC/ERS Guidelines suggest the appropriate methods and timing for re-assessment, namely 3–4 months after initiation or changes in therapy, in cases of clinical worsening and every 3–6 months additionally.

If pre-defined treatment goals are not met, therapy should be escalated by progressing to sequential combination therapy to target multiple pathways involved in PAH pathogenesis, as recommended by the ESC/ERS Guidelines. Although the optimal combination of drugs has yet to be determined, several studies have supported the efficacy of combination therapy. In COMPASS-3, the first clinical trial to implement a treat-to-target approach, patients on bosentan had to reach a 6-MWD threshold of > 380 m after 16 weeks of therapy, and if this target was not reached sildenafil was added. Despite enrolling a very severe population of patients, with a baseline 6-MWD of 150–360 m, 31% of patients were able to reach the pre-defined threshold, either on monotherapy or combination therapy. Notably, at week 28 the mean improvement in 6-MWD from baseline was 45 m and 34% of patients improved at least one FC, compared with baseline.

Considering the poor prognosis of PAH-SSc, including FC II as a mandatory treatment goal is a crucial aspect of disease management. By employing a treat-to-target strategy, we can strive towards better outcomes for our PAH-SSc patients.
Optimising Outcomes in Systemic Sclerosis – Combating Morbidity and Mortality

References

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In comparison to idiopathic pulmonary arterial hypertension (IPAH), PAH associated with systemic sclerosis (PAH-SSc) is a more severe and progressive disease. To maximise the benefits of treatment, aspects of PAH management that are particularly relevant to SSc patients must be specifically considered.

The high prevalence of cardiopulmonary manifestations in SSc patients, which include cardiac, pulmonary venous and parenchymal involvement, contribute to the complexity of managing PAH-SSc. PAH-SSc progression can be heterogeneous, and some patients with severely impaired functionality may not respond well to therapy. When assessing response to therapy, it is important to consider that the magnitude of any PAH treatment effect could be severely affected by co-morbidities. For example, SSc patients may have multiple co-morbidities that cause dyspnoea, independent of PAH, which make monitoring the response to therapy more difficult. The heterogeneous nature of SSc requires close collaboration between rheumatologists and cardiopulmonary specialists throughout the patient’s lifetime to optimise disease management. Rheumatologists must convey the importance of investigating the right heart to echocardiographers and cardiopulmonary specialists during diagnostic evaluation and patient monitoring, since this may not typically be the main focus when conducting echocardiography.

Inter-speciality collaboration plays a fundamental role in facilitating prompt diagnosis of PAH-SSc, enabling early therapeutic intervention. The importance of initiating therapy early was demonstrated by the EARLY trial, a study dedicated to WHO functional class (FC) II patients, including those with PAH-SSc. PAH-SSc patients were treated with bosentan reduced pulmonary vascular resistance ($p < 0.0001$) and delayed the time to clinical worsening ($p = 0.0114$) compared with placebo. Although improvement in 6-minute walk distance was not significant ($p = 0.076$), this may reflect the relatively well preserved exercise capacity of enrolled patients. The evidence-based treatment algorithm in the ESC/ERS Guidelines, which also applies to PAH-SSc patients, includes specific treatment recommendations for patients in FC II, emphasising the importance of early intervention in PAH-SSc. The guidelines also highlight the importance of tailoring therapy to meet pre-defined treatment goals, which is an important aspect of managing PAH-SSc.

Given the poor prognosis of PAH-SSc, improving long-term outcomes is critically important. Before the availability of endothelin receptor antagonists (ERAs), the Kaplan-Meier (KM) 1-year survival estimate for PAH-SSc patients was particularly poor, at just 55%. Following the availability of ERAs, long-term outcomes have improved. In the prospective, open-label TRUST study, the 2-year KM survival estimate for FC III patients with PAH associated with connective tissue disease (PAH-CTD) treated with bosentan was 82.4%. Data from a 6-year longitudinal study of 92 PAH-SSc patients at the Royal Free Hospital in London, revealed a 2-year KM survival estimate of 71% for patients receiving first-line bosentan therapy. Recently, long-term data in PAH-SSc patients treated with first-line bosentan, the majority of whom were in FC III/IV at diagnosis, revealed a 3-year KM survival estimate of 51%. For PAH-SSc patients diagnosed in FC II, the majority of whom were treated with first-line bosentan, a 3-year KM survival estimate of 80% was reported, emphasising the benefit of early diagnosis in this population.

Management of PAH-SSc is undoubtedly challenging. Nevertheless, with early therapeutic intervention, careful consideration of co-morbidities and a strong collaborative approach between specialists, the long-term outlook for PAH-SSc patients can be improved.
References

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Managing systemic sclerosis (SSc) patients with pulmonary arterial hypertension (PAH-SSc) is complex and demanding, due to their poor prognosis and the heterogeneous nature of SSc. Our ability to treat PAH-SSc has been greatly aided by the availability of dedicated treatment recommendations, such as the EULAR treatment recommendations for SSc and the specific information presented in the ESC/ERS Guidelines on PAH associated with connective tissue diseases. However, implementing these recommendations in everyday clinical practice presents physicians with many challenges. In this session, informative and practical advice will be provided on how best to manage PAH-SSc patients. A patient case will be used to illustrate key issues, such as implementing targeted therapy early and employing a treat-to-target approach to therapy. This interactive session will consolidate key information from the previous presentations, whilst placing a greater emphasis on the clinical practicalities of caring for PAH-SSc patients.

Notes
The underlying pathogenesis of systemic sclerosis (SSc) involves three key processes; vasculopathy, immunological response and fibrosis. Vasculopathy is thought to be a primary event resulting from endothelial cell activation and dysfunction, which leads to up-regulation of vasoconstrictive, thrombogenic, mitogenic and pro-inflammatory factors and the down-regulation of vasodilatory, anti-thrombogenic and anti-mitogenic factors. There is cross-talk between different cell types and different mediators. Activated endothelial cells release endothelin-1 (ET), a potent vasoconstrictor that promotes leucocyte adhesion to the endothelium, vascular smooth muscle cell proliferation and fibroblast activation. A concurrent reduction in the vasodilators prostacyclin and nitric oxide contributes to the vasoconstriction seen in SSc. There is also an overall reduction in vessel density and irregular vessel architecture. This results in reduced capillary blood flow and a consequent lack of nutrients, and severe tissue hypoxia ensues.

Angiogenesis is a normal physiological response to capillary breakdown and hypoxia. Patients with SSc, however, demonstrate an insufficient angiogenic response and a failure to replace damaged blood vessels, despite the up-regulation of a large number of pro-angiogenic mediators. There is also evidence to suggest that vasculogenesis may also be impaired in patients with SSc.

Vascular changes are frequently associated with stimulation of the innate and adaptive immune responses, resulting in T-cell and B-cell activation. Other modifications include autoantibody generation, and an increase in growth factors, e.g. transforming growth factor-β (TGF-β), vascular endothelial growth factor, interleukins (ILs) and chemokines. Activated T-cells can be detected in SSc patients and have been shown to play a role in fibrosis. Activated B-cells may drive the generation of autoantibodies seen in the majority of patients with SSc. Antibodies against endothelial cells have been shown to induce apoptosis and antifibrillin-1, which can activate fibroblasts and the release of TGF-β. Activated B-cells also secrete IL-6, which has been shown to be involved in fibrosis.

Fibroblasts provide structural support to connective tissue and may regulate the amount of extracellular matrix present, via a balance of ECM production and degradation. The activation of fibroblasts leads to an overproduction of collagen and the induction of collagen-modifying enzymes, and is thought to be regulated by a number of cytokines, including TGF-β, connective tissue growth factor and platelet-derived growth factor. Many of these factors have been elucidated through the use of mouse models for SSc. In SSc, the progressive replacement of tissue architecture by collagen-rich ECM results in functional impairment of affected organs.

Improvements in the understanding of SSc pathophysiology have identified pathways and mediators that can be targeted by pharmacological therapy, facilitating drug development. Nevertheless, there is still a shortage of effective therapies in SSc. Although there are some drugs available to target the underlying vasculopathy of SSc, treatments that target fibrosis and immune dysfunction are lacking. Development of novel therapies that target all three pathological processes will prove essential to improving the outlook for all SSc patients in the future.
References
Early diagnosis of SSc is important in facilitating the identification of organ-based complications, and has the potential to improve patient outcomes by preventing or slowing down disease progression. While it is nice to think that calcium channel blockers or other vasoactive drugs typically used in RP can prevent disease progression, there are no studies to show that this is true. Although anti-fibrotic agents are not yet available, they might be particularly beneficial for patients with early SSc. The use of angiotensin-converting enzyme inhibitors (ACEi) in patients with established SRC is essential to prevent irreversible vascular injury, and this has had a dramatic impact on SRC-related mortality. However, use of ACEi prior to the onset of SRC is associated with a trend towards poorer renal outcome. It has been demonstrated that treatment with the dual endothelin receptor antagonist bosentan is associated with a reduction in the number of new DU in SSc patients. Although SSc is invariably difficult to diagnose before the onset of organ involvement, early diagnosis may be crucial to improving patient outcomes. Recent improvements in diagnosis include the detection of autoantibodies, nailfold capillaroscopy and the recognition of early organ-based abnormalities. There is still, however, much room for improvement in both the early diagnosis and treatment of SSc.
Optimising Outcomes in Systemic Sclerosis – Combating Morbidity and Mortality

References


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Digital vasculopathy in systemic sclerosis (SSc) ranges in severity from Raynaud’s phenomenon (RP) to digital ulcers (DU) and tissue loss. Careful assessment and management of these complications is of paramount importance to the optimal care of SSc patients.

RP occurs in more than 90% of SSc patients and is most often the earliest manifestation of the disease. SSc-related RP is associated with an underlying vasculopathy, which can be evidenced through different functional and morphological tests. Nailfold capillaroscopy can detect a specific capillary microangiopathy that can help distinguish SSc-related RP from primary RP and secondary RP due to other causes. This technique allows early screening for SSc among patients with RP.

Approximately 50% of SSc patients develop DU. It is not currently understood why certain patients develop DU but others do not. In a recent study, a capillaroscopic skin ulcer risk index was developed to predict the onset of new DU using nailfold capillaroscopy, which may constitute an easy and rapid tool for clinical follow-up. DU lead to progressive ischaemic damage, tissue loss, impaired hand function, infection and in some cases permanent disability. Due to the clinical burden of DU, there is an unquestionable need for careful assessment and effective monitoring tools. DU can be evaluated in terms of their number, size, duration and effect on hand function. Subsetting according to DU morphology and natural course will enable more comprehensive clinical evaluation and staging.

Effective management of DU requires interdisciplinary care involving nurses, doctors and occupational therapists. Non-pharmacological management of DU should aim to reduce pain, restore hand function, improve digital circulation and prevent infection. Dry skin can be improved with simple topical moisturising creams and emulsifying ointments. Vasoconstriction can be reduced by avoiding precipitating factors such as cold, emotional stress and nicotine. If infection of DU is suspected, prolonged and/or rotating courses of antibiotics may be required.

Several pharmacological treatments have been investigated for healing existing DU and prevention of new DU. Potential pharmacological treatments include calcium channel blockers, intravenous prostanoids (particularly iloprost) and selective phosphodiesterase inhibitors. However, there remains a need for well-conducted, randomised controlled trials to evaluate the effect of potential therapies on DU healing, as the majority of trials to date have been single-centre studies with a limited number of patients. The RAPIDS programme, which enrolled more than 300 SSc patients, provided compelling evidence on the reduction of the occurrence of new DU with bosentan; no effect was seen for healing. In RAPIDS-1, bosentan significantly reduced the number of new DU by 48% compared with placebo over the 16-week study period. These data were confirmed by the RAPIDS-2 study; over 24 weeks, bosentan treatment was associated with a 30% reduction in the number of new DU compared with placebo.

Surgery may be performed for the treatment of severe digital vasculopathy, with amputation considered as a last resort. While prospective studies on surgical approaches are lacking, observational studies have shown that digital sympathectomy performed by an experienced hand surgeon can produce good pain relief and healing, and might be considered for patients with severe and refractory DU.

A better understanding of the pathogenesis of digital vasculopathy has led to the development of therapies that can minimise disease burden. Prevention, as well as treatment, of these complications is crucial to improving the outlook for SSc patients.
Optimising Outcomes in Systemic Sclerosis – Combating Morbidity and Mortality

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For the approved indications of Tracleer in Europe, please refer to the abbreviated SmPC at the end of this abstract book.
GASTROINTESTINAL DISEASE IN SS c

The gastrointestinal (GI) tract is affected in 75–90% of patients with systemic sclerosis (SSc). Oesophageal dysfunction is the most frequent GI manifestation, although patients may also experience dysfunction of the stomach, small intestine, colon and rectum. The pathogenesis of GI dysmotility may be explained by initial vascular damage, with initiating or concomitant immunological events. Among the most common symptoms of upper GI tract involvement are those related to gastro-oesophageal reflux disorder (GERD) and dysphagia. Chronic GERD can be complicated by Barrett’s oesophagus (in 6.8% of cases), which increases the risk of oesophageal adenocarcinoma. Moreover, the incidence of severe oesophageal motor impairment may correlate with interstitial lung disease onset, a primary cause of death in SSc.

Current therapies for upper and lower GI dysmotility in SSc patients include diet and anti-reflux measures, anti-secretory agents such as proton pump inhibitors and prokinetic agents, as well as other investigational therapies. Monthly rotating antibiotics may be used for the control of bacterial overgrowth related to intestinal dysmotility. Surgical treatment might be considered under exceptional circumstances for patients with life-threatening complications, such as bowel perforations or ischaemia; however, because surgery is associated with additional risks, especially prolonged ileus, it should not be recommended. In addition to oesophageal involvement, gastric dysfunction has been reported in at least 50% of SSc patients and results in significant morbidity/mortality in 15% of cases. While gastroparesis is the most predominant problem, other complications include GI haemorrhage and iron deficiency as a result of gastric antral vascular ectasia ("watermelon stomach").

Intestinal motility dysfunction is commonly reported in SSc, with a 40–88% prevalence rate. If nutritional status is not being maintained due to SSc-related intestinal failure, parenteral nutrition may be necessary to prevent or correct malnutrition. Other forms of artificial feeding, including oral supplementation, naso-jejunal feeding and feeding via percutaneous enterogastrostomy/jejunostomy tubes may be considered before initiation of parenteral nutrition.

Impaired relaxation and restricted dilation of the internal sphincter due to fibrosis in SSc patients can eventually lead to faecal incontinence and rectal prolapse. Anorectal dysfunction is reported in 50–70% of SSc patients. In addition to conventional therapies, such as dietary interventions and anti-diarrhoeal agents, sacral nerve stimulation is effective for the treatment of faecal incontinence, although it does not have long-term benefits. Posterior anal repair can be successful in treating faecal incontinence, while anterior resection of the rectal and sigmoid walls can relieve rectal prolapse.

Validated methods to assess GI involvement in SSc include 24-hour oesophageal pH, electrogastrogram, ultrasonography, hydrogen breath testing and manometric studies. As GI symptoms associated with SSc are often under-reported, patients should be regularly asked about GI symptoms. Given the underlying pathology of GI complications in SSc patients, specialised GI-focused instruments/surveys are needed to facilitate more accurate clinical assessments.

A better understanding of the pathogenesis of GI complications related to SSc is essential for the development of more effective and targeted therapeutic interventions. In addition, diagnostic methods that enable early identification of GI involvement in SSc are vital for optimising the management of debilitating symptoms and for the avoidance of life-threatening complications.
References
PARALLEL BREAKOUTS –
“MEET THE PROFESSOR” SESSIONS

The “Meet the Professor” sessions will give pre-registered participants the chance to discuss patient cases and obtain advice on managing patients in the practically focused interactive discussion groups. The sessions will be led by experts and are limited to a maximum of 60 pre-registered attendees per session so as to provide a more interactive and informal setting for the discussion of key clinical issues. Attendees are encouraged to actively involve themselves in the discussion, allowing them to gather useful information on how best to manage SSC patients and overcome various treatment issues in the clinic. The key topics that will be discussed are listed below:

PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH SSC (I)
Richard Channick | Harvard University, Boston, USA
Gerry Coghlan | Royal Free Hospital & University College Medical School, London, UK

PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH SSC (II)
Ulf Mueller-Ladner | Justus Liebig University Giessen, Giessen, Germany
Olivier Sitbon | Hospital Antoine Béclère, Clamart, France

DIGITAL ULCERS IN SSC (I)
Thomas Krieg | University of Cologne, Cologne, Germany
Marco Matucci Cerinic | University of Florence, Florence, Italy

DIGITAL ULCERS IN SSC (II)
Maurizio Cutolo | University of Genoa, Genoa, Italy
Eric Hachulla | Hospital Claude Huriez, Lille, France

MUSCULOSKELETAL MANIFESTATIONS IN SSC
Yannick Allamore | Cochin Hospital, Paris, France
Ariane Herrick | University of Manchester, Manchester, UK

RENAL DISEASE IN SSC
Christopher Denton | Royal Free Hospital & University College Medical School, London, UK
Loïc Guillevin | Cochin Hospital, Paris, France
THE REALITY OF MANAGING SSc – AN INTERACTIVE PATIENT CASE

Ariane Herrick | University of Manchester, Manchester, UK
Janet Pope | St. Joseph’s Health Care London, London, Canada

Due to the multifaceted nature of systemic sclerosis (SSc), the reality for many SSc patients involves living with a multitude of physical, psychological and social problems. Physical problems include skin thickening, contractures, pain, digital ischaemia, dyspnoea, muscle and joint problems, and upper and lower gastrointestinal problems. In this session, a patient case will be used to illustrate the significant disease morbidity associated with complications such as digital ulcers (DU) and dyspnoea, and the overall impact that SSc has on quality of life (QoL).

DU are a frequent complication of SSc, occurring in up to 50% of patients, and often appear relatively early in the course of the disease. DU have a major negative impact on QoL, as they cause severe pain and functional impairment, and can lead to gangrene, osteomyelitis and even amputation. Local management of DU (for example using topical antibiotics and occlusive dressings) should complement pharmacological treatment. Intravenous prostanooids (particularly iloprost) may be effective in healing DU and should be considered to treat active DU in SSc patients. Two small Raynaud’s phenomenon studies suggest that the phosphodiesterase-5 inhibitors sildenafil and tadalafil may show efficacy in healing DU; however, further larger studies are warranted. Atorvastatin may also aid in treating DU. DU are often slow to heal and frequently recur, so management strategies that focus on reducing the occurrence of new DU are essential. The RAPIDS programme has provided clinical evidence supporting the efficacy of bosentan in reducing the number of new DU in SSc patients. Recently, a capillaroscopic skin ulcer risk index has been developed that may represent a novel tool with the ability to predict the development of DU in SSc patients. Identifying patients who are likely to develop DU, preventing the occurrence of new DU and treating existing DU quickly and effectively are of paramount importance, and will help to improve the QoL of SSc patients who are afflicted with this debilitating complication.

Another symptom that occurs in up to 50% of SSc patients is the presence of dyspnoea. The first step to take when dyspnoea is encountered is to diagnose the underlying cause. Dyspnoea on exertion is the hallmark of two life-threatening complications of SSc, pulmonary hypertension and interstitial lung disease. However, there are other causes to consider, including anaemia (which may result from gastrointestinal bleeding, for example as a result of gastric antral vascular ectasia) and diastolic left ventricular dysfunction. Other less common causes include pericarditis, pericardial fibrosis and respiratory muscle involvement. For some of these conditions, pharmacological therapies are available that can alleviate dyspnoea. SSc patients who have difficulty breathing are more vulnerable to depressive symptoms, and dyspnoea is a significant independent predictor of QoL and function. Due to the detrimental impact of dyspnoea on QoL, optimal management of this symptom is of the utmost importance. By promptly investigating and diagnosing the underlying cause of dyspnoea, effective treatment can be initiated to improve the QoL of patients suffering from this distressing symptom.

SSc patients are affected by their disease physically and psychologically, and have an impaired health-related QoL. They also report significant disruptions in their social lives, a burden considered by many as the worst consequence of their disease. Emotional distress including depression, low self-esteem, concerns with physical appearance and uncertainty about future outcomes have a major effect on the overall well-being of SSc patients, and treating depressive symptoms should be considered a priority. Improving QoL is of the utmost importance to SSc patients, as illustrated by the fact that patients with SSc are willing to give up 12% of their life expectancy in exchange for perfect health. Certain symptoms correlate with physical health status or health-related QoL, including shortness of breath, number of gastrointestinal problems, skin score, swollen joint count, fatigue, pain and depression. Targeting these symptoms specifically represents one method of improving overall QoL for SSc patients. Rehabilitation programmes have also been shown to improve QoL, and should be considered in addition to pharmacological therapy.
In this session, a complex yet not atypical patient case will be used to illustrate the importance of relieving the significant morbidity experienced by SSc patients. By identifying the clinical factors that cause the greatest impact on QoL, and addressing these problems specifically, we can successfully improve the outlook for SSc patients.

Notes

References

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The development of novel drugs for diseases with unmet medical need, particularly those mediated by the endothelium, has been a major focus of research at Actelion since its creation in 1997. The key role of endothelin (ET) in pulmonary arterial hypertension (PAH) pathogenesis has been a particularly intense area of research. Bosentan, a dual ET\(_A/ET\_B\) receptor antagonist (ERA) developed at Actelion, was the first targeted oral PAH therapy, and was approved for PAH treatment (including PAH associated with connective tissue disease [PAH-CTD]) in the US in 2001 and in Europe in 2002.

Actelion’s commitment to research in CTD has been highlighted by recent investigations into the therapeutic potential of bosentan for several of the organ-based manifestations of CTD. Actelion’s pivotal trials with bosentan in PAH included PAH-CTD patients, and provided evidence for the safety and efficacy of bosentan in this patient population\(^1-3\). The TRUST study investigated the long-term effects of bosentan exclusively in a PAH-CTD population\(^4\). The BUILD-2 study also focused on pulmonary complications of CTD, investigating bosentan for the treatment of systemic sclerosis (SSc)-related interstitial lung disease\(^5\).

In BUILD-2, although bosentan was safe and well-tolerated, the primary endpoint of change in 6-minute walk distance at month 12 was not met. Actelion’s research has also focused on managing digital vasculopathy in CTD. Based on the results of RAPIDS-1\(^6\) and RAPIDS-2\(^7\), bosentan is the only approved therapy for reducing the number of new digital ulcers (DU) in patients with SSc and ongoing DU disease\(^8\).

Building on the successes of the past, Actelion remains focused on driving future progress in PAH and CTD. Evidence increasingly points to the ET system being tissular, with ET-1 exerting a paracrine or autocrine effect, e.g., 80% of ET-1 is secreted basolaterally, towards the tissue\(^9\). Macitentan is an oral, highly-potent dual ERA with tissue-targeting properties. It was designed to protect tissues from the deleterious effects of elevated ET via a comprehensive blockade of ET\(_A\) and ET\(_B\) receptors within the tissue compartment. Data from phase I and II studies indicate that macitentan is well-tolerated. Macitentan is currently under investigation in the phase III SERAPHIN study; the largest ever study in PAH. SERAPHIN is an event-driven study with a clearly defined morbidity/mortality primary endpoint\(^10\). A phase II double-blind study is also underway investigating the efficacy and safety of macitentan in patients with idiopathic pulmonary fibrosis.

In addition to the ET pathway, Actelion is investigating other pathways implicated in PAH pathogenesis. The prostacyclin pathway has a strong bearing on the development of PAH as vasoconstriction, vascular remodelling and thrombosis are all pathologically associated with PAH progression\(^11\). Selexipag is a first-in-class, orally-available, long-acting, non-prostanoid prostaglandin receptor agonist that targets the prostacyclin pathway\(^12\). In a phase II placebo-controlled study of selexipag, the compound was well tolerated and the primary endpoint (change from baseline in pulmonary vascular resistance) was met with statistical significance\(^13\). The efficacy and safety of selexipag is currently being investigated in the phase III GRIPHON study, an event-driven, multicentre, double-blind, placebo-controlled study in PAH patients\(^14\).

The efficacy of bosentan in the treatment of PAH and in reducing the number of new DU in patients with SSc and ongoing DU disease illustrates how targeting a central pathogenic mechanism can have a positive impact on different vascular complications. Given the potential for macitentan and selexipag to be effective in the treatment of vascular complications of SSc, studies are planned to investigate these compounds in SSc-related vasculopathy, including DU and Raynaud’s phenomenon. Through applying innovative approaches in drug development, Actelion will maintain its position as a global leader in the management of PAH and other ET-related diseases.
References

Some of the therapies outlined above are under investigation and are not approved in the indications mentioned. For the approved indications of Tracleer in Europe, please refer to the abbreviated SmPC at the end of this abstract book.
Systemic sclerosis (SSc) is a multisystem connective tissue disease associated with considerable morbidity and mortality. A recent study, which documents the considerable socio-economic burden of SSc\(^1\), represents a significant contribution to the SSc community and will be discussed during this session. In order to improve clinical outcomes in SSc, better tools for the evaluation of patients as well as identification of novel therapeutic targets are essential. With this in mind, two studies, one reporting the development of a genetic biomarker for skin involvement in diffuse cutaneous SSc (dcSSc)\(^2\), and another providing evidence for a novel therapeutic target in SSc\(^3\), will be examined in detail.

Fitness to work is a major component of life and is commonly affected in chronic and autoimmune diseases. In a recent cross-sectional survey of a French cohort of 87 SSc patients\(^1\), a high proportion were on sick leave or registered as disabled; with 60.9% on full-time sick leave, 35.6% receiving a disability pension and 31% having experienced occupational changes after SSc diagnosis. Factors significantly associated with sick leave status included hand and mouth disability and depression; however, there was no significant association between sick leave and visceral organ involvement. Disabled patients more frequently reported decreased income, lack of advancement and feelings of discrimination. This study showed that patients with SSc commonly have to change jobs or take full-time sick leave, with significant socio-economic consequences. Optimal management of SSc should consider disability and the effects on employment status in order to limit the socio-economic burden.

In SSc, the modified Rodnan skin score (mRSS) is the current standard for evaluating skin disease, but requires careful training to ensure consistent evaluation and is associated with inter-observer variability. In developing a more effective outcome measure, Farnia and colleagues\(^2\) investigated the potential of skin gene expression as an objective surrogate marker for skin score evaluations in dcSSc patients. Given the profibrotic role of transforming growth factor-\(\beta\) and evidence that type 1 interferons play a role in SSc pathogenesis, expression of genes known to be regulated by these molecules were studied. Four genes that individually had a moderate/weak correlation to the mRSS were used to calculate a biomarker skin score that strongly correlated with the mRSS (\(r^2 = 0.89\)). This “four-gene” biomarker could serve as a useful surrogate outcome measure of skin disease in dcSSc patients.

Endothelial (ET) cell activation and apoptosis are believed to be pivotal in the pathogenesis of SSc\(^3\). The mechanisms underlying ET cell function in SSc are not well understood. Recently, Barnes and colleagues\(^3\) demonstrated compelling evidence for the involvement of neutrophils and interleukin 6 (IL-6) in ET cell activation and apoptosis. This study showed that SSc serum induces ET cell apoptosis and E-selectin expression (a marker of ET cell activation) \textit{in vitro}. Notably these effects were observed only in the presence of neutrophils. In addition, immuno-depletion of IL-6 or addition of an IL-6 neutralising antibody decreased the effect of SSc serum on E-selectin expression. As endothelial cells do not express endogenous IL-6 receptors, and can only respond to IL-6 bound to soluble IL-6 receptors (sIL-6R), a trans-signalling mechanism involving sIL-6R generated from the neutrophil membrane has been proposed. These findings highlight IL-6 as a potential therapeutic target in SSc.

In summary, SSc is a major cause of disability with a considerable socio-economic burden. Recent findings have improved the evaluation of skin disease, as well as identifying a potential novel therapeutic target that offers the hope of improved outcomes for patients with SSc.
References

## COMPENDIUM: A COLLECTION OF KEY PUBLICATIONS

### REFERENCES

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<th>PAH background and guidelines</th>
<th>CONTENT OVERVIEW</th>
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### Key clinical studies

| Study 351: Results of a double-blind, placebo-controlled trial to investigate the efficacy of bosentan in relation to 6-MWD, haemodynamics, Borg dyspnoea index, WHO functional class, and clinical worsening in patients with IPAH or PAH-SSc. | Study 351: Results of a double-blind, placebo-controlled trial to investigate the efficacy of bosentan in relation to 6-MWD, haemodynamics, Borg dyspnoea index, WHO functional class, and clinical worsening in patients with IPAH or PAH-SSc. |
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### Key clinical studies

| Barst RJ, *et al.* *Clin Pharmacol Ther* 2003; 73:372–82. | BREATHE-3: Open-label study to investigate the pharmacokinetics, safety, and efficacy (haemodynamics and exercise testing) of bosentan in paediatric patients with PAH. |
| Galiè N, *et al.* *J Am Coll Cardiol.* 2003; 41:1390–6. | BREATHE-1 echocardiography sub-study: To investigate the effects of bosentan on echocardiographic and Doppler variables in patients with WHO class III or IV PAH (IPAH or PAH-CTD). |
This is a non-exhaustive list of studies and reviews published up to January 2011.

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in primary (idiopathic and familial) PAH, PAH secondary to scleroderma without significant interstitial pulmonary disease and PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger’s physiology. Some improvements have also been shown in patients with PAH WHO functional class II. Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

**REFERENCES**


**CONTENT OVERVIEW**

**Long-term outcomes**


**Quality of life**


**Digital ulcers**


**VITAL**


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Liver aminotransferase levels must be measured 2 weeks after any dose increase. Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. In the case of PAH clinical deterioration despite Tracleer treatment for at least 8 weeks, alternative therapies should be considered. However, some PAH patients who show no response after 8 weeks of treatment may improve after an additional 4 to 8 weeks of treatment. PAH patients not responding well to 125 mg twice daily of Tracleer may slightly improve their exercise capacity when the dose is increased to 250 mg twice daily. A careful benefit-risk assessment should be made, taking into consideration that the liver toxicity is dose-dependent. If the decision to withdraw Tracleer treatment is made, an alternative therapy is introduced.

Controlled clinical trial experience in patients with digital ulcers associated with systemic sclerosis is limited to 6 months and there are no data on the safety and efficacy in patients under the age of 18 years. The digital ulcer patient’s response to treatment and need for continued therapy should be re-evaluated.

Toxicity and side effects

Liver enzyme elevations in liver aminotransferases, jaundice, and other hepatic symptoms have been observed in 4.2% of bosentan-treated patients (AST and ALT, greater than 3 times the upper limit of normal). Although bosentan received a license for the treatment of PAH in patients with the WHO functional class I IPAH, it is not known if the benefit/risk balance of bosentan has not been established in patients with severe pulmonary arterial hypertension. Transfer to a therapy that is recommended at the same therapeutic class should be considered if the patient deteriorates. The benefit/risk balance of Tracleer has not been established in patients with WHO class I functional status of PAH. Tracleer should only be initiated if the systemic blood pressure is higher than 100/60 mm Hg, and Tracleer has not been shown to be more effective, and greater adverse event rates cannot formally be excluded in young children if the dose is increased in the presence of physical findings and associated with hepatitis and/or jaundice, hypersensitivity reactions including dermatitis, pruritus, angioedema, urticaria, rash, fever, anaphylaxis, anaphylactic shock, hypotension, flushing, or a para-neoplastic syndrome.

Hepatobiliary disorders

Very common Liver function test abnormal

Hepatobiliary disorders

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