

5th Annual Meeting of the Lupus Academy

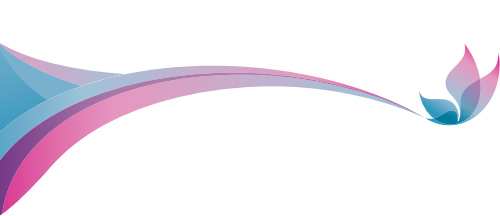
Abstract Book

NH Noordwijk Conference Centre
Leeuwenhorst, Noordwijkerhout
(near Amsterdam), The Netherlands
6–8th May 2016



LupusAcademy

Communicate. Educate. Treat.



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Participants from Europe

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Participants from other countries

CME accreditation by EACCME and ECMECs are recognised internationally by many national authorities across the globe. Please check with your local authority to confirm its validity for your purposes.

Meeting organisation

The content for this activity has been developed under the control of the meeting Chairs: Professor Ricard Cervera, Barcelona, Catalonia, Spain, Zahir Amoura, Paris, France, Professor Richard A. Furie, New York, USA and Professor Ronald F. van Vollenhoven, Amsterdam, The Netherlands, on behalf of the Steering Committee of the Lupus Academy. No supporting companies have had any influence over the presentation of any aspects of this meeting. For information about financial and in-kind support received to assist Lupus Academy in the delivery of its educational programme, please visit the website www.lupus-academy.org. CME compliance, accreditation and fulfilment has been facilitated by European CME Forum, on behalf of the Lupus Academy.



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There are various opportunities to support the Lupus Academy. Please contact us for further information secretariat@lupus-academy.org.

Welcome

Dear Friends and Colleagues,

We are delighted to welcome you to the 5th Annual Meeting of The Lupus Academy[†], which we hope will be one of the most rewarding and interactive learning programmes you will participate in this year.

Now in its fifth year, the Lupus Academy is a global initiative that continues to strengthen its commitment to providing high quality, insightful and clinically relevant education both through interactive meetings and eLearning. With this we aim will support you as you strive to provide best-in-class patient care and improve patient outcomes in lupus.

This Annual Meeting, which has been accredited by the European Accreditation Council for CME (EACCME), aims to provide latest insights into advances in global research and clinical practice in lupus and allied diseases. Delegate feedback from our previous annual meetings continues to guide us in selecting the topics and speakers you need to ensure translation of treatment advances into your clinical practice.

The scientific component of this programme, developed by our Steering Committee of 12 international experts in lupus, is designed to create a highly interactive forum through which we can all develop a logical approach to the management of lupus worldwide.

This meeting will give you the opportunity to meet like-minded clinicians and scientists and, through the sharing of clinical experience, develop your knowledge in this fast moving therapeutic area.

We sincerely hope that this meeting will provide you with new ideas for your clinical work, enriched enthusiasm for collaborative research, and fruitful discussions with your colleagues who care for patients with lupus.

We look forward to meeting and talking with you here in The Netherlands.

With kind regards,

The Lupus Academy Steering Committee

Professor Ricard Cervera

Course Director and
co-Chairman 2016

Professor Zahir Amoura

co-Chairman 2016

Professor Richard A. Furie

co-Chairman 2016

Professor Ronald

van Vollenhoven
co-Chairman 2016

Professor Andrea Doria

Professor Munther A. Khamashta

Professor Thomas Dörner

Professor Roger A. Levy

Professor Bevra H. Hahn

Professor Sandra V. Navarra

Professor David A. Isenberg

Professor Murray B. Urowitz

[†]The Lupus Academy is a long-term initiative dedicated to improving patient outcomes in SLE through an interactive educational forum dedicated to sharing best clinical practice through the dissemination and discussion of clinical and basic scientific research about SLE and allied diseases

Programme

Friday 6th May			Page
18:00	Opening Address	Ricard Cervera (Spain) & Ronald F. van Vollenhoven (The Netherlands)	
Keynote Lectures		Moderators: Ricard Cervera (Spain), Zahir Amoura (France) & Ronald F. van Vollenhoven (The Netherlands)	
18:10–18:35	The top SLE stories in 2015: Clinical aspects	Richard A. Furie (USA)	
18:35–19:00	The top SLE stories in 2015: Basic science	Thomas Dörner (Germany)	24
Discussion Forum: Issues and Answers		Moderators: Roger A. Levy (Brazil) & Jamal Al-Saleh (UAE)	
19:00–20:30	Does seronegative APS exist? The matter of the debate (15 minutes) Yes: (20 minutes + 10 minutes rebuttal) No: (20 minutes + 10 minutes rebuttal) Discussion (15 minutes)	Ricard Cervera (Spain) Munther A. Khamashta (UK/UAE) Vittorio Pengo (Italy)	26
20:30	Welcome Dinner		

Saturday 7th May			Page
07:00	Breakfast with the Professor I	Steering Committee	
Plenary I: New Horizons in Basic Science		Moderators: Ronald F. van Vollenhoven (The Netherlands) & Thomas Dörner (Germany)	
08:00	Inflammatory signals induce regulator B cells in healthy: what goes wrong in lupus patients?	Claudia Mauri (UK)	30
08:30	SLE redefined based on molecular pathways	Marta Alarcón Riquelme (USA)	32
09:00	Autoantibodies to neural antigens	Josep Dalmau (Spain)	34
09:30	Discussion		
Curbside Consults		Moderator: Richard A. Furie (USA)	
10:00	The experts tackle lupus nephritis and lupus arthritis	Bevra H. Hahn (USA), Murray B. Urowitz (Canada), David A. Isenberg (UK), Ronald F. van Vollenhoven (The Netherlands) & Jamal Al-Saleh (UAE)	36
10.30	Coffee		
Case Study Workshops (AM)			
11:00	Moderator: Ronald F. van Vollenhoven (The Netherlands) The lungs	 Murray B. Urowitz (Canada) & Andrea Doria (Italy)	40
11:00	Moderator: Bevra H. Hahn (USA) The gastrointestinal tract and the liver	 David A. Isenberg (UK) & Thomas Dörner (Germany)	44
11:00	Moderator: Richard A. Furie (USA) The nervous system	 Zahir Amoura (France) & Josep Dalmau (Spain)	48
11:00	Moderator: Roger A. Levy (Brazil) Pregnancy	 Rebecca Fischer-Betz (Germany) & Munther A. Khamashta (UK/UAE)	52
11:00	Moderator: Ricard Cervera (Spain) Paediatric and other lupus challenges in clinical practice	 Tadej Avčin (Slovenia) & Sandra V. Navarra (Philippines)	54
12:30	Lunch		

Saturday 7th May *continued* Page

Case Study Workshops (PM)				
13:30	<i>Moderator: Ronald F. van Vollenhoven (The Netherlands)</i> The lungs		Murray B. Urowitz (Canada) & Andrea Doria (Italy)	40
13:30	<i>Moderator: Bevra H. Hahn (USA)</i> The gastrointestinal tract and the liver		David A. Isenberg (UK) & Thomas Dörner (Germany)	44
13:30	<i>Moderator: Richard A. Furie (USA)</i> The nervous system		Zahir Amoura (France) & Josep Dalmau (Spain)	48
13:30	<i>Moderator: Roger A. Levy (Brazil)</i> Pregnancy		Rebecca Fischer-Betz (Germany) & Munther A. Khamashta (UK/UAE)	52
13:30	<i>Moderator: Ricard Cervera (Spain)</i> Paediatric and other lupus challenges in clinical practice		Tadej Avčin (Slovenia) & Sandra V. Navarra (Philippines)	54
15:00	Coffee			

Plenary II: Management of SLE–Compliance, Comorbidities and Drug Toxicities		<i>Moderators: David A. Isenberg (UK) & Bevra H. Hahn (USA)</i>		
15:30	The importance of assessing medication exposure in SLE	Zahir Amoura (France)		58
16:00	Managing fatigue in SLE	David D'Cruz (UK)		60
16:30	Using lower doses of glucocorticoids in SLE: less toxicity, same efficacy	Guillermo Ruiz-Irastorza (Spain)		62
17:00	Prevention of accelerated atherosclerosis in SLE: Should everyone be on a statin?	Bevra H. Hahn (USA)		64
17:30	Discussion			
18:00	Close			

Sunday 8th May Page

07:00	Breakfast with the Professor II	Steering Committee
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Plenary III: Management of SLE–Therapies Derived from Other Specialties		<i>Moderators: Richard A. Furie (USA) & Ricard Cervera (Spain)</i>		
08:00	Bortezomib in SLE	Reinhard Voll (Germany)		66
08:30	Eculizumab in SLE	Josep M. Campistol (Spain)		68
09:00	Romiplostim and eltrombopag for idiopathic thrombocytopenic purpura	Sacha Zeerleder (The Netherlands)		70
09:30	Discussion			
10:00	Coffee			

Plenary IV: Designing Clinical Trials in SLE		<i>Moderators: Roger A. Levy (Brazil) & Andrea Doria (Italy)</i>		
10:30	Lessons learned from SLE clinical trials	Richard A. Furie (USA)		72
11:00	How different is SLE? Applying lessons from other diseases to trials in lupus	Ronald F. van Vollenhoven (The Netherlands)		74
11:30	Discussion			
12:00	Summary and close	Ricard Cervera (Spain) & Zahir Amoura (France)		

Biographies



Dr Jamal Al-Saleh, MD, FRCP

Dubai Hospital, Dubai, UAE

Disclosures

None

Jamal Al-Saleh is a UK-trained Rheumatologist in practice for 21 years. Currently, he is the Head of the Rheumatology Section and Medical Director of Medicine at Dubai Hospital.

Dr Al-Saleh completed his undergraduate training at the Royal College of Surgeons in Ireland, graduating with honours in medicine and surgery in 1995. He obtained his membership of the Royal College of Physicians in the UK in 1999 and was awarded a Masters in Clinical Rheumatology from the University of Manchester in 2003. He was awarded his Fellowship of the Royal College of Physicians in London and Edinburgh in 2009 and 2010 respectively.

Dr Al-Saleh is an Examiner of the Royal College of Physicians and an International Advisor of the Royal College of Physicians (London) for the

UAE. He is a Senior Lecturer at the Dubai Medical School and is actively involved in undergraduate and postgraduate training. He is a Chairman and a member of several committees in the Dubai Health Authority, past-Chairman of the Emirates Society of Rheumatology and past-Chairman of Emirates Society of Osteoporosis.

Dr Al-Saleh has conducted several research projects on the prevalence and clinical and immunological features of lupus patients in Dubai including; Dubai Hospital Lupus Cohort and PRODUBAI, which researched the prevalence of Rheumatic diseases and Osteoporosis in Dubai. He has built the first Arthritis Registry in the Middle East which gathers data on six diseases. His current interest is systemic lupus erythematosus, early rheumatoid arthritis, seronegative spondyloarthritis and osteoporosis.



Professor Marta E. Alarcón-Riquelme, MD, PhD
Center for Genomics and Oncological Research, Granada, Spain

Disclosures

Grants/Research

Support: IMI project
PRECISEADS

Marta E. Alarcon-Riquelme is Head of the Medical Genomics Area at the Center for Genomics and Oncological Research (GENYO), Granada, Spain and Visiting Professor at the Karolinska Institutet, Stockholm, Sweden. Professor Alarcon-Riquelme studied Medicine in Mexico, before moving to Sweden in 1987 where she was awarded her PhD in Immunology from Stockholm University in 1994. After her PhD she began forming research collaborations, which allowed her to build banks of samples for genetics studies, families and case-control sets. These efforts, and financing from the European 4th Framework Programme, allowed her to publish the identification of the first gene resulting from genetic linkage analyses of systemic lupus erythematosus (SLE) families, PDCD1, and the very first example of how to analyse a genetic polymorphism with impact on transcription factor binding and gene expression. In several subsequent studies, Professor Alarcon-Riquelme identified BANK1 and developed understanding of the mechanisms through which genetic polymorphisms modulate gene function for IRF5, CD226 and fine mappings of various genes published in top journals. Following these research activities, Professor Alarcon-Riquelme was invited to become a member of the International Lupus Genetics Consortium.

Professor Alarcon-Riquelme has been Editorial Advisor for *Genes & Immunity* and has served as Advisory Editor of *Arthritis & Rheumatism* and has been an invited speaker to over 60 meetings and congresses since 1996. She has been a grant evaluator for the Swedish Research Council (presiding in 2006, 2008 and 2009), Wellcome Trust (2001, 2004), Arthritis Research Campaign (2004, 2007), European Young Investigator Awards for Sweden (2007), and Academy of Finland (2011–2013), among others.

Professor Alarcon-Riquelme has dedicated her career to the understanding of the autoimmune disease SLE, focusing on the identification of susceptibility genes and how these impact on cell function. Since 1997 she has trained Masters Students, PhD students and postdoctoral graduates and, since 2009, coordinated the European Research Network BIOLUPUS with members from 10 European countries funded through the European Science Foundation (2009–2014); this network consolidated clinical information from all European SLE patients and centralises data and samples for genetic analyses. Professor Alarcon-Riquelme also coordinates two large multicentre collaborations in Latin America on lupus (GENLES) and rheumatoid arthritis (GENAR) involving 60 clinical centres. Most recently, she has received important support from the Innovative Medicines Initiative-Joint undertaking of the European Union to study the molecular reclassification to find clinically useful biomarkers for systemic autoimmune diseases, a project she coordinates that includes 28 partners among which there are 5 major pharmaceutical companies; she has also support from the Alliance for Lupus Research to research the Influence of BANK1 in the In Vivo Development of Lupus and support from the Consejería de Economía, Innovación y Ciencia (Spain) to help characterise Spanish SLE patients for genetics studies.

Biographies



Professor Zahir Amoura, MD, MSc

French National Reference Center for SLE and APS, Pitié-Salpêtrière Hospital, Paris, France

Zahir Amoura is Professor of Internal Medicine and Head of the Department of Internal Medicine at the French National Reference Centre for Systemic Lupus Erythematosus at Pitié-Salpêtrière Hospital. Professor Amoura completed his Paris Hospital Medical Internship in 1988, and obtained a Master's degree in Immunopharmacology in 1989. He was subsequently awarded his MD (silver medal) in 1993 and his qualifying certification in internal medicine in 1994. Professor Amoura joined the Department of Internal Medicine at Pitié-Salpêtrière Hospital in 1995 as a Senior Lecturer and Senior Practitioner. He has been Professor of Internal Medicine there since 2003, and in 2009 became Head of the Department of Internal Medicine in the same institution.

In the last 15 years, he has published over 370 peer-reviewed papers, of which 170 focused on the immunopathological features of lupus.

Disclosures

Grants/Research

Support: Actelion; Amgen; BMS; Eli Lilly; GSK; Roche; Teva

Consultant/Advisor:

AstraZeneca; GSK

Meeting Honorarium/

Expenses: Amgen; BMS; GSK; Eli Lilly

Professor Amoura is co-Chair of the Lupus Academy (2016) and has been involved in the planning and development of the 5th Annual Meeting programme and materials.



Professor Tadej Avčin, MD, PhD

Children's Hospital, University Medical Center, Ljubljana, Slovenia

Tadej Avčin is Consultant Paediatric Rheumatologist and Head of the Department of Allergology, Rheumatology and Clinical Immunology at the Children's Hospital, University Medical Center Ljubljana, Slovenia.

Professor Avčin graduated in medicine from the University of Ljubljana in 1996 and completed his residency in paediatrics at the Children's Hospital, University Medical Center Ljubljana in 2003. He completed his fellowship in paediatric rheumatology at the Hospital for Sick Children, University of Toronto, Canada between 2004 and 2005. In 2004 he became an Associate Professor, and in 2010 Professor of Paediatrics at the University of Ljubljana Faculty of Medicine.

His main interest is paediatric rheumatology with an emphasis on juvenile idiopathic arthritides and systemic connective tissue diseases. He is the Principal Investigator of the International Registry of Paediatric Antiphospholipid Syndrome, Chairman of the EULAR Standing Committee on Paediatric Rheumatology and Chairman of the Education and Training committee of Paediatric Rheumatology European Society. Professor Avčin is the author of more than 90 peer-reviewed articles and 10 book chapters on paediatric rheumatology.

Disclosures

Meeting Honorarium/

Expenses: BMS; Octapharma

Speakers' Bureau:

AbbVie; Pfizer; Octapharma



Professor Josep M. Campistol, MD, PhD
Hospital Clinic, Barcelona, Catalonia, Spain

Disclosures

Grants/Research

Support: Alexion; Novartis; Pfizer

Consultant/Advisor:

Alexion; Novartis; Pfizer

Josep M. Campistol is currently the General Director of the Hospital Clinic of Barcelona, Spain, and former Medical Director of the same hospital as well as Director of the Clinical Institute of Nephrology and Urology (ICNU). He is also Professor of Medicine at the Nephrology Department of the University of Barcelona.

He received his medical degree from the University of Barcelona in 1983, and completed his residency in internal medicine and, subsequently, his fellowship in renal medicine at the Hospital Clinic of the same institution. Following his training as a fellow in renal medicine at the University of Barcelona, Professor Campistol continued his clinical work in renal transplantation within the Renal Transplant Unit at the Hospital Clinic. During this period, he also developed research interests into the pathogenesis of dialysis-related

amyloidosis, and undertook a visiting Fulbright Scholarship at Boston University School of Medicine in Boston, MA, USA (1991–1992). His doctoral thesis, which he obtained in 1990, was based on the '*Pathogenesis of dialysis-amyloidosis and the role of lymphocytes on beta-2-microglobulin synthesis and dialysis membranes*'.

Professor Campistol has published more than 500 experimental and clinical papers in international peer-reviewed journals. He is a member of many international transplant societies, on the editorial board of a number of major international transplant journals and a Principal Investigator in numerous clinical studies. His current research interests include the use of new immunosuppressive regimens in renal transplantation, mechanisms of allograft fibrosis and renal regenerative medicine.



Professor Ricard Cervera, MD, PhD, FRCP
Hospital Clinic, Barcelona, Catalonia, Spain

Disclosures

Consultant/Advisor:

GSK

Professor Cervera is Programme Director and co-Chair of the Lupus Academy (2016) and has been involved in the planning and development of the 5th Annual Meeting programme and materials.

Ricard Cervera is co-Founder and Head of the Department of Autoimmune Diseases at Hospital Clinic, Barcelona. He is also leader of the Research Team on Systemic Autoimmune Diseases at the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and Professor at the University of Barcelona where he coordinates the Masters Course on Autoimmune Diseases. He qualified in medicine in 1983 from the University of Barcelona and received his PhD in 1988 for his thesis on anticardiolipin antibodies. He spent 2 years at the Lupus Research Unit at The Rayne Institute, St Thomas' Hospital, London.

Professor Cervera is an Associate Editor of the journal *Lupus Science & Medicine* and is on the Editorial Boards of 20 medical journals. He is coordinator of the European Forum on Antiphospholipid Antibodies and of the European Working Party on Systemic Lupus Erythematosus (SLE) (Euro-Lupus Group). He is Chairman of the Medical Advisory Board of the Catalan Association of Lupus Patients and Medical Advisor to Lupus-

Europe. He chaired the 6th and 8th International Congresses on Autoimmunity, the 1st and 2nd Latin-American Congresses on Autoimmunity, the 5th Meeting of the European Forum on Antiphospholipid Antibodies and the 8th European Lupus Congress.

Professor Cervera's research interests include clinical and epidemiological aspects of systemic autoimmune diseases, particularly SLE and antiphospholipid syndrome, with special focus on its 'catastrophic' variant. He has presented over 300 invited lectures and published more than 800 scientific papers (H-factor, 60), including original articles in the *New England Journal of Medicine*, *The Lancet*, *Annals of Rheumatic Diseases*, *Arthritis & Rheumatism*, *American Journal of Medicine* and *Medicine* (Baltimore). He is co-Editor of 25 books, including 'The Antiphospholipid Syndrome', 'Vascular Manifestations of Systemic Autoimmune Diseases' and 'Diagnostic Criteria in Autoimmune Diseases'.

Biographies



Professor Josep Dalmau, MD, PhD
Hospital Clinic, Barcelona, Catalonia, Spain

Disclosures

Grants/Research

Support: Euroimmun;

Fundació Privada CELLEX

Josep Dalmau is Research Professor at the Catalan Institution for Research and Advanced Studies (ICREA) in IDIBAPS/Hospital Clinic, University of Barcelona, and Adjunct Professor of Neurology at the University of Pennsylvania. He received his M.D. and Ph.D. from the Autònoma University of Barcelona, Spain, after which he trained in Neuro-oncology at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York and afterwards was appointed to the faculty. After 11 years at MSKCC, Professor Dalmau took a position as co-Director of Neuro-oncology at the University of Arkansas for Medical Sciences. In 2002 he moved to the Department of Neurology and Abramson Cancer Center of the University of Pennsylvania as Professor of Neurology.

Professor Dalmau's research is funded by a variety of agencies including the USA National Institutes of Health (NIH) and the Spanish Health Institute (ICIII). His research is focused on autoimmune and paraneoplastic neurological disorders and his recent work has revealed a new category of disorders mediated by antibodies to neuronal cell surface and CNS synaptic proteins.

In 2015, Professor Dalmau was elected member of the National Academy of Medicine (USA). He is a member of many academic societies, Editor of *Neurology: Neuroimmunology* and *Neuroinflammation*, and associate editor of *Neurology*.



Professor David D'Cruz, MD, FRCP
Guys and St Thomas' Hospital, London, UK

Disclosures

Grants/Research

Support: Aspreva/Vifor

Pharma; Suppremol

Meeting Honorarium/

Expenses: GSK; Roche

Speakers' Bureau: Eli Lilly;

UCB

David D'Cruz is a Consultant Rheumatologist and is the Clinical Team Lead at the Louise Coote Lupus Unit at Guys and St Thomas' Hospital, London, an internationally renowned tertiary referral centre for autoimmune rheumatic disorders. He also leads the Louise Coote Lupus Clinical Trials Unit which has a portfolio of investigator and industry led trials.

Professor D'Cruz trained at St Mary's Hospital Medical School in London. Senior House Officer and Registrar rotations at University College and the Royal London Hospitals were followed by a clinical registrar post and an ARUK Clinical Research Fellowship at St Thomas' Hospital. He was appointed Senior Lecturer in Rheumatology at St Bartholomew's and The Royal London Hospitals following a Senior Registrar post in General Internal Medicine and Rheumatology.

Professor D'Cruz has published widely in the field of autoimmune rheumatic disorders. He is one of the Managing Editors of the journal *Lupus* and was Editor in Chief of the *Journal of Autoimmune Diseases* 2004–2009. He is a past President of the Rheumatology Section of the Royal Society of Medicine.

His major clinical and research interests are systemic lupus erythematosus, the antiphospholipid syndrome and systemic vasculitis. His research portfolio includes a translational medicine programme in collaboration with basic science laboratories in the Division of Immunology, Inflammation and Infectious Diseases, Kings College School of Medicine, London.



Professor Andrea Doria, MD
University of Padova, Italy

Disclosures

Consultant/Advisor:
GSK

Professor Doria is a member of the Lupus Academy Steering Committee, has been involved in the planning and development of the Lupus Academy's 5th Annual Meeting programme and materials.

Andrea Doria is Professor of Rheumatology and Head of the Unit of Connective Tissue Disease and Rare Rheumatic Diseases, Division of Rheumatology, Department of Medicine, University of Padua, Italy.

Professor Doria received his medical degree and qualification in Rheumatology from the University of Padua. He was Council member of the Italian College of Rheumatology (CRO) between 1999 and 2005 and a Council member of the Italian Society of Rheumatology (SIR) from 2007 to 2010 and from 2013 until now. He is also a member of American College of Rheumatology (ACR).

Professor Doria has organised over ten international conferences on autoimmunity and was involved as "expert" in the European League Against Rheumatism (EULAR) Standing Committee for the development of clinical and therapeutic recommendations: (1) EULAR recommendations for the management of systemic lupus erythematosus (SLE)—Assessment of the SLE patient (2008–2009); (2) EULAR recommendations for the management of SLE Part II—Neuropsychiatric disease (2008–2009); (3) Joint EULAR and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis (2012). Professor Doria is a member of the Lupus Academy Steering Committee and co-Chaired the 4th Annual Meeting held in Rome 27th February to 1st March 2015. He will also chair the 10th European Lupus Meeting which will be held in Venice (Italy) 5–8th October 2016.

Professor Doria is on the Editorial Boards of several rheumatology and immunology journals, including *Lupus*, *Autoimmunity*, *Clinical and Experimental Rheumatology*, *Autoimmunity Reviews*, *Journal of Autoimmunity*, *Experimental Biology and Medicine*, *Rheumatology Reports*, *Journal Autoimmunity Highlights* and *Reumatismo* (the official journal of Italian Society of Rheumatology).

He has authored over 250 ISI publications on SLE and other connective tissue diseases. These include clinical studies describing new manifestations or subgroups of autoimmune disorders, prognostic risk factors, diagnostic tests and therapeutic interventions, as well as immunochemical studies that evaluate autoantibodies, epitopes and complementary epitopes of autoantigens. In addition, he has authored and co-authored three books, over 90 book chapters and conference proceedings, and over 500 abstracts for national and international conferences.

Professor Doria has long-standing experience of the clinical management of patients with connective tissue diseases. The Unit in which he works is a tertiary referral rheumatology centre, within Italy, for the diagnosis and management of patients affected with systemic connective diseases. In addition, he has expertise in the management and follow-up of pregnant patients with systemic rheumatic diseases. Professor Doria has also trained over 30 students in Rheumatology.

Biographies



Professor Thomas Dörner, MD
Charité University Hospitals Berlin, Germany

Disclosures

Grants/Research

Support: Janssen/J&J;
Roche/Chugai; Sanofi;
UCB

Meeting Honorarium/

Expenses: Eli Lilly; Roche;
UCB

Speakers' Bureau: Eli Lilly;
Roche; UCB

Professor Dörner is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the 5th Annual Meeting programme and materials.

Thomas Dörner is a board certified Rheumatologist and Professor of Rheumatology and Hemostaseology at Charité University Hospitals, Berlin, and group leader at the German Research Center of Rheumatology, Berlin (DRFZ). He qualified in medicine in 1990 at Charité University Hospitals, Berlin, and received his board certification in internal medicine in 1995 before undertaking a postdoctoral fellowship at the University of Texas, Southwestern Medical Center at Dallas, where he researched delineating molecular aspects of B-cell receptor gene usage in autoimmune diseases.

Professor Dorner has received a number of international and national awards, including the Senior Scholar Award of the American College of Rheumatology, the H Schultze Award of the German League Against Rheumatism, the Randy Fischer Prize for Excellence in flow cytometry and the Schoen Award of the German Society of Rheumatology.

Professor Dorner has served as a member of Editorial Boards of leading journals in rheumatology and immunology, including *Arthritis & Rheumatism*, *Arthritis Research & Therapy*, *Annals of the Rheumatic Diseases*, *Global Arthritis Research Network (GARN)*, *Current Reviews in Rheumatology*, *the Brazilian Journal of Rheumatology*, *the European Journal of Immunology*, *Lupus Science & Medicine* and *Rheumatology Reviews*.

Professor Dorner has led various clinical trials on rheumatic diseases, including systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis and seronegative spondyloarthropathies. His research interests focus on the characterisation of disturbances of humoral autoimmunity and abnormalities of B cell subsets in the blood versus tissue (lupus, neonatal lupus syndromes, Sjogren's syndrome), exploring innovative therapeutic approaches with particular focus on B-cell directed therapy as well as improving diagnostic tools in autoimmune diseases.



Dr Rebecca Fischer-Betz, MD
Heinrich-Heine-University, Dusseldorf, Germany

Disclosures

Grants/Research: UCB;
GSK

Consultant/Advisor: UCB;
GSK; Pfizer; AbbVie; MSD;
Roche; Chugai

Rebecca Fischer-Betz is Deputy Director of the Department of Rheumatology at Heinrich-Heine-University Hospital in Dusseldorf. Following Medical School at Westfalian-Wilhelms-University Munster, Germany and Boston University, USA, she took up a residency at Westfalian-Wilhelms-University Hospital and at Heinrich-Heine-University Hospital in the departments of gastroenterology, endocrinology and rheumatology before being appointed to her current position. Dr Fischer-Betz has also attended a programme in clinical effectiveness at the Harvard School of Public Health, USA.

Dr Fischer-Betz sits on the Board of the German Society of Rheumatology, is Chair of the Pregnancy in Rheumatic Disease Study Group, and is on the Steering Committee of the European League Against Rheumatism (EULAR) task force for "Points to consider for use of antirheumatic drugs before pregnancy and during pregnancy and lactation". She is also on the Editorial Boards for the *Zeitschrift für Rheumatologie* and *Lupus Science & Medicine*.

Dr Fischer-Betz's primary research interests include systemic lupus erythematosus and pregnancy in autoimmune diseases.



Professor Richard A. Furie, MD

Hofstra Northwell School of Medicine, New York, USA

Disclosures

Grants/Research

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Biogen Idec; BMS;
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Pharmaceuticals; Sanofi;
Takeda; UCB

Consultant/Advisor:

AbbVie; Biogen Idec; BMS;
Boehringer-Ingelheim;
Celgene; Chugai; Eli Lilly;
Estrela (Janssen); Exagen;
Genentech/Roche; GSK;
MedImmune; Novartis;
Onyx; Pfizer; Mallinckrodt
Pharmaceuticals;
Regeneron; Sanofi;
Takeda; UCB

Investigator: AbbVie;

Amgen; Anthera; Biogen
Idec; BMS; Boehringer-
Ingelheim; Celgene;
Dynavax; Eli Lilly; Exagen;
Genentech/Roche; GSK;
Medimmune; Mallinckrodt
Pharmaceuticals;
Regeneron; Sanofi;
Takeda; UCB

*Professor Furie is co-Chair
of the Lupus Academy
(2016) and has been
involved in the planning
and development of
the 5th Annual Meeting
programme and materials.*

Richard Furie is Chief of the Division of Rheumatology at Northwell Health, New York, and Professor of Medicine at the Hofstra Northwell School of Medicine. He is a rheumatologist whose activities, for several decades, have focused on patient care, physician education and clinical research in the area of anti-rheumatic drug development. He directs The Program in Novel Therapeutics—the Health System's clinical research programme in musculoskeletal disease. He also directs the hospital's SLE and Autoimmune Disease Treatment Center, which has become internationally recognised for its role in the development of new therapies for SLE.

Regarded as one of the senior rheumatologists in the New York metropolitan area, Professor Furie has been on the Boards of Directors of the local chapters of the Arthritis Foundation and the Lupus Alliance of America and is a member of the Medical-Scientific Advisory Council of the Lupus Foundation of America as well as its Lupus News Editorial Board. He also is on the Medical and Scientific Advisory Board of the SLE Foundation as well as the Alliance for Lupus Research Scientific Advisory Board. Professor Furie has served on many committees of the American College of Rheumatology for nearly twenty years.

Biographies



Professor Bevra H. Hahn, MD
University of California, Los Angeles, USA

Disclosures

Grants/Research

Support: BMS

Consultant/Advisor:

Biogen/Idec; Eli Lilly

Professor Hahn is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the 5th Annual Meeting programme and materials.

Bevra Hahn is Distinguished Professor of Medicine (Emeritus, recalled for part time work) in the Division of Rheumatology at the University of California, Los Angeles (UCLA). She received her medical degree and Rheumatology training at Johns Hopkins University School of Medicine in Baltimore, Maryland. She was Chief of Rheumatology at UCLA for 30 years.

Professor Hahn has published research in clinical investigations and basic studies of immune tolerance (including the invention of a tolerizing peptide) and T-cell biology as they apply to systemic lupus erythematosus (SLE). For these works she and her colleagues have received

several awards, including the Carol-Nachman International Award for Rheumatology Research, awards from the British Society for Rheumatology and the Dutch Society for Rheumatology, the James Klinenberg Medal of the US Arthritis Foundation, an award from the Canadian Rheumatism Society, and the Gold Medal of the American College of Rheumatology (ACR). Professor Hahn was President of the ACR (1999–2000). She is co Editor, with Daniel Wallace, of the 'Dubois' Lupus Erythematosus textbook and is first author of the ACR guidelines for the management of lupus nephritis. She continues to work in clinical and basic research devoted to the study of SLE.



Professor David A. Isenberg, MD, FRCP, FAMS
University College London, UK

Disclosures

Professor Isenberg does not accept personal honoraria but asks that an equivalent sum is given to an arthritis charity of his choosing.

Professor Isenberg is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the 5th Annual Meeting programme and materials.

David Isenberg is the Arthritis Research UK Diamond Jubilee Professor of Rheumatology at University College London (UCL). He graduated from St. Bartholomew's Hospital, London, in 1973, and trained in general medicine, rheumatology, neurology, psychiatry and gastroenterology, becoming a Research Fellow at UCL/The Middlesex Hospital in 1979. He was awarded his MD in 1984, based on his studies of myositis. During a year of research at Tufts University, Boston, he became interested in autoantibody structure/function and origin. He was appointed Consultant Rheumatologist in 1984, Professor in 1991 and became the arc Diamond Jubilee Chair of Rheumatology at UCL in 1996. He has fellowships of both the Royal College of Physicians and the Academy of Medical Sciences.

Professor Isenberg is on the Editorial Boards of five journals, including the *Journal of Rheumatology*. He is Chair of the British Isles Lupus Assessment Group (BILAG) and Lupus UK's Research

Committee and was Chair of the Systemic Lupus International Collaborating Clinics group (SLICC) (1998–2003). During the past 20 years, Professor Isenberg has undertaken many roles at Arthritis Research UK and currently sits on the Executive Board. He is past-President of the British Society for Rheumatology (2004–2006) and he chaired the Society's Biologics Register Committee for 5 years (2006–2011). Professor Isenberg was the 2010 recipient of the Evelyn V. Hess Prize from the Lupus Foundation of America for his contribution to lupus research and treatment. He has authored over 550 original articles, 275 reviews/chapters and 18 books, many on topics related to lupus.

Professor Isenberg's principal clinical interests are the development of disease activity and damage assessment tools in patients with lupus. His specialist interest is autoimmune rheumatic diseases, notably systemic lupus erythematosus, Sjogren's syndrome, myositis and antiphospholipid antibody syndrome.



Professor Munther A. Khamashta, MD, PhD, FRCP
St. Thomas' Hospital, London, UK. Dubai Hospital, Dubai, UAE

Disclosures

Grants/Research

Support: Bayer

Consultant/Advisor:

GSK; INOVA Diagnostics;
Medimmune/AstraZeneca;
UCB

Meeting Honorarium/

Expenses: GSK; INOVA
Diagnostics; Medimmune/
AstraZeneca

Professor Khamashta is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the 5th Annual Meeting programme and materials.

Munther Khamashta is Professor/Consultant Physician and Director of the Lupus Research Laboratory at St Thomas Hospital, London. He studied medicine in Barcelona and internal medicine in Madrid, Spain, where he developed an interest in connective tissue diseases and received his PhD. He was awarded the MRCP in 1999 and FRCP in 2002. He joined the Lupus Unit in London 30 years ago and has been instrumental in developing it into an internationally recognised tertiary centre receiving referrals from all over the UK. He is currently on sabbatical leave setting up lupus services at Dubai Hospital, United Arab Emirates.

Professor Khamashta has served on the Editorial Boards of many journals, including *Clinical & Experimental Rheumatology*, *Lupus* and *Current Rheumatology Reviews*. He is a member of several professional societies, including the International Society of Internal Medicine, the American College of Rheumatology (ACR), and the Spanish Society of Rheumatology. He is a member of the Steering Committee of the International Board on the Study of Antiphospholipid Antibodies and of the Steering

Committee of the International Advisory Board for Systemic Lupus Erythematosus. He is a founding member of the Lupus Academy and APS-ACTION. He has received several international awards for his work, including the European League Against Rheumatism (EULAR) and International League Against Rheumatism (ILAR) prizes.

Professor Khamashta has a strong research interest in lupus and connective tissue diseases, with a special interest in pregnancy and antiphospholipid syndrome. He has published extensively in Lupus, Hughes Syndrome and related areas, with more than 700 original papers.

Biographies



Professor Roger A. Levy, MD, PhD
The State University of Rio de Janeiro, Brazil

Disclosures

Grants/Research

Support: AbbVie; GSK; Servier

Meeting Honorarium/

Expenses: AbbVie; GSK; INOVA; Janssen; Pfizer; Roche

Speakers' Bureau:

AbbVie; GSK; Roche; UCB

Professor Levy is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the 5th Annual Meeting programme and materials.

Roger Levy is Associate Professor of Rheumatology at The State University of Rio de Janeiro. Graduating from medical school at the Federal University of Rio de Janeiro in 1986, he subsequently completed a fellowship programme at the Hospital for Special Surgery, Cornell Medical College, New York in 1989 and received his PhD in Biological Sciences from the Biophysics Institute – Immunology, at the Federal University of Rio de Janeiro in 1994. That same year he joined the staff at State University Hospital and started the pregnancy clinic dedicated to patients with rheumatic conditions.

Professor Levy holds positions on a number of Editorial Boards including the journals of *Arthritis and Rheumatology*, *Arthritis Care and Research*, *Clinical Rheumatology*, *Lupus*, *Lupus Science & Medicine*, *Seminars of Arthritis and Rheumatism*, *Rheumatology*, *Autoimmunity Reviews* and *The Brazilian Journal of Rheumatology* (of which he is a former Editor). He was the Scientific Director

of the XXV Brazilian Congress of Rheumatology and chaired the 2nd Latin American Congress of Autoimmunity (Rio de Janeiro, 2006). Professor Levy is past-President of the Rio de Janeiro Rheumatology Society (2007–2008) and is currently the Scientific Director. He has coordinated the Vasculitis and Thrombophilias Committee of the Brazilian Society of Rheumatology since 2009 and chaired the extremely successful XIV International Antiphospholipid Congress (APLA) and IV Latin American Congress of Autoimmunity (LACA) that were held in Rio de Janeiro in September 2013 for almost 700 attendees.

Professor Levy's research is based around the clinical and immunologic aspects of systemic lupus erythematosus, antiphospholipid syndrome, Sjogren's syndrome and pregnancy in rheumatic patients. He has published 110 articles in medical journals, over 200 abstracts, four books, 20 book chapters and has lectured in many countries.



Professor Claudia Mauri, PhD
University College, London, UK

Disclosures

None

Claudia Mauri is Professor of Immunology and Vice-Dean of the International Faculty of Medical Science, University College, London. She received her Doctor of Biology with magna cum laude in 1989 and PhD equivalent in 1996 from the University La Sapienza in Rome, Italy. She did postdoctoral work in London at The Kennedy Institute of Rheumatology, Imperial College, UK. She moved to University College London in 2002 where she established her group.

Professor Mauri's main research interest lies in understanding the mechanisms driving autoimmunity, with a particular interest in understanding the function of regulatory cells in experimental models of rheumatic disease and in patients with systemic lupus erythematosus and rheumatoid arthritis.

Her group was amongst the first to identify a novel subset of B cells with a powerful immuno-suppressive capacity. Her work was seminal in the identification of CD40 activation for regulatory B-cell activation and how the adoptive transfer of this B-cell subset can efficiently prevent disease

development and ameliorate established arthritis. More recently, she has shown that inflammation itself seems to be the primary requisite for Breg development. In arthritis, the inflammatory process is controlled by the gut-microflora, which promotes the differentiation of Bregs in lymphoid organs. Drastic alteration in the inflammatory process imposed by changes in the gut microbiome, either by antibiotic treatment or changes in the sterility of housing conditions, leads to a reduction in the production of IL-1b and IL-6, and concurrently in the number and functional capacity of Bregs.

Professor Mauri's group has also translated the results obtained from experimental models to healthy individuals. She demonstrated that, in healthy individuals, Bregs can directly suppress both pro-inflammatory cytokine production by, and proliferation of, naïve, memory and auto-reactive T cells, whilst supporting the differentiation of regulatory T cells via the release of IL-10. However, in autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus, Bregs have lost their capacity to suppress pro-inflammatory T-cell responses.

Biographies



Professor Sandra V. Navarra, MD, FPCP, FPRA
University of Santo Tomas, Manila, Philippines

Disclosures

Grants/Research

Support: GSK; Pfizer

Speakers' Bureau: GSK; Pfizer; Roche

Professor Navarra is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the 5th Annual Meeting programme and materials.

Sandra Navarra is Professor and Head of Rheumatology at University of Santo Tomas and Consultant Rheumatologist at St. Luke's Medical Center in the Philippines. She served as Secretary-General, Head of the Education Committee, chaired the special interest group on systemic lupus erythematosus (SLE) of the Asia Pacific League of Associations for Rheumatology (APLAR), and was past-President of the Philippine Rheumatology Association.

Professor Navarra co-founded the Arthritis Care and Research Foundation of the Philippines, where she is currently Scientific Programmes Director, and the Lupus Foundation of the Philippines, where she has served as Medical Adviser. Currently President and CEO of the Rheumatology Educational Trust Foundation Inc. (RETFI), she is the prime mover of the Lupus Inspired Advocacy (LUISA) Project for lupus education and research, and the People Empowerment for Arthritis and Lupus (PEARL) Movement for lay education and medical assistance programmes.

Professor Navarra is an experienced clinical trials investigator and has published widely in the field of lupus and other rheumatic diseases. She is a well-known lecturer in a broad range of topics in rheumatology and has received several university and national awards for her contributions to education and research.

Professor Navarra has organised several national and regional educational meetings including the Ten Topics in Rheumatology – Asia (November 2009), the first Asian Lupus Summit (November 2012), the Asian Lupus Summit by Lupus Academy (March to April 2014), and the Lupus Nephritis Forum (July 2015) all held in the Philippines.



Professor Vittorio Pengo, MD
Padova University School of Medicine, Padova, Italy

Disclosures

Consultant/Advisor: Bayer Healthcare; Daiichi-Sankyo

Speaker's bureau: Bayer Healthcare; Daiichi-Sankyo; Boehringer Ingelheim; Instrumentation Laboratory; Roche Diagnostics

Vittorio Pengo is Associate Professor of Cardiology, Department of Cardiac Thoracic and Vascular Sciences, Padova University School of Medicine. He received his certificate in Internal Medicine in 1980 and in Cardiology in 1985. He has been a Research Fellow and visiting scientist at the Cardeza Foundation, Jefferson Medical College, Philadelphia (1984–1986 and 1988) and Chief of the European Core Laboratory of Antiphospholipid Syndrome (APS) Action America. Professor Pengo sits on the Editorial Board of the *Journal of Thrombosis and Haemostasis*, and is also an Editor of the *Internal and Emergency Medicine Journal* and reviewer for numerous other journals. He is also Founder and past-President of the Italian Federation of Thrombosis Centers.

Professor Pengo is President of the Scientific Board for Standardization of the International Society of Thrombosis and Haemostasis in the field of lupus anticoagulant and antiphospholipid antibodies. In the 1999–2000 academic year he was awarded the excellence prize for scientific production. His H-index is 48 (Scopus).

Professor Pengo's clinical and research interests include the primary/secondary prevention and treatment of venous and arterial thromboembolism.



Professor Guillermo Ruiz-Irastorza, MD, PhD

Autoimmune Research Unit at Cruces University Hospital, Bizkaia, Spain

Disclosures

None

Guillermo Ruiz-Irastorza is Head of the Autoimmune Research Unit at Cruces University Hospital, Bizkaia, Spain, where he has been since 2001.

Professor Ruiz-Irastorza received his MD from the Universidad Autónoma de Madrid, Spain in 1990 and became a specialist in Internal Medicine in 1996. Following his PhD from the University of the Basque Country, Spain in 1999, he spent a year as a Research Fellow at the Lupus Research Unit, St Thomas' Hospital, UK, before returning to the Hospital Universitario Cruces as Consultant Physician in Internal Medicine. He became Professor of Medicine at the University of the Basque Country, Spain in 2004.

Professor Ruiz-Irastorza is a member of the Editorial Board of *Lupus*, and a reviewer of several journals in the fields of rheumatology and autoimmune diseases, including *Annals of Rheumatic Diseases*, *Arthritis & Rheumatology*, *Rheumatology*, *Journal of Rheumatology*, and *Lupus Science & Medicine*.

He is a member of the Grupo de Estudio de las Enfermedades Autoinmunes Sistémicas (GEAS), and coordinator of the first Spanish national lupus inception cohort study (RELES). He has been member of the Systemic Lupus International Collaborating Clinics (SLICC) since 2008.

Professor Ruiz-Irastorza's clinical and research interests focus on systemic lupus erythematosus, antiphospholipid syndrome, and pregnancy and autoimmune diseases. He is author of 138 peer-reviewed publications and 20 book chapters.

Biographies



Professor Murray B. Urowitz, MD

University of Toronto, Canada

Disclosures

Grants/Research

Support: GSK

Consultant/Advisor: GSK;
Eli Lilly; Teva; UCB; XTL Bio

Professor Urowitz is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the 5th Annual Meeting programme and materials.

Murray Urowitz is Professor of Medicine at the University of Toronto and Director of the Centre for Prognosis Studies in the Rheumatic Diseases and the University of Toronto and the Lupus Clinic at the Toronto Western Hospital. Professor Urowitz received his MD from the University of Toronto and completed his postgraduate training in rheumatology at the Johns Hopkins University, Baltimore and at the University of Toronto. He was a Staff Rheumatologist at the Wellesley Hospital in Toronto from 1974–1987 and Physician in Chief from 1987–1995. He has also been a Senior Staff Rheumatologist at the Toronto Western Hospital and Senior Scientist at the Toronto Western Research Institute since 1995.

Professor Urowitz established the University of Toronto Lupus Clinic and Lupus Databank Research Program in 1970. This extensive longitudinal database is one of the largest such databanks in the world with over 1800 patients and has allowed for numerous findings that have changed the way lupus is diagnosed and managed. His teaching excellence is exemplified by having won the outstanding clinical teacher award in the medical school for a remarkable eight times. He was the Associate Dean of Postgraduate Medical Education at the University of Toronto between 1995 and 2005. This lifelong commitment to medical education has resulted in him being the recipient of the Royal College of Physicians and Surgeons of Canada 2004 Duncan Graham Award.

Professor Urowitz is a founding member of the Ontario Lupus Association (now Lupus Ontario) and past-President of the Lupus Council of the American Rheumatology Association. He is a founding member of the Systemic Lupus International Collaborating Clinics (SLICC) group and currently directs the SLICC Registry for Atherosclerosis. In 1995 he was the recipient of the Distinguished Rheumatologist Award of the Canadian Rheumatology Association and in 2009 he was recipient of the Evelyn V. HESS Award for outstanding contributions to lupus research, awarded by the Lupus Foundation of America. In 2012 he was awarded a Queen Elizabeth Diamond Jubilee Medal (nominated by the Canadian Rheumatology Association) in recognition of his longstanding contributions to lupus research and his work in the field of rheumatology. In 2016 he was awarded a Lupus Ontario Lifetime Achievement Award “for loyal dedication and unwavering commitment to our goals”

Professor Urowitz has published over 300 peer reviewed papers and 40 book chapters, and has supervised the training of over 100 fellows in rheumatology, mainly in systemic lupus erythematosus. He has been an invited speaker around the world.



Professor Ronald F. van Vollenhoven, MD, PhD

Amsterdam Rheumatology and Immunology Center, Amsterdam, The Netherlands

Disclosures

Grants/Research

Support: AbbVie; Amgen; BMS; GSK; Pfizer; Roche; UCB

Meeting Honorarium/

Expenses: AbbVie; Biotest; BMS; Crescendo; GSK; Janssen; Eli Lilly; Merck; Pfizer; Roche; UCB; Vertex

Professor van Vollenhoven is co-Chair of the Lupus Academy Annual Meeting (2016) and has been involved in the planning and development of the 5th Annual Meeting programme and materials.

Ronald F van Vollenhoven is the Director of the Amsterdam Rheumatology and Immunology Center and Chief of the Department of Rheumatology and Clinical Immunology at the Academic Medical Center, and the Department of Rheumatology at Vrije Universiteit Medical Center in Amsterdam, the Netherlands. He is also Chair of the Rheumatology Research Council at Reade, and continues some of his responsibilities as Chief of the Unit for Clinical Therapy Research (ClinTRID) at the Karolinska Institute.

He received his MD and PhD degrees from the University of Leiden in The Netherlands. After graduating in 1984 he did immunology research at Cornell Medical College in New York, followed by in Internal Medicine at the State University of New York at Stony Brook, and a fellowship in Rheumatology at Stanford University in Palo Alto following which he received American Board of Internal Medicine certification in both Internal Medicine and Rheumatology.

From 1993 to 1998 Professor van Vollenhoven was Assistant Professor of Medicine and then Medical Services Chief and Fellowship Director in the Division of Immunology and Rheumatology at Stanford University.

In 1998 Professor van Vollenhoven moved to Stockholm, Sweden, where he worked as a Senior Physician and Chief of the Clinical Trials Unit in the Department of Rheumatology at the Karolinska University Hospital and Associate Professor of Rheumatology; and in 2010, he was appointed as Professor and Unit Chief at the Karolinska Institute.

Professor van Vollenhoven's research interests focus around the development and systematic evaluation of biological and immunomodulatory treatments for the rheumatic diseases. With his co-workers, he established the Stockholm registry for biological therapies (the STURE database), which supports research projects relating to clinical efficacy, pharmacology, outcomes and pharmacoeconomics. He has been Principal Investigator in many clinical trials of novel therapies in rheumatic diseases and has contributed to a number of important investigator-initiated trials including the recently published SWEFOT trial. He has published over 260 original papers (H-index: 56), book chapters and reviews, and is editor and author of several text books. In 2004, Professor van Vollenhoven was awarded the Scandinavian Research Foundation Prize for excellence in clinical research in rheumatology. He is the Editor-in-Chief of *Lupus Science & Medicine*, Chair of the EULAR Standing Committee on Clinical Affairs, member of many editorial boards, past-Chair of the Swedish Rheumatology Society Professors' Council, co-Founder of the IRBIS registry for biologics in SLE, the CERERRA registries collaboration and the NORD-STAR collaboration for Nordic trials in the rheumatic diseases, and the initiator of the Treat-to-Target-in-SLE initiative.

Biographies



Professor Reinhard E. Voll, MD

University Medical Center, University of Freiburg, Germany

Reinhard Voll is Medical Director of the Division of Rheumatology and Clinical Immunology at the University Medical Center, University of Freiburg, Germany.

Professor Voll received his MD degree from the University Erlangen-Nürnberg, Germany. After completing his MD thesis, which was focused on regulatory proteins of HIV-1, he continued research as a postdoctoral fellow at the Max-Planck Research Groups for Rheumatology, University Hospital Erlangen. In 1996 he received a fellowship from the German Research Society (DFG) to investigate the transcription factor NF- κ B in lymphocytes in the laboratory of Dr. Sankar Ghosh, Section of Immunobiology, Yale University School of Medicine, USA. In 1999 he returned to the University Hospital Erlangen, Germany, to complete his clinical training in internal medicine (2004) and rheumatology (2006). From 2003 to

2009 he was Head of the “IZKF Young Investigator Research Group N2” at the Interdisciplinary Center for Clinical Research Erlangen. He served as senior attending physician at the Department of Rheumatology, University Hospital Erlangen for 6 years until he became Chair of Rheumatology and Clinical Immunology at the University Medical Center Freiburg.

Professor Voll's main research interests are the immunopathogenesis of systemic lupus erythematosus, plasma cell biology and plasma cell-targeted therapies. Other projects in his laboratory investigate cell type-selective interference with intracellular signaling pathways using the sneaking ligand approach.

Professor Voll has published more than 130 papers in peer reviewed journals including *Nature* and *Nature Medicine*.

Disclosures

Grants/Research

Support: BMS; Pfizer; Roche

Meeting Honorarium/

Expenses: Abbott; BMS; GSK; Novartis; Pfizer; Roche



Dr Sacha Zeerleder, MD, PhD

Academic Medical Center, Amsterdam, The Netherlands

Sacha Zeerleder is an Internist-Haematologist at the Academic Medical Center in Amsterdam (The Netherlands). He is the Director of the haematopoietic stem cell transplantation programme and Medical Head of the special haematology and transfusion laboratory of the Academic Medical Center.

Dr Zeerleder obtained his medical degree at the University of Berne (Switzerland) in 1997. He trained as an Internist Haematologist in different university and district hospitals in Switzerland and at the Academic Medical Center in Amsterdam. In 1999 he completed his doctoral thesis on thromboembolism in congenital factor XII deficiency at the University of Berne, and in 2007 his PhD thesis on inflammation and coagulation pathways in sepsis at the University of Amsterdam. Since 2010 Dr Zeerleder has been a senior staff haematologist at the Academic Medical Center in Amsterdam. He is also a senior staff member at the department of immunopathology at Sanquin Research in Amsterdam.

His research is dedicated to the role of innate immunity in haematological diseases. This mainly includes studies on the mechanisms by which damage associated molecular patterns (DAMPs) are released, the regulation thereof, and how they induce systemic inflammation with a special interest in the role of plasma proteins (complement, coagulation) and plasma inhibitors herein. To study these concepts the main focus lies on diseases of systemic inflammation, such as systemic lupus erythematosus and sepsis, graft-vs-host disease, autoimmune haemolytic anaemia, paroxysmal haemoglobinuria and sickle cell disease.

Disclosures

Grants/Research

Support: Viropharma

Meeting Honorarium/

Expenses: Alexion

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Moderators: Professor Ricard Cervera (Spain), Professor Zahir Amoura (France) & Professor Ronald F. van Vollenhoven (The Netherlands)



Professor Richard A. Furie, MD
Hofstra Northwell School of Medicine,
New York, USA



Professor Thomas Dörner, MD
Charité University Hospitals Berlin, Germany

The top SLE stories in 2015: Clinical aspects and basic science

The top SLE Stories is a new feature for the Lupus Academy in 2016. The amount of medical information which we need to learn is growing at an incredible rate. In 2015, for example, there were 3550 SLE articles (keywords: lupus, SLE) and another 540 antiphospholipid articles. With increasing demands on physicians' schedules,

there is relatively little time for educational endeavors. The Steering Committee of the Lupus Academy endorsed this new session as they believe it is a concise method for bringing some of the noteworthy publications of the prior year to attention of the audience.

References

(Clinical aspects)

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Learning Objectives

- Review noteworthy articles related to clinical aspects and basic science in SLE published in 2015

Notes

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Notes

activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis*. 2016;75(2):332–40.

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References

(Basic science)

1. McKinney EF, Lee JC, Jayne DR, Lyons PA, Smith KG. T-cell exhaustion, co-stimulation and clinical outcome in autoimmunity and infection. *Nature*. 2015;523(7562):612–6.

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Abstracts

Discussion Forum: Issues and Answers

Moderators: Professor Ricard Cervera (Spain),
Professor Roger A. Levy (Brazil) & Dr Jamal Al-Saleh (UAE)



Professor Munther A. Khamashta, MD, PhD, FRCP
St. Thomas' Hospital, London, UK. Dubai Hospital, Dubai, UAE

Does seronegative APS exist? Yes

References

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4. Cousins L, Pericleous C, Khamashta M, et al. Antibodies to domain I of beta-2-glycoprotein 1 and IgA antiphospholipid antibodies in patients with 'seronegative' antiphospholipid syndrome. *Ann Rheum Dis.* 2015;74(1):317-9.

In daily clinical practice, it is not unusual to find patients with clinical manifestations suggestive of Antiphospholipid Syndrome (APS) who are persistently negative for routinely used assays to detect anticardiolipin antibodies (aCL), lupus anticoagulant (LA) and anti- β 2-glycoprotein 1 (anti- β 2-GP1) antibodies. Therefore, the term "seronegative" APS (SNAPS) has been created to include these patients, with clinical features suggestive of APS, who are persistently negative for antiphospholipid antibodies (aPL).^{1,2} Diagnosis of APS relies predominantly on laboratory results, where the detection of aPL is mandatory. However,

routine screening tests (aCL, LA and anti- β 2GPI) might miss some cases of true seropositive APS by failing to detect those cases with other antibodies directed against different phospholipids or protein cofactors, such as prothrombin, phosphatidylethanolamine, annexin V and vimentin/cardioliipin complex.^{3,4} Clinicians should consider that the possibility of SNAPS can exist in patients with strong evocative clinical evidence of the disease and that appropriate treatment may prevent thrombosis from recurring and improve foetal and maternal outcomes.

Learning Objectives

- Understand the clinical and laboratory criteria for classification of APS
- Introduce the concept of "seronegative" APS
- Review new emerging antiphospholipid antibody assays

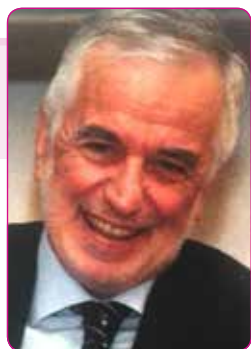
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Abstracts

Discussion Forum: Issues and Answers

Moderators: Professor Ricard Cervera (Spain),
Professor Roger A. Levy (Brazil) & Dr Jamal Al-Saleh (UAE)



Professor Vittorio Pengo, MD

Padova University School of Medicine, Padova, Italy

Does seronegative APS exist? No

References

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Diagnosis of antiphospholipid syndrome (APS) is essentially based on the detection of circulating antiphospholipid (aPL) antibodies. The clinical relevance of the aPL profile has come from prospective cohort studies in populations with a homogeneous antibody profile supporting the view that triple positivity is a high-risk pattern in patients and carriers. This is most likely related to the fact that only a particular anti- β 2-glycoprotein 1 (anti- β 2-GP1) antibody with lupus anticoagulant activity, the one directed to domain 1 of the molecule, is highly associated with the clinical features of APS. Evidence that triple positivity can identify anti-domain 1 antibodies in triple positive patients comes from studies on affinity purification of antibodies to β 2-GP1 from plasma of these patients: when spiked into normal plasma, they reproduce the positivity in all three tests as the original plasma. Thus, APS with triple positivity is a true autoimmune disease as the corresponding antigen as well as the specific epitope are known, an autoimmune reaction is identified in the form of autoantibody, and an analogous response causes a similar disease in experiments in animals.

Learning Objectives

- Understand that triple positivity is associated with thrombosis and pregnancy loss in antiphospholipid syndrome
- Recognise that triple positivity is associated with antibodies directed to domain 1 of 2-GP1
- Understand that affinity-purified antibodies to 2-GP1 from triple positive APS patients spike into normal plasma to reproduce the full positive antibody profile of original plasma
- Recognise that APS with triple positivity is a true autoimmune disease

Notes

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Abstracts

Plenary I: New Horizons in Basic Science

Moderators: Professor Ronald F. van Vollenhoven (The Netherlands) & Professor Thomas Dörner (Germany)



Professor Claudia Mauri, PhD
University College, London, UK

Inflammatory signals induce regulatory B cells in healthy: what goes wrong in lupus patients?

References

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Over the last decade, the importance of regulatory B cells (Bregs) in the maintenance of tolerance has been well established. Bregs are negative regulators of the immune system which suppress pathological immune responses, primarily via the provision of IL-10.^{1–3} Current focus is towards understanding the signals that drive the differentiation of Bregs, in order to exploit their therapeutic potential. Emerging data from mouse models imply a role for inflammatory signals in the differentiation of immunosuppressive Bregs.⁴ However, signals controlling the generation of human Bregs remain largely uninvestigated. Here we identify plasmacytoid dendritic cells (pDCs) as master regulators of human Breg differentiation; pDCs drive the differentiation of B cells into

Bregs and plasmablasts in an IFN α -dependent manner.⁵ We also report the existence of a previously unappreciated auto-regulatory feedback mechanism between pDCs and Bregs. In patients with systemic lupus erythematosus (SLE), defects in the pDC-Breg crosstalk were found to contribute to disease pathogenesis, by skewing the B-cell response towards plasmablast differentiation and failure to induce Bregs. This altered B-cell response in SLE patients was recapitulated in healthy B cells upon exposure to a high concentration of IFN α . Of note, the pDC-B-cell interaction was normalised in patients with SLE responding to B-cell depletion therapy. Taken together, these results highlight a fine balance between inflammatory signals, induction of Bregs and autoimmunity.

Learning Objectives

- Identify signals that expand human Bregs: IFN α production by pDCs
- Report an additional mechanism of Breg-mediated immune regulation: suppression of IFN α production by pDCs
- Explain the reason for the loss of Breg function and increase in autoantibody-producing plasma cells in SLE: excessive production of IFN α by hyperactivated pDCs
- Identify a possible reason as to why only some patients, but not others, respond to rituximab therapy, upon B-cell population: due the presence of an elevated IFN α -induced gene signature
- Discover a potentially more effective way of treating SLE patients with B-cell depletion therapy: presence or absence of an elevated IFN α -induced gene signature could predetermine response to therapy

[illegible]

Abstracts

Plenary I: New Horizons in Basic Science **Moderators:** Professor Ronald F. van Vollenhoven (The Netherlands) & Professor Thomas Dörner (Germany)



Professor Marta E. Alarcón-Riquelme, MD, PhD
Center for Genomics and Oncological Research, Granada, Spain

SLE redefined based on molecular pathways

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Advances in understanding of genetics and gene expression have allowed for the exponential advancement in our understanding of systemic lupus erythematosus (SLE) and the mechanisms behind the disease. It has become clear that, in general, the genetic contribution to SLE is shared across several ethnicities.¹⁻³ Gene expression studies⁴ have provided important information on the interferon signature and such genomic data can be used as a basis for the analysis of several systemic autoimmune diseases expanding the data to other “-omics” sources. Bioinformatics have become increasingly important in the analysis and integration of the data. Furthermore, data

can be used in connection with public data on the effects of genes or drugs in, for example, gene expression patterns to help identify new potential drugs, a strategy known as drug repurposing or repositioning. The PRECISEADS project aims to reclassify the systemic autoimmune diseases through the complete characterisation of several “-omics”, including genomics, transcriptomics, epigenomics, metabolomics and proteomics. The data will be analysed to identify clusters of individuals that share patterns across the data. The project includes 18 clinical centres from Europe, five Pharmaceutical companies and other academic partners.

Learning Objectives

- Review the impact of genetic studies in SLE
- Understand the impact of gene expression studies in the clinic
- Appraise the use of “-omics” studies in finding new drugs for the disease

Notes

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Abstracts

Plenary I: New Horizons in Basic Science **Moderators:** Professor Ronald F. van Vollenhoven (The Netherlands) & Professor Thomas Dörner (Germany)



Professor Josep Dalmau, MD, PhD
Hospital Clinic, Barcelona, Catalonia, Spain

Autoantibodies to neural antigens

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1. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* 2016;15(4):391-404.
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In the last 10 years a new category of autoimmune disorders of the synapse has emerged. There are currently 16 such disorders, all characterised by autoantibodies to cell-surface and synaptic proteins involved in synaptic signaling and plasticity. Recognition of these potentially lethal, but now treatable, diseases has changed the diagnostic approach to many neuropsychiatric disorders. The pathogenic effects of some of these antibodies have been demonstrated in cultured neurons and in animals. Some antibodies impair

the surface dynamics of the target receptors eliminating them from synapses (e.g., NMDA receptor), other antibodies block the function of the antigens without changing their synaptic density (e.g., GABA β receptor), and yet others appear to interfere with synapse formation (e.g., neurexin-3 α). This presentation will review the most frequent of these disorders and focus on anti-NMDA receptor encephalitis to illustrate the clinical impact of these discoveries and the antibody pathogenicity.

Learning Objectives

- Facilitate the diagnosis of autoimmune encephalitis associated with autoantibodies against synaptic receptors and neuronal cell surface proteins
- Recognise the immunological triggers and associated comorbidities
- Improve understanding of the underlying mechanisms of disease

[illegible]

Curbside Consults



Moderator: Professor Richard A. Furie (USA)

Professor Richard A. Furie, MD

Hofstra Northwell School of Medicine, New York, USA

Panellists: Bevra H. Hahn (USA), Murray B. Urowitz (Canada), David A. Isenberg (UK), Ronald F. van Vollenhoven (The Netherlands), Jamal Al-Saleh (UAE)

Curbside consults: The experts tackle lupus nephritis and lupus arthritis



Curbside Consults may be a new feature for the Lupus Academy in 2016, but it is an old practice that occurs in every country and every hospital. Confronted with a difficult clinical problem, the physician “curbsides” another physician for what is an informal opinion about the case. The answer may be based in evidence or it may be purely opinion. Regardless, this type of transfer of information occurs all the time. Nothing is written and money is not exchanged. In fact, most of the time, the “consultant” doesn’t even see the patient. These educational interactions are very efficient with a rapid transfer of knowledge or experience in a short period of time.



Lupus Academy 2016 Curbside Consults feature a distinguished panel of rheumatologists who will render their views about challenging clinical scenarios. The first area chosen for this session deals with the lupus nephritis patient who has had a partial response to a therapeutic intervention. We all have such patients, but we all have different views about how to proceed. The second topic deals with the lupus patient who has an erosive form of arthritis, the “rhupus” patient. Should this type of complication be treated differently than conventional lupus arthritis? The discussions will focus on these themes in our inaugural session of Curbside Consults.



Learning Objectives

- Recognise therapeutic options for the treatment of patients with lupus nephritis who partially respond to induction therapy
- Describe therapeutic approaches to the patient with erosive arthritis



Notes

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Case Study Workshops

Saturday 7th May

Morning (11:00) Parallel Case Study Workshops

<i>Moderator: Ronald F. van Vollenhoven (The Netherlands)</i> The lungs		Murray B. Urowitz (Canada) & Andrea Doria (Italy)
<i>Moderator: Bevra H. Hahn (USA)</i> The gastrointestinal tract and the liver		David A. Isenberg (UK) & Thomas Dörner (Germany)
<i>Moderator: Richard A. Furie (USA)</i> The nervous system		Zahir Amoura (France) & Josep Dalmau (Spain)
<i>Moderator: Roger A. Levy (Brazil)</i> Pregnancy		Rebecca Fischer-Betz (Germany) & Munther A. Khamashta (UK/UAE)
<i>Moderator: Ricard Cervera (Spain)</i> Paediatric and other lupus challenges in clinical practice		Tadej Avčin (Slovenia) & Sandra V. Navarra (Philippines)

Saturday 7th May

Afternoon (13:30) Parallel Case Study Workshops

<i>Moderator: Ronald F. van Vollenhoven (The Netherlands)</i> The lungs		Murray B. Urowitz (Canada) & Andrea Doria (Italy)
<i>Moderator: Bevra H. Hahn (USA)</i> The gastrointestinal tract and the liver		David A. Isenberg (UK) & Thomas Dörner (Germany)
<i>Moderator: Richard A. Furie (USA)</i> The nervous system		Zahir Amoura (France) & Josep Dalmau (Spain)
<i>Moderator: Roger A. Levy (Brazil)</i> Pregnancy		Rebecca Fischer-Betz (Germany) & Munther A. Khamashta (UK/UAE)
<i>Moderator: Ricard Cervera (Spain)</i> Paediatric and other lupus challenges in clinical practice		Tadej Avčin (Slovenia) & Sandra V. Navarra (Philippines)

Please Note

These workshops will be held in breakout rooms. Please follow the appropriate signs/symbols corresponding to the workshops you are registered to attend.



Moderator: Professor Ronald F. van Vollenhoven (The Netherlands)

Presenters: Professor Murray B. Urowitz (Canada) & Professor Andrea Doria (Italy)

The lungs



Professor Murray B. Urowitz, MD

Case 1: Refractory serositis

A 44-year-old Caucasian female was diagnosed with systemic lupus erythematosus (SLE) in 2010 based on polyarthritis, malar rash, mucosal ulcerations, pleuritis, Raynaud's, photosensitivity, positive ANA, positive anti-dsDNA antibodies and low complement (C3). She was treated with prednisone 60 mg/day and hydroxychloroquine (HCQ) 400 mg/day.

In February 2011, assessment revealed bilateral pleuritic pain, polyarthritis and low C3, and negative anti-dsDNA antibodies. She continued treatment with HCQ 400 mg/day, began tapering her steroid and started on methotrexate (MTX) 20 mg/week. During the course of the year her pleuritic pain was refractory, she underwent many thoracenteses and colchicine was added to her treatment. Following MTX failure (9 months' treatment), mycophenolate mofetil (MMF) 3 g/day was added. In November 2012, pleural biopsy revealed non-specific chronic inflammation. During the following year, she had refractory serositis and bilateral chest drains were removing up to one litre of pleural fluid per day. After 15 months, treatment with MMF was stopped and cyclophosphamide 500 mg IV pulses were given every 2 weeks for six doses. In June 2013, she experienced acute cardiac tamponade, deterioration of pleuritis and decreasing C3. Pleural biopsy revealed non-specific chronic inflammation. In November 2013, she was started on belimumab 10 mg/kg BW q4w, prednisone 15 mg/day and HCQ 400 mg/day. She remains asymptomatic, with normal C3 and has reduced her prednisone dose to 5 mg/day.

Discussion point: *Consecutive approaches to refractory serositis*



Professor Murray B. Urowitz, MD

Case 2a: Acute shrinking lung syndrome

A 50-year-old female of East Indian origin was diagnosed with SLE in 2011 based on polyarthritis, malar rash, Raynaud's, photosensitivity, pleuritic chest pain, positive ANA, anti-dsDNA, Ro, LA, Sm, RNP antibodies and low complement. She was prescribed prednisone 10 mg/day, HCQ 400 mg/day and azathioprine (AZA) 100 mg/day.

In January 2013 assessment revealed active/intermittent arthritis, skin involvement and pleuritic pain, but no radiologic evidence of effusion. She continued treatment with prednisone 5–15 mg/day, HCQ 400 mg/day and AZA 100 mg/day. In March 2014, she presented with acute dyspnoea, left pleuritic pain, low C3/C4, but no fever or leukocytosis. Radiological examination revealed left base atelectasis and elevation of left hemidiaphragm and pulmonary function tests showed a restrictive pattern. Treatment with prednisolone 40 mg/day, HCQ 400 mg/day, AZA 100 mg/day, β_2 agonists and corticosteroids. Shrinking lung volume was resolved in May 2014 and pulmonary function improved.

Discussion point: *Treatment of acute shrinking lung syndrome*

Professor Murray B. Urowitz, MD

Case 2b: Chronic shrinking lung syndrome

A 47-year-old Caucasian female was diagnosed with SLE in 1974 based on malar rash, diffuse – proliferative lupus nephritis, neuropsychiatric involvement, positive ANA, LE cell preparation. Prednisone, chloroquine and aspirin were prescribed.

In 1978 she presented with acute dyspnoea and orthopnoea. Tests revealed elevated left hemidiaphragm, “sluggish” diaphragmatic movement and severe restrictive defect. Prednisone dose was increased, resulting in symptomatic improvement within a few weeks, after which the dose was tapered to 5 mg/day. In 1982,

she was admitted to hospital with a rash, diffuse arthralgias, dyspnoea and bradycardia (HR 40/min). She had complete atrioventricular dissociation and chest X-ray revealed bilaterally elevated hemidiaphragms (more pronounced on the left side). She suffered a cardiac arrest during surgery, several attempts for extubation were unsuccessful. Electromyography showed proximal myopathy and normal phrenic nerve potentials, while fluoroscopy revealed complete absence of diaphragmatic movement (myasthenia was excluded with Tensilon test). She succumbed to bronchopneumonia/sepsis and died.

Discussion point: *Consequences of undertreatment of acute shrinking lung syndrome*

Professor Murray B. Urowitz, MD

Case 3: Pulmonary arterial hypertension

A 40-year-old Caucasian female was diagnosed with SLE in 1993 based on malar rash, polyarthritis, pleuritic chest pain, positive ANA, anti-dsDNA, anti-Ro and low complement (C3/C4). She was treated with HCQ 400 mg/day. In January 1998 she presented with exertional dyspnoea, fatigue; right ventricular systolic pressure (RVSP) was 78 mmHg. She was treated with prednisone 60 mg/day and warfarin for 12 months. In January 1999 her RVSP was 42 mmHg and there was no arthritis or skin involvement; she was maintained on treatment with prednisone 60 mg/day, chloroquine 250 mg/day and warfarin. Investigations for pulmonary embolism/chronic thromboembolic pulmonary disease revealed negative CT (helical thorax), normal perfusion-ventilation scan negative antiphospholipid antibody. High resolution thorax CT showed no evidence of interstitial lung disease. Treatment included addition of AZA 100 mg/day and tapering of prednisolone to 7.5 mg/day. At follow up in 2001 she was asymptomatic, she discontinued chloroquine and AZA due to irritable bowel syndrome. She experienced a lupus flare with increased RVSP, polyarthritis and worsening serology, which was managed with prednisone 30 mg/day, MMF 3 g/day, HCQ 400 mg/day and bosentan 125 mg/day. Between 2004 and 2006, she experienced intermittent dyspnoea and her bosentan dose was increased to 250 mg/day. In 2006 she had a lupus flare, due to pulmonary arterial hypertension, with worsening serology. In 2007, sildenafil 60 mg/day was added, then epoprostenol IV added in 2008 following right heart catheterisation. She is currently clinically stable (RVSP = 50 mmHg) and maintained on prednisone 7.5 mg/day, sildenafil 60 mg/day, epoprostenol IV and digoxin 0.125 mg/day.

Discussion points:

Differential diagnosis of pulmonary hypertension in a patient with SLE

Treatment of acute and chronic pulmonary hypertension in SLE

Professor Andrea Doria, MD

Case 4: 21-year-old male

A 21-year-old male patient presented with slight fever, fatigue, cough, polyarthralgias and malar rash, showing positive anti-dsDNA and low complement at laboratory assessments. He rapidly developed renal failure with nephrotic proteinuria and hypertension.

After 3 days of pulse steroids (500 mg methylprednisolone each) he developed sudden anaemia with haemoglobin dropping from 12.5 g/dl to 10.1 g/dl in 24 hours. Later in the night, his breath became swift and he developed bronchospasm with loud thoracic wheezing and rales at auscultation. Pulse oxygen was 95%. He was administered oxygen, IV methylprednisolone and salbutamol with partial improvement at auscultation. However, after some hours the patient became frayed and dizzy. Pulse oxygen dropped to 80%, arterial blood pO₂ was 60 mmHg, heart rate raised to 115 bpm and he had haemoptysis. He underwent intubation with blood pouring into the tube. Chest CT showed diffuse ground glass opacification changes admixed with area of consolidation. Bronchoscopy demonstrated the presence of blood within the large airways. He was moved to the intensive care unit and treated with further pulses of methylprednisolone, plasmapheresis and IV cyclophosphamide 0.75 mg/m² with slow recovery.

Discussion points:

How to recognise and treat diffuse alveolar haemorrhage

Bronchospasm as the first sign of lung bleeding

Professor Andrea Doria, MD

Case 5: 34-year-old female

A 34-year-old female patient affected with systemic lupus erythematosus since 2002. Her systemic lupus erythematosus onset was characterised by fever, polyarthritis, anemia, leuko-lymphopaenia, positive ANA, anti-Sm, anti-U1RNP and anti-SSA antibodies. She was treated with corticosteroids and



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hydroxychloroquine. In 2003 she developed cutaneous vasculitis with ulcers and she was treated with thalidomide, stopped for sensory neuropathy after 10 months. In 2004 she was admitted to our unit with abdominal pain, vomiting and fever with anaemia, leucopaenia and low C3 and C4. She underwent colonoscopy which showed a feature indicative of intestinal vasculitis (then confirmed by histological examination) and thus she was treated with high-dose corticosteroids and intravenous Immunoglobulin. Some months later, she had persistent pancytopenia and was treated with cyclosporine. In 2010 she presented with fever $>38^{\circ}\text{C}$, persistent nonproductive cough, dyspnoea, polyarthralgias and fatigue. She was treated with cephalosporin and macrolide therapy without benefit, so she was admitted to our unit. Chest X-ray showed bilateral basal opacities. A high-resolution computed tomography showed multiple interstitial areas with ground glass densities with subpleural and peribronchial distribution in both upper and basal lobes. She was diagnosed with bronchiolitis obliterans organizing pneumonia (BOOP) and effectively treated with high doses of corticosteroids and mycophenolate mofetil.

Discussion points:

How to recognize and treat BOOP

BOOP evolution/prognosis

Learning Objectives

- Recognise the spectrum of presentations of lung involvement in SLE, including:
 - Serositis
 - Pneumonitis
 - Shrinking lung syndrome
 - Intra-pulmonary haemorrhage
 - Pulmonary fibrosis
 - Pulmonary hypertension
- Recognise unusual presentations of the common lung manifestations
- Recognise common therapeutic approaches to the usual lung manifestations
- Recognise unusual therapeutic approaches to the uncommon lung manifestations

Notes

[illegible]



Moderator: Professor Bevra H. Hahn (USA)

Presenters: Professor Thomas Dörner (Germany) & Professor David A. Isenberg (UK)

The gastrointestinal tract and the liver



Professor David A. Isenberg, MD, FRCP, FAMS

Case 1: 44-year-old male – KP

KP presented in his early 40s with a photosensitive rash, thrombocytopaenia, arthritis, Raynaud's phenomenon and proteinuria. A renal biopsy, done approximately 6 months after he presented, showed the presence of diffuse proliferative glomerulonephritis. Investigations revealed an anti-nuclear antibody (titre 1:160) but, intriguingly, neither the dsDNA antibodies nor a low C3, although he was lymphopaenic. A diagnosis of systemic lupus erythematosus (SLE) was made and treatment with corticosteroids and azathioprine commenced. He did well for the next 9 months until his 4 year-old daughter passed on a contagious illness resulting in him becoming extremely ill and being admitted to the Intensive Care Unit (ICU).

After 2 weeks in the ICU, the patient improved sufficiently to be moved to the general ward from which he was discharged and continued corticosteroid and azathioprine treatment for another 3 years. At that point he first began to complain of abdominal pain and bloody diarrhoea. Investigations including an ultrasound suggested some swelling of the large bowel and a biopsy demonstrated the presence of ulcerative colitis, which on colonoscopy was revealed to be affecting most of the large bowel.

He was subsequently treated on a decreasing dose of steroids, oral mesalazine and enemas. During a further 10 years of follow-up his lupus has become inactive with a normal protein/creatinine ratio and normal creatinine and glomerular filtration rate, but his colitis continues to trouble him intermittently.

Discussion point: *Review the frequency with which concomitant major bowel diseases occur in SLE*



Professor David A. Isenberg, MD, FRCP, FAMS

Case 2: 17-year-old female – VO

VO presented dramatically with a short history of arthritis, a malar rash and a 24-hour history of her fingers going blue. Her ANA was 1:2,560 with positive anti-dsDNA and anti-RNP antibodies, a lupus anti-coagulant and a low C3. She had a needle phobia [having watched her mother inject herself when she was a heroin addict]. With great difficulty she was persuaded to have IV methylprednisolone and cyclophosphamide and subsequently received IV prostacyclin for several weeks.

Five weeks after the start of treatment she developed a fever, slightly swollen abdomen, abdominal tenderness but no overt effusion and no gut swelling was observed on ultrasound. A laparotomy was performed.

Discussion point: *Laparotomy outcomes and problems of assessing the acute abdominal pain in patients with lupus*

Professor David A. Isenberg, MD, FRCP, FAMS

Case 3: 34-year-old female – RN

RN presented with a complex medical history. During her late teens to mid-twenties she had low platelets ($40\text{--}100 \times 10^9/\text{L}$) recurrent fever, arthralgia, abdominal pain and three miscarriages. She had weakly positive IgG anti-cardiolipin antibodies, positive lupus anticoagulant; ANA $>1:320$, but her anti-dsDNA antibodies were usually normal and her complement (C3) was low.

Between her late twenties and the age of 31 years she experienced falling albumin to $15\text{--}20 \text{ g/L}$ (normal $34\text{--}50 \text{ g/L}$) and a liver biopsy indicated changes compatible with autoimmune hepatitis. She required repeated blood transfusions due to recurrent anaemia. At age 32 years, ultrasound revealed blocked portal and splenic veins.

At age 34 years RN experienced two 3-day episodes of confusion, memory loss, some “jumbling of words”, and she could not name pieces of fruit accurately. MRI revealed a high T1 signal at the basal ganglia. Neurological consultation suggested this was the result of a metabolic disturbance arising from her autoimmune hepatitis causing deposition of compounds such as manganese in the basal ganglia. She died following a massive haematemesis.

Discussion points:

Not every low albumin in a lupus patient is due to kidney disease

Diagnosing the precise pathology in CNS lupus can be very difficult

Professor Thomas Dörner, MD

Case 4: 33-year-old Caucasian female

A 33-year-old female with a 15-year history of SLE had received prednisone, cyclophosphamide, hydroxychloroquine, azathioprine and finally mycophenolate mofetil due to increased kidney function failure. However, she developed end-stage renal disease 3 years ago requiring haemodialysis.

Within the last few months she presented with recurrent and very severe diarrhoea resulting in hospital admission. Before admission she also had erythema, fever, painful flank regions and paraesthesia. CT during hospitalisation revealed intestinal visceromegaly and bilateral hydronephrosis. Urine testing identified *E. coli* in culture (>20000 units) requiring antibiotic treatment with ciprofloxacin for one week. Despite treatment, the patient persisted with fever, pain and abdominal distention without an obvious focus of sepsis or subsepsis.

Subsequently, she developed a lupus flare with pleuritis, polyarthritis, thrombocytopaenia, reduced C3 and C4, and increased dsDNA titre (1:16) [resulting in an overall SLEDAI of 8]. She received oral steroids starting with 40 mg prednisolone/day, which was tapered to 15 mg over a period of 3 weeks. The GI symptoms improved within the first 3-4 days of being given corticosteroids and a reduction of lactate dehydrogenase was noted together with an abnormal abdominal CT scan. The clinical picture was consistent with an intestinal pseudo-obstruction. Although the patient improved and was discharged, she subsequently developed the same GI symptoms again, but unrelated to other lupus activity. She again received steroids on readmission leading to further clinical improvement.

Discussion points:

Differential diagnosis of abdominal pain in SLE

Use of certain imaging modalities and therapeutic approaches

Professor Thomas Dörner, MD

Case 5: 28-year-old Caucasian female – MK

A 28-year-old female with SLE was admitted with a complaint of oedema and pain in both legs for the last 2 months. Her initial SLE diagnosis was based on kidney manifestations (haematuria, proteinuria, azotaemia), anaemia and thrombocytopaenia, C4 hypocomplementaemia, increased ANA 1:1280 with positive anti-dsDNA antibody and positive anti-Sm antibody about 5 years ago. She has never taken oral contraceptives. Initially she had received methotrexate 10 mg/week with prednisolone 7.5 mg at another hospital. Her anticardiolipin antibody was 85 GPL IU/mL with positive lupus anticoagulant; both were persistently elevated or positive, respectively. For a long time, she also had prolonged partial thromboplastin time (108 sec, normal <30) suggesting the presence of a lupus anticoagulant. Her oedema and the pain in her legs were not related to a deep vein thrombosis including iliac and inferior cava veins.

On admission, she had polyarthralgia with very severe constitutional symptoms (nausea, unclear loss of productivity, etc.) but did not complain of fever, malar rash, photosensitivity, oral ulcers, Raynaud's phenomenon, xerostomia, xerophthalmia and alopecia. Chest auscultation and abdomen palpation revealed no abnormalities and peripheral arterial pulsation was normal. She had had livedo for several years but no cutaneous vasculitis.

Abnormal lab data comprised haemoglobin 10 g/dL, white blood cells 7.2 with lymphopaenia of 10% and platelets $84 \times 10^3/\text{mm}^3$, proteinuria 0.6 g/day. Urinalysis showed 0–2 WBC and 10 RBC per high power fields. Liver enzymes were elevated with AST was 67 IU/L. ALT 72 IU/L, alkaline phosphatase 229 IU/L, g-GT 76 0.7 mg/dL. The prothrombin time was 11.8 sec (control 12.1 sec) and activated partial thromboplastin time 59.2 sec (control 26.6 sec). ANA was positive (homogenous pattern, titre 1:1280),



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anti-dsDNA antibody 5 IU/mL, C3 21 mg/dL and C4 15 mg/dL. Rheumatoid factor was negative. Lupus anticoagulant was positive by the Kaolin clotting test. Anti-ENA and anti-Ro antibodies were all negative. The direct and indirect Coombs tests were both negative. Viral hepatitis tests revealed that hepatitis Bs (HBs) antigen was negative, anti-HBs IgG antibody positive and hepatitis C virus antibody negative. Antimitochondrial antibodies including M-2 antibodies were negative.

Abdominal ultrasonography revealed typical findings of intrahepatic vein occlusions with subsequent signs of portal hypertension (splenomegaly). Abdominal CT was consistent with this finding. Gastroscopy identified oesophageal varicosis, grade 2, including gastric fundal varicosis. Primary sclerosing cholangitis could be largely excluded.

Subsequent treatment of the SLE with azathioprine 100 mg/day was initially combined with low molecular weight-heparin at intermediate dose and subsequently bridged to vitamin K antagonists within INR 1.8–2.4. We have followed her up at the outpatient clinic for 5 years during which her clinical course has been stable.

Discussion points: *Consideration of associated antiphospholipid syndrome in SLE and abdominal manifestations*

Professor Thomas Dörner, MD

Case 6: 25-year-old Caucasian female – CS

In 2012, a 25-year-old female developed periorbital oedema, which progressed within months to generalised oedema and ascites. She reported infrequent episodes of watery diarrhoea during the past 1.5 years with a maximum of 7–8 stools per day, including during the night. There was no bloody diarrhoea and notably no abdominal pain. She had no proteinuria or haematuria and no features of renal impairment were found. In addition, liver function tests were normal and there were no findings consistent with cardiac failure. There was no previous history of SLE or other inflammatory diseases. Except for generalised oedema, her examination was unremarkable.

She had non-specific hypoproteinaemia (47 g/L) with striking hypoalbuminaemia (20 g/L). Additionally, there were hypoglobulinaemia, hypocomplementaemia, reduced antithrombin 72% and hypertriglyceridaemia/cholesterolaemia. Erythrocyte sedimentation rate was 102 mm/h and persistent leucopaenia (3.2) and thrombocytopenia (102) were present. Antinuclear antibodies were 1:1280 with positive dsDNA antibody, APLs and anti-Ro/La antibodies were negative. Creatinine clearance, liver ultrasonograph and transthoracic echocardiogram were normal.

Oesophagogastroduodenoscopy and colonoscopy were normal. Ultrasound of the abdomen was unremarkable with the exception of slightly increased bowel gas and increased ileal thickness. Therapy was started with oral steroids and azathioprine; the patient responded with regression of the oedema (with the exception of moderate periorbital oedema in the morning) and the diarrhoea and normalisation of protein parameters in the circulation. SLEDAI was reduced from 11 to 3 after 4 months, demonstrating the effectiveness of treatment.

Discussion points:

*Recurrent diarrhoea in SLE – awareness of protein losing gastroenteropathy
Imaging findings and differential therapeutic considerations*

Learning Objectives

- Understand that GI manifestations in SLE are quite common, although the serious complications are rare and may have life threatening potential, such as:
 - Pancreatitis
 - Hepatitis
 - Intestinal pseudo-obstruction
 - Associated ulcerative colitis
 - Venous and arterial occlusions frequently associated with coexistent anti-phospholipid syndrome
 - Awareness of the wide range of GI problems in SLE and their differential diagnosis is important. Serious GI disease is unlikely to occur in the absence of other lupus manifestations

Notes

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Moderator: Professor Richard A. Furie (USA)

Presenters: Professor Zahir Amoura (France) & Professor Josep Dalmau (Spain)

The nervous system



Professor Zahir Amoura, MD, MSc

Case 1: 37-year-old female

A 37-year-old woman was hospitalised for neuropathic pain of the lower limbs. Three years earlier, she received a diagnosis of systemic lupus erythematosus (SLE) based on polyarthritis, photosensitivity, malar rash, positive anti-nuclear antibody test (1/2560) and positive anti-ds DNA (Farr assay 18 UI; N <9 UI). All her symptoms resolved with hydroxychloroquine 400 mg/day and prednisone 15 mg/day. Prednisone was progressively tapered and finally stopped 18 months later.

On examination, pulse rate was 80 bpm, blood pressure 122/74 mmHg and temperature 37°C. She was walking with a high stepping gait with toe walking on right side. Power of flexors and extensors of the right ankle joint was diminished with hypotonia. Her ankle and knee jerks were diminished, plantar response was absent on the right side and there was sensory loss in the lateral aspect of her right foot and leg. Atrophy was absent. Her left lower limb was painful but neurological examination was normal. Both upper limb examinations were normal. Sensorium and cranial nerves were not involved. Respiratory, cardiovascular, joint and skin examination was normal. Investigations revealed haemoglobin 11.5 gm, MCV 81.7, total leukocyte 9900/μL, neutrophil 8800/μL, lymphocyte 860/μL, eosinophil 122/μL, without any abnormal cells. Erythrocyte sedimentation rate was 122 mm in 1st hour and CRP 0.6 mg/dL. Blood sugar, serum urea, creatinine and LFT were normal. Routine urine examination was normal and culture revealed no growth. Farr assay was increased (33 UI; N <9); C3 was low (0.65 g/L); C4 was low ≤0.08 g/L.

Discussion points: *Diagnosis and management of peripheral nervous system manifestations of SLE*



Professor Zahir Amoura, MD, MSc

Case 2: 31-year-old female

A 31-year-old woman was hospitalised in January 2016. She has had a medical history of SLE diagnosed in December 2012. Malar rash (acute cutaneous lupus), photosensitivity, diffuse alopecia, oral ulcerations, bilateral pleurisy, proteinuria with a kidney biopsy showing class IV glomerulonephritis according to ISN classification, positive anti-double stranded DNA antibody test (Farr assay 78 UI; N <9 UI), low C3 fraction, positive lupus anticoagulant, negative anticardiolipin antibody ELISA (IgG and IgM), negative anti-β2GP1 ELISA (IgG and IgM). She had no thrombotic or obstetric history. She first received three pulses of methylprednisolone (1000 mg each) followed by oral prednisone 0.6 mg/kg/day + mycophenolate mofetil (MMF) 2 g/day + ACE inhibitors. Steroids were tapered to 5 mg/day at 6 months. Daily proteinuria decreased to 1 g at Month 3 and 0.5 g at Month 6. C3 returned to normal level at Month 6. Steroids were stopped at Month 24 and hydrocortisone 20 mg/day was given instead. Mycophenolate mofetil 2 g/day was decreased to 1 g/day in September 2015.

She was hospitalised in January 2016 for altered sleep-wake cycle, hyperactivity, intense anxiety, ideas of persecution and auditory hallucinations. She had no arthritis and no mucocutaneous manifestation. Her physical examination was normal with no neurological abnormalities. Laboratory test showed: normal red and white blood cell and platelet counts, creatinine 69 μmol/L, proteinuria 0.2 g/L, urine sterile with no haematuria, creatininuria 8.9 mmol/L = ratio 0.02 g/mmol, albuminaemia 43 g/L, CRP <5 mg/L. Farr assay 18 UI, N <9 UI, normal C3 fraction. At that time, she was treated with hydrocortisone 20 mg/day + MMF 1 g/day. A diagnosis of acute psychosis was made by the psychiatrist.

Discussion points: *Diagnosis and management of psychiatric manifestations of SLE*

Professor Josep Dalmau, MD, PhD

Case 3: Young man with altered mental functions and a large thymoma

A 23-year-old man presented with acute development of short-term memory loss, refractory seizures and psychosis. The cerebrospinal fluid revealed 52 WBC/mL and 100 mg/dL proteins. The electroencephalogram (EEG) demonstrated theta activity. Systemic tumour screening showed a large thymoma, but his Karnofsky performance status was considered too low (30/100) for treatment.

The patient was transferred to Hospital Clinic, Barcelona under pharmacologically induced coma and mechanical ventilation. Brain MRI showed changes suggestive of widespread cortical damage. Cerebrospinal fluid and serum studies revealed antibodies against a synaptic receptor.

He underwent intensive immunotherapy and tumour removal, and had substantial clinical recovery.

This case suggests caution in clinically assessing autoimmune encephalitis using Karnofsky or similar neurological scales for treatment decisions.

Discussion point: *Why should we exercise caution when using Karnofsky or similar neurological scales for treatment decisions in the case of autoimmune encephalitis?*

Professor Josep Dalmau, MD, PhD

Case 4: Young female with psychosis and a long-delay in diagnosis

A 16-year-old female with a history of encephalopathy and temporal lobe seizures in 2005 presented with the return of bizarre behaviour in 2008. Her presentation in 2005 was associated with episodes of lip smacking, tangential speech, paranoia and hallucinations. Her speech remained fluent but became more bizarre, paranoid and hyperreligious. She was found on video EEG to have intermittent temporal lobe seizures and was started on oxcarbazepine. While her seizures appeared to be controlled, she continued to have auditory and visual hallucinations, paranoid ideation, word repetition and aggression. Abnormal movements such as grasping at the air, leg shaking, and pill-rolling hand movements were observed without EEG correlate. She also had episodes of tachycardia and hypertension with blood pressure approaching 170/100. She was given haloperidol for agitation and became more lethargic with drooling and then developed dystonic upper extremity posturing and tightening of the mouth that resolved with benztropine and discontinuation of the haloperidol. She was started on quetiapine for her psychotic symptoms and zolpidem for frequent awakenings throughout the night. Magnetic resonance imaging (MRI) and magnetic resonance angiogram (MRA) of the brain were normal. The cerebrospinal fluid (CSF) analysis revealed 2 WBC/mL. She was given a 5-day pulse of methylprednisolone sodium succinate. Cognitively, over the next few weeks she returned to baseline. A normal mental status examination was documented at a routine clinic visit in 2006.

In June, 2008, she had the return of behavioural outbursts, insomnia, and trembling episodes without loss of consciousness. On the night of admission, she threw a glass at her parents and threatened to jump from a second story window. She had not slept for several days and tried to leave her room, throwing objects, spitting, and screaming profanities for which security was called and physical restraints were placed. Visual hallucinations of "men in grey beards walking on all fours" were reported. A video EEG was normal with an appropriate background. Multiple antipsychotic drugs were tried, including quetiapine, olanzapine, and ziprasidone and she had periods of hypertension and tachycardia that were attributed to the medication. She was transiently admitted to a psychiatric facility with a diagnosis of mania and re-admitted the following month for an episode of eye fluttering and tachycardia thought to be seizure. She was being treated at that time with lithium and olanzapine and was about to start electroconvulsive therapy (ECT) for refractory psychosis. When she arrived in the emergency room, she was extremely agitated and biting herself. On repeat CSF examination, she had 14 WBC/mL. She was admitted to the adolescent floor but was transferred to the intensive care unit when her creatine kinase was found to be 18,000 U/L. Her temperature was normal. She had extreme hypertension requiring rescue doses of labetalol. Repeat video EEG monitoring revealed background slowing but no epileptic activity; there was no EEG correlate with the episodes of agitation, pupillary dilatation, and tachycardia. MRI of the brain was normal. She was discharged to a psychiatric facility where she received ECT treatments and continuing psychiatric care.



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Several weeks later, she was found to have antibodies against the NMDA receptor in the CSF that was collected in 2005. As her mental state was improving other than deficits in memory, no further treatment was initiated. However, her symptoms again worsened in late 2008 with episodes of agitation and violence. A repeat lumbar puncture revealed persistence of antibodies and she received both intravenous immunoglobulin and methylprednisolone that resulted in substantial neurological improvement over the next 3 weeks.

Several months after immunotherapy, she had no focal neurological deficits, cognitive functions were close to normal baseline but she remained home-schooled due to episodes of agitation and aggression that are progressively subsiding. She continued with significant social and behavioural problems for several years until she recovered.

Discussion points:

Missed diagnosis due to limited knowledge of the disease (case studied in 2005)

Enhanced risk of neuroleptic malignant syndrome in anti-NMDA receptor encephalitis

The appropriate diagnosis would have avoided electroconvulsive therapy

Protracted recovery

Learning Objectives

- Describe neuropsychiatric manifestations of antibody-mediated disorders of the synapse
- Discuss common pitfalls in diagnosis and treatment of these disorders.
- Understand the treatment approach of antibody-mediated disorders of the synapse
- Describe central nervous system manifestations of SLE
- Describe the peripheral nervous system manifestations of SLE
- Understand how to manage nervous manifestations of SLE
- Understand how to manage psychiatric manifestations of SLE

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Moderator: Professor Roger A. Levy (Brazil)

Presenters: Dr Rebecca Fischer-Betz (Germany) & Professor Munther A. Khamashta (UK, UAE)

Pregnancy



Dr Rebecca Fischer-Betz, MD

Case 1: 37-year-old female - Biggy

A 37-year-old female Office Assistant presents with 8-year history of systemic lupus erythematosus (SLE). Past manifestations of SLE included polyarthritis, pleuritis, positive ANA and dsDNA antibodies and low complement. She had been initially treated with corticosteroids and hydroxychloroquine. Two years ago she had a flare with polyarthritis and treatment with methotrexate was added. Currently she is feeling well. She asks about the possibility of a pregnancy. Her menstruation is regular and she has had no previous pregnancies.

Laboratory tests revealed haemoglobin 12.8 g/dL; platelet 233 K/ μ L; leucocytes 3.800/ μ L; anti-dsDNA 122 (<80 IU/mL), and normal complement. She is currently taking methotrexate 12.5 mg SC/week and hydroxychloroquine 200 mg/day.

Discussion points:

How to perform pregnancy counselling in women with SLE?

What treatment options are available prior to conception and during pregnancy?



Dr Rebecca Fischer-Betz, MD

Case 2: 29-year-old female - Rena

Rena is a 29-year-old female from Sri Lanka living with her husband in Germany for the past 5 years. She was diagnosed with SLE about one year ago based on the presence of fever, fatigue, leucopaenia, positive antinuclear antibodies, positive anti-dsDNA and low complement. In addition she had proteinuria (>5 g/24 hours) and abnormalities of urinary sediment. A renal biopsy showed Class IV proliferative lupus nephritis. She was initially treated with prednisolone and cyclophosphamide (Euro Lupus protocol) followed by mycophenolate mofetil (MMF). She had an early abortion 3 years ago (unplanned pregnancy). Her menstruation cycle has been irregular since she stopped taking an oestrogen-containing pill after diagnosis. She worries about infertility. She currently reports joint pain and fatigue and sleeps a lot. Her physical examination is unremarkable, no arthritis, no oedema and her blood pressure is 125/85 mmHg. Laboratory tests reveal haemoglobin 10.8 g/dL (12–16 g/dL), creatinine 1.1 (<0.9) mg/dL, urinalysis 40 RBC, Pr/Cr 2.1 g/g, anti-dsDNA 433 (<80 IU/mL), complement C3 66 (90–180 mg/dL), C4 <6 (10–40 mg/dL). Antiphospholipid antibodies are negative. She is presently taking prednisone 10 mg, MMF 2 g/day, ramipril 5 mg/day and furosemide 20 mg. Her older brother also suffers from lupus nephritis. He stopped immunosuppressive treatment several months ago and is doing well.

Discussion point: *When and how to plan pregnancy in a patient with lupus nephritis*

Professor Munther A. Khamashta, MD, PhD, FRCP

Case 3: 35-year-old female

A 35-year-old female sustained a stroke 2 years ago and is on warfarin. Her laboratory profile shows IgG.ACA 85 GPL (high) and IgG anti- β 2 GP1 75 (high). She has been married for 10 years and she wishes to conceive. She seeks advice for the management of her anticoagulation therapy should she become pregnant.

Case 4: 29-year-old female

A 29-year-old female married

revealed IgG ACA 90 GPL (high), IgM ACA 75 MP L (high), and positive lupus anticoagulant (LAC). This patient is planning for in vitro fertilisation (IVF) and has read extensively about antiphospholipid syndrome (APS); she is therefore seeking advice on the best approach to prevent complications secondary to APS should her pregnancy be successful. She is also questioning whether or not she should receive anticoagulation during her IVF cycle.

Case 5: 24-year-old female

A 24-year-old female has sys

(moderate) and IgM ACA 45 MPL (moderate). Her medical history reveals one pregnancy loss secondary to intrauterine foetal demise during the second trimester. Her lupus is well controlled and she wishes to become pregnant again. She tested positive for anti-Ro antibodies and is seeking advice on the best medical approach for management during her pregnancy.

Learning Objectives

- Understand the influence of SLE on pregnancy and vice versa
- Describe the main predictors of pregnancy complications in women with SLE
- Describe currently accepted management of SLE prior to conception and during pregnancy
- Understand the importance of pregnancy counselling in SLE patients
- Provide the most appropriate contraceptive scheme for individual SLE patients
- Understand how to manage a pregnant woman with positive anti-Ro/SS-A antibodies
- Diagnose and manage antiphospholipid syndrome (APS) during pregnancy.
- Differentiate between pre-eclampsia, lupus nephritis and APS microangiopathy, and treat accordingly

Notes

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Moderator: Professor Ricard Cervera (Spain)

Presenters: Professor Tadej Avčin (Slovenia) & Professor Sandra V. Navarra (Philippines)

Paediatric and other lupus challenges in clinical practice



Professor Tadej Avčin, MD, PhD

Case 1: Lupus nephritis

A 15-year-old Caucasian girl was admitted to the rheumatology department with a one-month history of swollen eyelids in the morning and one day history of swollen ankles and feet. For the last month she also felt tired and was subfebrile up to 37.8°C. She had normal appetite, no headaches, normal urine and normal stool. On admission she was pale, blood pressure 150/95 mmHg, and had mild eyelid oedema and leg swelling. Otherwise, her physical examination was unremarkable.

Laboratory testing showed elevated erythrocyte sedimentation rate (ESR), normal c-reactive protein (CRP), mild anaemia and thrombocytopaenia, normal electrolytes, elevated urea 5.6 mmol/L and creatinine 111 µmol/L, hypoalbuminaemia, low complement C3 and C4, microscopic haematuria and nephrotic range proteinuria. Immunoserology testing showed antinuclear antibody (ANA) 1:640, positive anti-dsDNA and highly positive IgG anticardiolipin antibodies. Anti-β2-glycoprotein 1 (anti-β2-GP1) antibodies and lupus anticoagulants were negative.

Kidney biopsy was performed and revealed diffuse endocapillary proliferation involving 55% of all glomeruli, necrotising lesions and crescent formation. Immunofluorescence and electron microscopy revealed diffuse subendothelial immune deposits of IgG, IgM, IgA and C3 in glomerular capillary walls and mesangium. Tubulointerstitial immune deposits were present in 30% of tubules. According to the ISN/RPS classification the patient had Class IV-G (A) lupus nephritis with activity score 15 and chronicity score 0.

Overall, this patient with childhood-onset systemic lupus erythematosus (SLE) presented with acute nephritic syndrome and was treated aggressively with pulse IV methylprednisolone followed by oral prednisone and cyclophosphamide according to the Euro-Lupus Nephritis Trial protocol. The patient responded well to this treatment and induction of remission was gained.

Discussion points:

Diagnostic investigations in a child with suspected lupus nephritis including assessment of proteinuria at different ages

Induction and maintenance immunosuppressive treatment in a child with diffuse proliferative lupus nephritis Class IV

Tools for monitoring disease activity in children

What follow up and further investigations does a child with lupus nephritis need?



Professor Tadej Avčin, MD, PhD

Case 2: Neuropsychiatric involvement in childhood-onset SLE

A 13-year-old Caucasian girl initially presented with 1½-month history of weakness, weight loss, skin rash and joint pain. On examination she had malar rash, mouth ulcers and polyarthritis. Laboratory analyses revealed ESR 45 mm/h, normal CRP, normal complete blood count, normal biochemistry testing, normal complement level and normal urine. Immunoserology testing showed ANA >1:640 (homogeneous immunofluorescence pattern), positive anti-dsDNA, hypergammaglobulinaemia with IgG 24 g/L, negative anticardiolipin and anti-β2-GP 1 antibodies, and positive lupus anticoagulants. She was initially treated with hydroxychloroquine 200 mg/day, and prednisone 0.25 mg/kg/day and went into remission.

One year after the initial presentation she had disease flare with signs of tubulointerstitial nephritis which was confirmed by biopsy. Azathioprine was added to her treatment with good clinical recovery.

At the age of 16 years she presented to the emergency department with sudden onset of choreoathetotic movement disorder. She had complete loss of movement control and was bed ridden and dysarthric. Laboratory investigations showed ANA 1:640, negative anti-dsDNA antibodies, highly positive IgG anticardiolipin antibodies and highly positive lupus anticoagulants. Infectious work-up was negative and MRI examination of her head was normal.

Due to her recent onset neurological manifestations she was aggressively treated with pulse IV methylprednisolone, pulse IV cyclophosphamide, intravenous immunoglobulin and symptomatic therapy. With combined treatment she made an excellent recovery with nearly complete regression of choreoathetotic movement disorder in 8 days. She has mild residual impairments of both cognitive functions and fine motor skills.

Discussion points:

Neuropsychiatric manifestations in childhood-onset SLE

Treatment in a child with SLE and newly onset neuropsychiatric manifestations

Assessment of cognitive functions in adolescent with SLE and differential diagnosis

Professor Tadej Avčin, MD, PhD

Case 3: Macrophage activation syndrome as a life-threatening complication of childhood-onset SLE

A 15-year old, previously healthy girl presented to the paediatric emergency department with fever, difficulty breathing, abdominal pain, vomiting and watery diarrhoea. On admission her temperature was 40.0°C, heart rate 100/min and blood pressure 100/60 mmHg. She had no rashes, mucous membrane abnormalities, hepatosplenomegaly, lymphadenopathy or arthritis. Her laboratory examinations showed ESR 28 mm/h, WBC $3.1 \times 10^9/L$, haemoglobin 115 g/L, platelet count $232 \times 10^9/L$, elevated liver transaminases, normal urea and creatinine, and elevated lactate dehydrogenase. Her infectious disease work-up showed positive urine (*E. coli* $>10^6$ cfu/L) and stool (toro-virus) cultures, and she was initially treated with intravenous broad-spectrum antibiotics. Bone marrow aspirate obtained on the 13th day of illness showed mild to moderate dyserythropoiesis, and no evidence of haemophagocytosis.

Over 2 weeks, her symptoms did not improve and laboratory studies showed worsening pancytopenia and rising liver transaminases. Further testing showed a positive ANA 1:1280, positive anti-dsDNA and anti-RNP antibodies, positive Coombs' test and decreased level of complement C3. Urinalysis showed microhaematuria and few red blood cell casts. A diagnosis of childhood-onset SLE was made, complicated with concurrent macrophage activation syndrome (MAS). Treatment with intravenous infusion of gamma globulin was started together with IV pulse methylprednisolone. A repeat bone marrow aspirate obtained on the 21st day of illness showed mildly hypocellular marrow with significant number of haemophagocytic cells confirming the diagnosis of MAS, and treatment with etoposide and cyclosporine was prescribed. Renal histology showed lupus nephritis Class IIB with mesangial hypercellularity and mesangial deposits of immune complexes (IgG, M, A, complement C3 and fibrinogen).

Discussion points:

Early recognition of life-threatening complications in childhood-onset SLE

Treatment of MAS in a child with SLE

Professor Sandra V. Navarra, MD, FPCP, FPRA

Case 4: Lupus nephritis in an adolescent male with high risk sexual behaviour

A 17-year-old Asian male presents with prolonged fever of 6 weeks, accompanied by erythematous rashes on the face and upper extremities, dry cough, and "bubbly" urine. Four weeks ago, he had worsening cough with occasional haemoptysis; he also had episodes of gum bleeding. Two weeks later, he noticed swelling of his right leg.

The patient is an out-of-school juvenile, smokes occasionally and drinks alcoholic beverages; he denies any illicit drug use. He is sexually active, having had his first sexual encounter at age 15 with a female partner. He currently has two female and three male sexual partners, on an (unprotected) sex-for-fee basis. He lost 8 kg in a month (from 50 kg to 42 kg). He was orphaned at age 12 years, lived for years as a street mendicant before recently being assigned to a legal guardian.

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On admission, he appeared frail, with blood pressure 140/100, respiration 26/min, pulse rate 116/min, temperature 37.7°C, body mass index 18 kg/m². There were maculopapular rashes with scabs and crusts on the neck, upper and lower extremities and face. He was pale, with oral ulcers and whitish plaques on hard palate, and bleeding gums. He had swollen cervical and inguinal lymph nodes, and decreased breath sounds on both lung bases. There was bipedal oedema, with more swelling of the right leg and positive Homan's sign. Peripheral pulses and neurologic exam were normal. Haemoglobin was 85 g/L, WBC $3.6 \times 10^9/L$ (neutrophils 0.68, lymphocytes 0.25, monocytes 0.07), platelets $71 \times 10^9/L$. Urine showed +4 proteinuria with RBC's 15-20/hpf, hyaline and granular casts; urine protein: creatinine ratio was 2.65. Blood urea nitrogen was 12.8 mg/dL (ULN 23), creatinine 1.22 mg/dL (ULN 1.2), serum albumin 1.83 g/dL (LLN 4), globulin 4.1(ULN 3.4), sodium 139 mmol/L, potassium 4.93 mmol/L. Anti-nuclear antibody tested positive up to 1:640 (homogenous pattern), anti-ds DNA at 1:20; low serum complement (C3) 0.15 mg/dL (LLN 0.9). Antibodies to Sm, RNP, Ro, La, cardiolipin and lupus anticoagulant were negative. Chest radiograph showed bilateral pleural effusion. Echocardiography showed minimal pericardial effusion, no valvular vegetations. Abdominal ultrasound showed minimal ascites with normal organs. Venous duplex scan showed extensive thrombosis of the right external iliac vein, common femoral vein, deep femoral vein, superficial femoral vein, popliteal vein, peroneal vein, and anterior and posterior tibialis vein. Blood cultures grew no microorganisms. Viral serology for Epstein-Barr virus and cytomegalovirus were negative. (Following counselling and consent of patient and legal guardian) HIV screening by ELISA was indeterminate, and confirmatory testing by Western Blot was negative. He was started on prednisone, enalapril, hydroxychloroquine, and low molecular weight heparin overlapped with warfarin.

Discussion points:

Review the similarities and differences in clinical manifestations of SLE and HIV

Discuss special psycho-emotional, social and ethical considerations in adolescent SLE

Professor Sandra V. Navarra, MD, FPCP, FPRA

Cases 5–7: Lupus or not (cutaneous) lupus? A tale of three women

Case 5

A 43-year-old female diagnosed with SLE 12 years ago has had quiescent disease in the past few years and is maintained on prednisone 5 mg/d and hydroxychloroquine 200 mg/d. Six years ago, she developed a troublesome, persistent draining sinus on the left perineal area; thorough gynaecologic and lower gastrointestinal work-up including imaging studies and fistulography were negative, and tissue histopathology showed non-specific chronic inflammation. Four months ago, she developed low-grade fever, arthralgias, ankle synovitis and appearance of erythematous, with tender nodular and vesicular lesions on the arms, upper back and abdomen. Laboratory tests were normal except for elevated ESR 54 mm/hr and CRP 96 U/mL. Chest X-ray showed upper lobe infiltrates, and tuberculin skin test was positive at 20 mm. She was started on an anti-tuberculosis regimen, prednisone was increased to 40 mg/d slowly tapered to 5 mg/d. Two months later, she was afebrile, with resolving skin lesions and ankle arthritis, as well as resolution of the draining sinus at the perineal area.



Case 6

A 42-year-old female was referred to the rheumatology department because of prolonged fever lasting 6 months accompanied by oral ulcers, arthritis and cervical lymphadenopathy. Two months before, she developed papules on the left cheek, which would spontaneously develop superficial erosions exuding serous discharge followed by crusting; similar lesions also developed on the anterior chest, left thigh and both upper arms, then behind her right ear; there was also knee arthritis. Haemoglobin was 89 g/dL, WBC $9.3 \times 10^9/L$, platelets $815 \times 10^9/L$, ESR 112 mm/1st hr, normal urinalysis, positive anti-nuclear antibody 1:320 (speckled pattern), negative anti-dsDNA and normal serum complement (C3) 1204 mg/L. Skin biopsy and synovial fluid examination were performed.



Case 7

A 27-year-old female was referred to Rheumatology because of prolonged fever, alopecia, oral ulcers and multiple skin lesions evolving over 4 months. Laboratory tests showed pancytopenia, proteinuria, hypocomplementaemia, and high titre antinuclear antibody and anti-dsDNA. Skin involvement included malar rash, multiple petechial to purpuric rashes, and annular crusted lesions bordered by erythema on the extremities, trunk and ear lobes. A biopsy of one of the crusted lesions was performed.

Discussion points:

Review the various skin involvement in lupus from non-specific to specific skin lesions

Discuss differential diagnoses for nodular vasculitis, skin erosions/ulcers and crusting lesions in the context of SLE



Learning Objectives

- Understand the diagnostic investigations and management of children with lupus nephritis
- Describe the tools and investigations needed to continue follow-up assessment of children with lupus nephritis
- Review and discuss effective treatment of neuropsychiatric manifestations of lupus in children
- Identify and treat life-threatening complications in childhood-onset SLE
- Review similarities and differences in clinical manifestations of SLE and HIV including renal involvement
- Consider the special psycho-emotional, social and ethical considerations in adolescent SLE
- Describe the various types of skin involvement in lupus from non-specific to specific skin lesions
- Discuss differential diagnoses for nodular vasculitis, skin erosions/ulcers and crusting lesions in the context of SLE

Abstracts

Plenary II: Management of SLE—Compliance, Comorbidities and Drug Toxicities

Moderators: Professor David A. Isenberg (UK) & Professor Bevra H. Hahn (USA)



Professor Zahir Amoura, MD, MSc

French National Reference Center for SLE and APS, Pitié-Salpêtrière Hospital, Paris, France

The importance of assessing medication exposure in SLE

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Ensuring adequate drug exposure is one of the new challenges of current therapeutic strategies in systemic lupus erythematosus (SLE). The pharmacokinetic profiles (absorption, distribution, metabolism, and excretion) of several drugs, given at a fixed dose, are strongly affected by multifactorial (environmental, genetic, and disease-specific) determinants, which may impair their bioavailability. Inter-individual pharmacokinetic variability may induce insufficient exposure to many drugs used in SLE, leading to both apparent inefficacy of treatments and inappropriate therapeutic escalation. Individual assessment of exposure to mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil (MMF), could

be used to determine whether a given patient received adequate doses of MMF.^{2,3} Measuring blood concentrations of hydroxychloroquine could be used as an efficient way to assess adherence, which is a critical issue since poor adherence is the primary source of treatment failure in a significant proportion of refractory SLE patients.

These pharmacokinetic concepts, which were originally developed in solid-organ transplantation where they have contributed to improving patient outcomes by optimising therapeutic strategies, are now being transposed for the management of patients with SLE.

Learning Objectives

- To know the importance of assessing MPA AUC in SLE
- To know the importance of assessing hydroxychloroquine blood levels in SLE
- To know the importance of assessing the blood levels of azathioprine and of its metabolites in SLE

Notes

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Abstracts

Plenary II: Management of SLE—Compliance, Comorbidities and Drug Toxicities

Moderators: Professor David A. Isenberg (UK) & Professor Bevra H. Hahn (USA)



Professor David D'Cruz, MD, FRCP
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Managing fatigue in SLE

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Systemic lupus erythematosus (SLE) is a chronic illness that may be life-threatening when major organs are affected, but it more commonly results in chronic debilitating ill health. No single cause for SLE has been identified, though factors such as sunlight and drugs may precipitate the condition and there is a complex genetic basis. Autoantibodies may be present for many years prior to the clinical onset of the disease and there may be a crescendo of increasing numbers of antibodies just before symptoms develop, pointing to a multifactorial pathogenesis.

Fatigue is a common and debilitating symptom that has proved difficult to evaluate and treat. In fact fatigue is the one symptom that patients report that has the biggest impact on their quality

of life. The pathogenesis of lupus fatigue is complex and factors determining fatigue include depression, pain, poor sleep quality, poor physical fitness, perceived social support and disease activity.^{1,2} Fatigue can be severe even when lupus is in remission. Identification of contributory factors such as anaemia and hypothyroidism are worthwhile as is treatment for depression, a common occurrence in any chronic illness. Clinical trials of supervised exercise programmes showed benefit in terms of aerobic capacity, quality of life and depression, and one study showed improvements in fatigue without causing disease flares, although the beneficial effects disappeared on stopping the exercise programmes.^{3,4} Therapy with antimalarials may also be useful in combating fatigue, though there are no trials to support this.

Learning Objectives

- Discuss the prevalence and clinical associations of fatigue in SLE
- Assess fatigue in patients with SLE with objective scoring tools
- Discuss a management strategy for patients with SLE and fatigue

Notes

[illegible]



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Using lower doses of glucocorticoids in SLE: less toxicity, same efficacy

References

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Glucocorticoids have long been one of the cornerstones of the treatment of inflammatory conditions, including systemic lupus erythematosus (SLE). The use of high doses of oral prednisone/prednisolone is recommended by most guidelines in cases of moderate to high lupus activity.^{1,2} However, such recommendations are based more on custom than on true evidence.

According to the pharmacological basis of the effects of glucocorticoids, the genomic pathway is almost fully saturated at doses of prednisone over 30 mg/d, which means that toxicity associated with transactivation is close to maximum above those levels. On the contrary, the non-genomic pathway is responsible for a rapid and powerful anti-inflammatory response, mostly free from the secondary effects of the genomic pathway; this pathway is activated at doses over 100 mg/d, being fully active over 250 mg/d.³

Results from clinical studies corroborate these data. It has been consistently shown that glucocorticoid-related damage is dose-dependent, with doses below 5–7.5 mg/d being probably safe and doses >30 mg/d being associated with a sharp increase in the frequency of side effects. The use of pulses of methyl-prednisolone has been also free from secondary damage in most studies.^{4,5}

Moreover, recent data from observational studies and a small clinical trial support the fact that lower doses of oral prednisone are as effective as high doses in treating active lupus, particularly, but not only, renal disease.^{6–8} Thus, a door has been opened to a more rational use of glucocorticoids, taking advantage of their unquestionable anti-inflammatory and immunomodulatory properties whilst reducing the risks for the also unquestionable toxicity.

In our experience, combination therapy with hydroxychloroquine, immunosuppressive drugs and, especially, pulses of methylprednisolone (no need to exceed 500 mg per pulse; a 250 mg pulse is usually enough) help reduce the initial doses of prednisone to less than 30 mg/d with very rapid tapering, and offer high efficacy minimising short- and long-term secondary effects.

Learning Objectives

- Understand the role of the genomic and non-genomic pathways in the therapeutic and toxic effects of glucocorticoids
- Review published data in SLE patients showing the association of different doses of glucocorticoids with side effects including damage
- Discuss the results from recent studies on the efficacy and toxicity of therapeutic schemes using lower doses of prednisone in severe lupus
- Use practical guidelines for using lower doses of prednisone in the setting of active lupus

Notes

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Prevention of accelerated atherosclerosis in SLE: Should everyone be on a statin?

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Atherosclerosis leading to fatal cardiovascular events (CVE), including myocardial infarcts and strokes, is a major problem in patients with systemic lupus erythematosus (SLE). Approximately one third of patients have atherosclerosis, including carotid intimal thickness, coronary artery calcifications and regional abnormalities in cardiac contractility, with CVE accounting for the majority of deaths in patients who have had SLE for more than 10 years. Incidence of CVE is 5 to 10 times higher than the general population.¹ Patients with SLE are predisposed to atherosclerosis due to multiple autoantibodies against endothelial and vascular components, T cells directed against peptides from vascular cells, high levels of cytokines and chemokines that activate and damage endothelium, and abnormal lipids which include oxidised high density lipoprotein (HDL) that cannot protect arterial vessels from accumulation of low density lipoprotein (LDL), cholesterol and formation of plaques.^{1,2}

Factors that indicate an individual SLE patient is at higher risk for CVE include the typical “Framingham” factors (advancing age, hypertension, current smoking, diabetes mellitus) and in addition premature menopause, sedentary lifestyle, longer disease duration, increased waist-to-hip ratios and high cumulative dose or high duration of glucocorticoid therapy.^{1–4} Recent work has shown combinations of multiple factors are better than any single biomarker to predict formation or enlargement of carotid plaques (the best combination – with high positive predictive and negative predictive values – was age, diabetes, and serum levels of pro-inflammatory HDL, soluble TWEAK, leptin, and homocysteine – a positive PREDICTS score associated with a hazard ratio [HR] of 27.7 for carotid plaque). Measuring standard serum lipid levels was not predictive in this relatively small cohort of 300 SLE patients (reviewed in McMahon et al 2014).¹

Regarding therapies, in addition to controlling blood pressure to levels of 130/80 or less and minimizing glucocorticoid doses, there

is reasonable evidence that low dose aspirin, hydroxychloroquine and mycophenolate mofetil each reduces the risk of CVE and cardiovascular death.^{1,4} The evidence that statin therapies are useful is controversial. In several studies of relatively small numbers of patients with SLE (reviewed in McMahon et al 2014 and Sahebkar et al 2016)^{1,5} (the largest study being 200 patients divided between statin and placebo) there has been little evidence of reduction of surrogates for CVE, such as carotid intimal thickening, plaque or coronary calcification. Conversely, a recent study from Taiwan⁶ (a retrospective nested case control of 950 patients with SLE and hyperlipidaemia) analysed use of statin therapy and showed those treated with a statin for one year or more had a statistically significant lower incidence of CVE and overall mortality than those not treated with a statin. Additionally, post-hoc analysis of a statin trial in children with SLE showed that in a subset with puberty plus high plasma levels of high-sensitivity c-reactive protein (hsCRP), statin treatment significantly slowed thickening of carotid intima (reviewed in Sahebkar et al 2016 and Arnaud et al 2015).^{4,5}

In summary, it is recommended that patients with SLE be evaluated annually for factors that increase risk for CVE, and that statin therapy be considered for those with elevated hsCRP, elevated total cholesterol or LDL-C, known evidence of arterial disease, or other worrisome indicators. Statins other than simvastatin should be chosen since it has the highest incidence of statin myopathy, and low doses of other statins should be used when effective, as higher doses are more highly associated with myopathies, transaminitis and cytopenias. In prospective trials, adverse effects of statins have not been more common in patients with SLE than in the general population treated with statins. Most authorities recommend that virtually all SLE patients be treated with hydroxychloroquine, which reduces disease flares as well as reducing clotting events. Low dose aspirin should be considered, particularly if SLE patients have antiphospholipid antibodies, which promote clotting.

- Understand the features of SLE that predispose to atherosclerosis
- Review the current state of studies of statins in patients with SLE
- Review the therapeutic options for prevention of atherosclerosis in addition to or in place of statins

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Abstracts

Plenary III: Management of SLE-Therapies Derived from Other Specialties

Moderators: Professor Richard A. Furie (USA) & Professor Ricard Cervera (Spain)



Professor Reinhard E. Voll, MD

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Bortezomib in SLE

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Refractory disease courses of systemic lupus erythematosus (SLE) may be caused by long-lived plasma cells secreting pathogenic antibodies, which are resistant to conventional therapies including high dose cyclophosphamide. Due to their extremely high production of antibodies within the endoplasmic reticulum (ER), plasma cells are highly sensitive towards proteasome inhibition, which blocks the degradation of misfolded proteins, thereby inducing ER stress and the terminal unfolded proteins response leading to apoptotic cell death.¹ We demonstrated that the proteasome inhibitor bortezomib, which is approved for treatment of multiple myeloma, can efficiently deplete short- as well as long-lived plasma cells in mice and thereby, ameliorates murine lupus nephritis.²

In a case series the outcomes of 15 patients with SLE were analysed, who had not sufficiently responded to standard treatment and hence, were offered treatment with bortezomib.³ The disease activity score SLEDAI and anti-dsDNA antibody titres decreased upon treatment. In all patients with active lupus nephritis, proteinuria declined within 6 weeks after start of bortezomib treatment. Total IgG concentrations decreased in most patients by approximately 25%, however, they usually remained within normal limits. All adverse events were mild or moderate.

Hence, the proteasome inhibitor bortezomib may represent a promising new treatment in patients with refractory SLE. Pathogenic autoantibodies are markedly decreased by bortezomib. Vaccine titres decrease as well, but usually stay within protective ranges. Clinical trials are ongoing to explore the use of proteasome inhibitors as a new treatment option in patients with SLE.

Learning Objectives

- Understand the relevance of the ubiquitin-proteasome system for plasma cell survival
- Explore the role of long-lived plasma cells for refractory disease courses of antibody-mediated diseases
- Learn about effects and adverse events of proteasome inhibitor treatment in patients with refractory SLE

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Abstracts

Plenary III: Management of SLE–Therapies Derived from Other Specialties

Moderators: Professor Richard A. Furie (USA) & Professor Ricard Cervera (Spain)



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Eculizumab in SLE

References

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Eculizumab is a humanised monoclonal antibody against factor V of complement in paroxysmal nocturnal haemoglobinuria and atypical uraemic haemolytic syndrome. Treatments in both pathologies have been very successful.

It is known that in severe forms of systemic lupus erythematosus (SLE), thrombotic microangiopathy (TMA) may develop due to endothelial injury, and antibodies that can (and probably will) activate complement develop in severe forms of TMA. In these cases, the use of eculizumab might be useful to reverse the TMA and stop or avoid injury or slow pathophysiologic processes.

It is clear that eculizumab treatment in these cases should not be long term. However, a basic treatment is needed to control the process of SLE that causes the synthesis of antibodies. A few months of eculizumab treatment may reverse the endothelial injury and thus avoid organic injury.

At the moment, evidence only comprises clinical cases and studies are needed to analyse the true impact of eculizumab in the management of SLE.

Learning Objectives

- Understand the importance of controlling the process of SLE that causes the synthesis of antibodies
- Understand the importance of managing thrombotic microangiopathy in severe forms of SLE
- Discuss the potential therapeutic benefits of eculizumab in SLE

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Abstracts

Plenary III: Management of SLE-Therapies Derived from Other Specialties

Moderators: Professor Richard A. Furie (USA) & Professor Ricard Cervera (Spain)



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Romiplostim and eltrombopag for idiopathic thrombocytopenic purpura

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Immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterised by isolated thrombocytopenia (platelet count $<100,000/\mu\text{L}$) due to autoantibodies to platelet antigens resulting in an accelerated clearance and/or decreased production of platelets.¹ There is evidence that, in some cases, complement activation may contribute to this process of accelerated destruction and decreased production. As a consequence bleeding is the most prominent clinical symptom, which correlates with the severity of thrombocytopenia. In recent years it has become clear that ITP is a heterogeneous disease in which an imbalance of the immune system due to e.g. infections (molecular mimicry), coexisting immune deficiencies, lymphoproliferative syndromes or autoimmune diseases (SLE), results in the production of autoantibodies to platelets.² Finally, environmental and genetic factors may impact platelet turnover, bleeding risk and the chance to respond to different treatment strategies. In a considerable percentage (80%) of patients, no underlying disease explaining the dysregulation of the immune system can be identified (primary

ITP).² A platelet count $<30,000/\mu\text{L}$ and/or bleeding complications are generally considered as an indication to start treatment.³ As a matter of fact, treatment of an underlying disease is a *sine qua non* in order to achieve optimal treatment response. Steroids as a first-line therapy may result in a complete response rate of up to 30% with prednisolone and up to 70% with high-dose dexamethasone.³ In cases of steroid refractoriness, splenectomy results in response percentages up to 70%.³ Given the short- and long-term complications of splenectomy anti-CD20 treatment (rituximab) has been widely applied as a second-line treatment in ITP refractory to steroids, showing complete response percentages up to 40% with convincing safety profile.³ Thrombopoietin receptor agonists (TPO-RA), romiplostim and eltrombopag, as second-line treatment of steroid refractory ITP, resulted in complete response rates of up to 90% with a beneficial short-term safety profile. However, treatment with TPO-RA is considered a chronic treatment and only few patients can discontinue this treatment. In addition, the long-term safety of this treatment remains to be established.⁴

Learning Objectives

- Understand that pathogenesis of immune thrombocytopenia cannot be reduced to autoantibodies to platelets, but is based on a complex dysregulation of the immune response
- Learn that indication to start treatment is depending on relevant factors, such as risk and extent of bleeding, comorbidities predisposing to bleeding, potential treatment related complications, activity and lifestyle and patient worries/anxieties about disease burden
- Understand the advantages and disadvantages of current treatments for ITP

Notes

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Lessons learned from SLE clinical trials

References

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The lupus community has witnessed major treatment breakthroughs in nearly every decade over the last 70 years. In the late 1940s the discovery of compound E, cortisone, revolutionised the treatment of patients not only with lupus but across all inflammatory diseases. During the 1950s, azathioprine was introduced as a chemotherapeutic agent, but it was adopted soon thereafter as a drug for patients with rheumatic diseases. The antimalarial quinacrine was also first used in the early 1950s. Subsequently, cyclophosphamide became the eighth cytotoxic anticancer drug approved by the Food and Drug Administration (FDA) and its application to patients with severe forms of lupus remains to this day. In the late part of the twentieth century, mycophenolate mofetil received approval for acute kidney transplant rejection, and in the early part of the twenty-first century, it was adopted as a rival to cyclophosphamide for lupus nephritis (although not FDA-approved for this condition). The twentieth century closed with a foray into clinical trials in an effort to discover safer and more efficacious drugs

for our lupus patients. While the outcomes of such efforts have been largely unsuccessful, two positive Phase 3 studies with belimumab led to its approval in 2011.^{1–3} Along the way, experience with other biologics, such as rituximab⁴ and abatacept⁵ was gained, and while these drugs are not approved for lupus, they are used by many physicians to treat their lupus patients. What will the next decade bring? There is currently unprecedented activity in the area of drug development in patients with lupus.^{6–11} However, the obstacles to drug development are many. For example, in 2015, two large development programmes came to a grinding halt. Between the tabalumab and epratuzumab Phase 3 programmes, over 3500 patients with lupus were enrolled. It is crucial for the lupus community to understand the reasons for the failures and apply a “lessons learned” approach in order to deliver more efficacious and safer therapies in the future. There is little doubt that rheumatologists will soon have an expanded treatment armamentarium.

Learning Objectives

- Recognise unmet needs in the treatment of patients with lupus
- Understand issues related to clinical trial design
- Discuss strategies for drug development in lupus
- Review clinical trial efforts currently underway

Notes

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How different is SLE? Applying lessons from other diseases to trials in lupus

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While the failure of some Phase 2 and 3 clinical trials must be inevitable, the relatively high proportion of failed trials in systemic lupus erythematosus (SLE) has suggested that perhaps some aspects of methodology and trial design could be improved. Meanwhile, there have been many successful trials in other disease areas in rheumatology and beyond. What lessons can we learn from such trials that could also be applied to SLE?

For rheumatoid arthritis (RA), an important early milestone in developing clinical trial methodology was the selection of a core set of RA outcomes, reducing more than eighty different outcomes to just seven. Based on these, a composite trial outcome was developed that could be shown to be more sensitive to change than any of the individual outcomes: the ACR20. Notably, the fact that the ACR20 was not primarily chosen for being “clinically relevant” was not an impairment to its widespread use or to its adoption as a primary outcome in many trials.

Rheumatoid arthritis trials also benefited from the development of measurements of disease state (as opposed to response), such as the DAS28, that in turn allowed cut-offs for desirable goals of therapy such as remission to be set. Also, in parallel, systems for quantitative assessment of radiographs were developed that could also be used as (co-)primary outcomes in trials.

Trials in other rheumatic diseases, such as ankylosing spondylitis and psoriatic arthritis, were also made possible through the application of well-characterised outcomes.

The use of surrogate markers as key outcomes has not been a feature of clinical trials in rheumatology. However, therapeutics for multiple sclerosis are often developed based on their ability to decrease the occurrence of new lesions on MRI, and it would therefore not seem impossible to use such an approach in trials of other autoimmune diseases as well.

Finally, clinical trial design is the result of a complex interplay between many ‘stakeholders’, including patients, specialists and health professionals, regulators, industry and others. In this complex interplay, a clear and unified voice from patients and their physicians can have a great impact.

Learning Objectives

- Understand which properties are most important when measures of disease state or changes in disease parameters are used as outcomes in clinical trials
- Understand the essentials of outcome characteristics such as face validity, sensitivity to change, and clinical relevance
- Gain insight into the developments that made it possible for many successful trials to be performed in RA
- Learn how aspects of clinical trials design in RA, psoriatic arthritis, ankylosing spondylitis and multiple sclerosis could also be applied to clinical trials in SLE

Notes

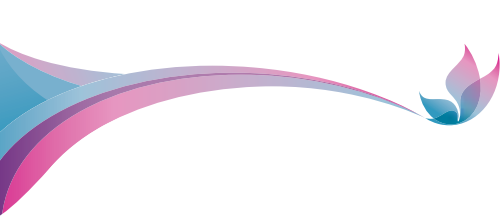
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Notes

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