

6th Annual Meeting of the Lupus Academy

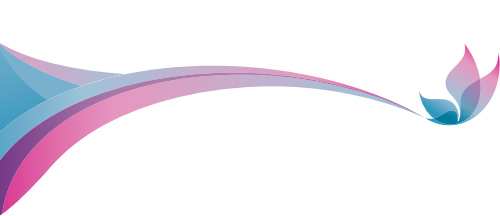
Abstract Book

Lisbon, Portugal
5–7th May 2017



LupusAcademy

Communicate. Educate. Treat.



European Accreditation Council for Continuing Medical Education (EACCME) Accreditation



The Lupus Academy/European CME Forum is accredited by the European Accreditation Council for Continuing Medical Education (EACCME) to provide the following CME activity for medical specialists. The '6th Annual Meeting of the Lupus Academy 2017' is designated for a maximum of 11 hours of European external CME credits, event code: 15723. Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity. The EACCME is an institution of the European Union of Medical Specialists (UEMS), www.uems.eu.

Participants from Europe

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Participants from USA

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Participants from Canada

Live educational activities occurring outside of Canada, recognized by the UEMS-EACCME for ECMEC credits are deemed to be Accredited Group Learning Activities, (Section 1) as defined by the Maintenance of Certification Program of The Royal College of Physicians and Surgeons of Canada.

Participants from other countries

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Meeting organisation

The content for this activity has been developed under the supervision of the meeting Chairs: Professor David Isenberg, UK and Professor Munther Khamashta, UK/UAE, 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.



Supporters

The Lupus Academy's education programme is supported through financial and in-kind support.

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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 6th Annual Meeting of The Lupus Academy[†], which we hope you will find engaging, informative, and rewarding.

The Lupus Academy is committed to continuing the development of high quality educational programmes, focused on providing insightful and clinically relevant content through both live meetings and eLearning environments. With this, we aim to 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 and scientific 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 Lisbon.

With kind regards,

The Lupus Academy Steering Committee

Professor David Isenberg

Course Director and co-Chairman 2017

Professor Munther Khamashta

co-Chairman 2017

Professor Zahir Amoura

Professor Richard Furie

Professor Ronald van Vollenhoven

Professor Ricard Cervera

Professor Bevra Hahn

Professor Murray Urowitz

Professor Andrea Doria

Professor Roger A. Levy

Professor Thomas Dörner

Professor Sandra Navarra

[†]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.



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Programme

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18:00	Opening Address	Munther Khamashta (UK/UAE) & David Isenberg (UK)	
Keynote Lecture		<i>Moderators: David Isenberg (UK) & Munther Khamashta (UK/UAE)</i>	
18:00–18:30	Lupus and Malignancy: The risk and the reasons	Ann Clarke (Canada)	20
18:00–18:45	Discussion		
The Great Debate: This house believes the term ‘mixed connective tissue disease’ is archaic and should be replaced		<i>Moderators: Ricard Cervera (Spain) & Munther Khamashta (UK/UAE)</i>	
18:45–20:15	The matter of the debate (15 minutes)	Ricard Cervera (Spain)	
	For the motion: (20 minutes + 10 minutes rebuttal)	David Isenberg (UK)	22
	Against the motion: (20 minutes + 10 minutes rebuttal)	Andrea Doria (Italy)	24
	Discussion (15 minutes)		
20:15	Welcome dinner		

Saturday 6th May			Page
07:30	Breakfast with the Professor I	Steering Committee (x6)	
Plenary I: Biomarkers in SLE Update		<i>Moderators: Ronald van Vollenhoven (Netherlands) & Richard Furie (USA)</i>	
08:30	dsDNA antibodies: New insights	David Pisetsky (USA)	26
08:55	Atherosclerosis biomarkers	Anisur Rahman (UK)	28
09:20	Renal biomarkers	Richard Furie (USA)	30
09:45	CNS biomarkers	Raquel Faria (Portugal)	32
10:10	Discussion		
10:30	Coffee		
Case Study Workshops (AM)			
11:00	<i>Moderator: Thomas Dörner (Germany)</i> Lupus and the skin	 Roger A. Levy (Brazil) & Ricard Cervera (Spain)	36
11:00	<i>Moderator: David Isenberg (UK)</i> Management of clotting issues	 Munther Khamashta (UK/UAE) & Hannah Cohen (UK)	38
11:00	<i>Moderator: Andrea Doria (Italy)</i> Lupus and the heart and great vessels	 Murray Urowitz (Canada) & Ronald van Vollenhoven (Netherlands)	40
11:00	<i>Moderator: Bevra Hahn (USA)</i> Lupus and the musculoskeletal system	 Zahir Amoura (France) & Sandra Navarra (Philippines)	42
12:30	Lunch		

Programme

Saturday 6th May <i>continued</i>				Page
Case Study Workshops (PM)				
14:00	<i>Moderator: Thomas Dörner (Germany)</i> Lupus and the skin		Roger A. Levy (Brazil) & Ricard Cervera (Spain)	36
14:00	<i>Moderator: David Isenberg (UK)</i> Management of clotting issues		Munther Khamashta (UK/UAE) & Hannah Cohen (UK)	38
14:00	<i>Moderator: Andrea Doria (Italy)</i> Lupus and the heart and great vessels		Murray Urowitz (Canada) & Ronald van Vollenhoven (Netherlands)	40
14:00	<i>Moderator: Bevra Hahn (USA)</i> Lupus and the musculoskeletal system		Zahir Amoura (France) & Sandra Navarra (Philippines)	42
15:30	Coffee			
Plenary II: Management of SLE			<i>Moderators: Zahir Amoura (France) & Sandra Navarra (Philippines)</i>	
16:00	Drug-induced lupus		Robert Rubin (USA)	44
16:25	Optimising lupus management in pregnancy		Catherine Nelson-Piercy (UK)	46
16:50	Immunisation of patients with SLE		Bevra Hahn (USA)	48
17:15	Discussion			
17:45	Close			
Sunday 7th May				Page
07:30	Breakfast with the Professor II	Steering Committee (x6)		
Plenary III: New Insights in SLE			<i>Moderators: Murray Urowitz (Canada) & Bevra Hahn (USA)</i>	
09:00	Where do new oral anticoagulants fit in SLE?		Hannah Cohen (UK)	50
09:25	Immunopathology in SLE: The pathogenic engines		Thomas Dörner (Germany)	52
09:50	Discussion			
Curbside Consults			<i>Moderator: Munther Khamashta (UK/UAE)</i>	
10:00	The experts tackle three short and challenging cases		Zahir Amoura (France) Ann Clarke (Canada) Sandra Navarra (Philippines) Anisur Rahman (UK)	54
10:45	Coffee			
Plenary IV: Therapy Updates in SLE			<i>Moderators: David Isenberg (UK), Peter Lydyard (UK) & Roger A. Levy (Brazil)</i>	
11:15	Where are we now with blocking B-cell activating factors?		Ronald van Vollenhoven (Netherlands)	56
11:40	Targeting the interferon pathway in SLE		Richard Furie (USA)	58
12:05	Discussion			
12:20	Summary and close		Munther Khamashta (UK/UAE) & David Isenberg (UK)	

Biographies



Professor Zahir Amoura, MD, MSc

French National Reference Centre 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; GSK; Lilly; Roche; Teva

Consultant/Advisor:

Amgen; BMS; GSK; Lilly

Professor Amoura is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the Lupus Academy's 6th Annual Meeting programme and materials.



Professor Ricard Cervera, MD, PhD, FRCP

Hospital Clinic, Barcelona, Catalonia, Spain

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.

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.

Disclosures

Consultant/Advisor:

AstraZeneca; Celgene; GSK; Pfizer; UCB

Professor Cervera is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the Lupus Academy's 6th Annual Meeting programme and materials.

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

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, 67), 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 Ann Clarke, MD, MSc, FRCPC
University of Calgary, Alberta, Canada

Disclosures

Consultant/Advisor:
AstraZeneca; Exagen

Ann Clarke is a Professor in the Division of Rheumatology, Cumming School of Medicine, University of Calgary, Alberta, Canada, and holds The Arthritis Society Chair in Rheumatic Diseases. She is also the Director of the University of Calgary Lupus Clinic.

Professor Clarke is an established investigator in the epidemiology, economics, and outcomes of systemic lupus erythematosus (SLE). She currently serves as Chair of the Systemic Lupus International Collaborating Clinics (SLICC), a group of leading lupus clinician scientists. SLICC has contributed to the development of standardised

measures for lupus disease activity, damage, patient assessment, and outcomes analysis, and has initiated several major cohort studies on cardiovascular, neuropsychiatric, renal, and economic outcomes in SLE. Professor Clarke's research team has conducted pivotal research on the risk and determinants of malignancy in SLE. Professor Clarke has received support from numerous Canadian and American peer-reviewed granting agencies, has published over 300 manuscripts, and is very involved in the training of the next generation of lupus clinicians and investigators.



Dr Hannah Cohen, MBChB, MD, FRCP, FRCPath
University College London, UK

Disclosures

Grants/Research
Support: Bayer
Consultant/Advisor: Bayer

Hannah Cohen is Consultant and Honorary Reader in Haematology at University College London (UCL) Hospitals NHS Foundation Trust and University College London, UK. She is Trust Clinical Lead in anticoagulation and venous thromboembolism, leads the thrombosis and haemostasis service for Women's Health, and is Haematology Lead for the UCL undergraduate curriculum. She studied medicine at the University of Manchester, trained in haematology at the Middlesex and UCL Hospitals, and was awarded her MD degree for studies on haemostasis in renal allograft recipients.

In the first randomised controlled trial (RCT) in women with antiphospholipid antibodies and recurrent miscarriage, Dr Cohen established a regimen that has become standard treatment internationally. She led the Rivaroxaban in Antiphospholipid Syndrome (RAPS) trial, the first RCT of a direct oral anticoagulant in thrombotic APS. She is a co-Investigator in the prospective RCT on Hydroxychloroquine versus placebo during Pregnancy in women with Antiphospholipid Antibodies (HYPATIA) and in the study of the Clinical Relevance of Brain Microbleeds in Stroke (CROMIS-2). She is also leading the RISAPS (Rivaroxaban in Stroke Patients with APS) trial.

She is a Founder member, Executive Committee member, and UK Core Laboratory Director of APS ACTION. She co-Chairs the International Society of Thrombosis and Haemostasis (ISTH) Women's Health Scientific Subcommittee, where she has led ISTH guidance on the management of direct oral anticoagulants in relation to pregnancy. She has published over 200 peer-reviewed articles.

As a Founder member and Steering Group Chair of the Serious Hazards of Transfusion (SHOT) UK confidential enquiry into transfusion risks, Dr Cohen established SHOT as an international gold standard in haemovigilance. SHOT recommendations underpinned initiatives that have led to improved patient safety in the UK.



Professor Andrea Doria, MD

University of Padova, Italy

Disclosures

Consultant/Advisor:

Baxalta; BMS; GSK; Pfizer

Speakers' Bureau:

BMS; GSK

Professor Doria is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the Lupus Academy's 6th 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.

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 was the chair of the 10th European Lupus Meeting, 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: Roche/Chugai;
Sanofi; UCB

Consultant/Advisor: Eli
Lilly; Roche; Sanofi; UCB

Professor Dörner is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the Lupus Academy's 6th 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 Raquel Faria, MD
University of Porto, Portugal

Disclosures

Grants/Research

Support: GSK

Consultant/Advisor: GSK

Raquel Faria is specialist in General Internal Medicine with a specialist interest in autoimmune and systemic inflammatory diseases. She graduated in 2004 from the University of Porto, Portugal and trained in general internal medicine, emergency medicine, neurology and rheumatology. She was tutored by Carlos Vasconcelos (Porto) and David Isenberg (London).

Dr Faria is currently working in Unit of Clinical Immunology, Hospital Santo António, Porto, and working on her PhD.

Dr Faria has a specialist interest in neuropsychiatric lupus and is part of a collaborative group working with neurologists, psychologists, basic immunologists, and geneticists. She has been part of international collaborative projects like BioLupus and PRECISEADS.



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

Disclosures

Grants/Research

Support: AstraZeneca;
 BiogenIdec; BMS;
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Consultant/Advisor:

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AstraZeneca; BiogenIdec;
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 MedImmune; Pfizer;
 Sanofi; UCB

Committee Member:

American College of
 Rheumatology; Lupus
 Foundation of America;
 Lupus Alliance of America;
 Lupus Research Alliance;
 LuCin; The Lupus
 Academy

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 has also served on the Medical and Scientific Advisory Board of the SLE Foundation as well as the Alliance for the Lupus Research Scientific Advisory Board, and continues to volunteer in the activities of the merged foundations, now known as the Lupus Research Alliance. Professor Furie has served on many committees of the American College of Rheumatology for nearly 20 years.

Professor Furie is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the Lupus Academy's 6th Annual Meeting programme and materials.

Biographies



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

Disclosures

Grants/Research

Support: BMS

Professor Hahn is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the Lupus Academy's 6th 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 Isenberg, MD, FRCP, FAMS
University College London, UK

Disclosures

Professor Isenberg is Programme Director and co-Chair of the Lupus Academy (2017) and has been involved in the planning and development of the 6th 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 and Lupus UK's Research Committee and was Chair of the Systemic Lupus International

Collaborating Clinics group (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 19 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. In 2016 he became a Master of the American College of Rheumatology.



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

Disclosures

Professor Khamashta is co-Chair of the Lupus Academy (2017) and has been involved in the planning and development of the 6th 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 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, 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 and International League Against Rheumatism 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.



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

Disclosures

Grants/Research Support:
BMS; GSK; Janssen; Pfizer; Sanofi; UCB

Professor Levy is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the Lupus Academy's 6th 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. He will be the Chairperson of the 35th Congress of the Brazilian Society of Rheumatology in September 2018.

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 144 articles in medical journals, over 250 abstracts, four books, 20 book chapters and has lectured in many countries.

Biographies



Professor Peter Lydyard, MD, PhD, FRCP
University College London, UK

Disclosures

None

Peter Lydyard is an Emeritus Professor of Immunology at University College London. He has been involved in research into several rheumatological diseases including rheumatoid arthritis and systemic lupus erythematosus, and has a keen interest in science and medical education. He has held six European Tempus grants for Higher Education in the Southern Caucasus over the last 21 years and is an honorary Professor at three universities in Georgia. He has published several text books and is active in teaching and research.



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

Disclosures

Consultant/Advisor: Pfizer
Speakers' Bureau: GSK;
JnJ; Pfizer; Novartis

Professor Navarra is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the Lupus Academy's 6th 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 Catherine Nelson-Piercy, MA, FRCP, FRCOG
Guy's and St Thomas' NHS Foundation Trust, London, UK

Disclosures

Consultant/Advisor:
Alliance Pharma; UCB

Catherine Nelson-Piercy is a Consultant Obstetric Physician at Guy's and St. Thomas' Hospitals Trust and Queen Charlotte's and Chelsea Hospital in London, UK. In 2010 she was awarded the title of Professor of Obstetric Medicine at King's College London. Her undergraduate studies were at King's College, Cambridge University, and St Bartholomew's Hospital, London. She trained as a physician, and was taught Obstetric Medicine by Professor Michael de Swiet.

Professor Nelson-Piercy is the immediate past President of the International Society of Obstetric Medicine (ISOM). She is founding co-Editor in Chief of the journal *Obstetric Medicine: the medicine of pregnancy*.

Professor Nelson-Piercy has been involved in the development of several evidence-based National Guidelines, notably for 'Contraception in Women with Heart Disease', British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN), 'Asthma in Pregnancy', and Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guidelines on 'Thrombosis and Embolism during Pregnancy and the Puerperium, Reducing the Risk', and 'Management of nausea and vomiting of pregnancy and hyperemesis gravidarum'. She has published over 200 papers, edited five books, and written the successful Handbook of Obstetric Medicine, now in its fifth edition. She is also one of the central physician assessors for the UK Confidential Enquiry into Maternal Deaths.



Professor David Pisetsky, MD, PhD
Duke University Medical Center, North Carolina, USA

Disclosures

Grants/Research
Support: Pfizer

David Pisetsky is Professor of Medicine and Immunology at Duke University Medical Center and Chief of Rheumatology at Veterans Administration Medical Center Durham, North Carolina, USA. He received his BA from Harvard College in 1967 and his PhD and MD degrees from the Albert Einstein College of Medicine in 1973. Following house staff training at the Yale New Haven Hospital, he became a clinical associate at the National Cancer Institute. He joined the faculty of Duke University Medical Center in 1978 as Chief of Rheumatology at the Durham Veterans Administration Hospital where he has remained since.

Professor Pisetsky has conducted basic and translational research on the pathogenesis of systemic lupus erythematosus, the specificity of anti-DNA antibodies and the immunological properties of nuclear macromolecules. More recently, he has investigated the immune activities of HMGB1 as well as looking at microparticles. In 2001 he was awarded the Howley Prize from the Arthritis Foundation for his work on the immune properties of DNA. In 2016 he received the Presidential Gold Medal from the American College of Rheumatology.

From 2000–2005, Professor Pisetsky served as Editor of the journal *Arthritis and Rheumatism* and, from 2006–2011, he was the first Physician Editor of *The Rheumatologist*. He is currently the President of the United States Bone and Joint Initiative.

Biographies



Professor Anisur Rahman, PhD, FRCP
University College London, UK

Disclosures

Clinical trial adjudication
committee member:

Neovacs SA

Anisur Rahman is Professor of Rheumatology at University College London, UK. He qualified from Oxford University in 1988 after which he trained in rheumatology in London. He obtained his PhD for research into the molecular properties of autoantibodies that cause tissue damage in systemic lupus erythematosus and antiphospholipid syndrome (APS). In 2000, Professor Rahman began to build up his own research group and was appointed as a Senior Lecturer at University College London. He was awarded the Michael Mason Prize for this research by the British Society of Rheumatology in 2004 and was promoted to a personal Chair in rheumatology in 2008.

As well as continuing his basic science research Professor Rahman has developed clinical research programmes in autoimmune rheumatic disease and chronic pain. As a member of both the British Isles Lupus Assessment Group (BILAG) and the Systemic Lupus International Collaborative Clinics (SLICC) he is involved in large multicentre research projects in the field of lupus. Professor Rahman's basic science group is developing a potential new therapeutic agent for APS.

Professor Rahman has forged a successful collaboration with researchers in primary care at Barts and The London School of Medicine and Dentistry and together they are working on studies of beliefs and expectations about chronic pain in different ethnic groups. This collaboration has also carried out National Institute for Health Research (NIHR)-funded research into development of a self-management programme for people with chronic pain in the community.



Professor Robert Rubin, PhD
University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

Disclosures

None

Robert Rubin is a Professor in the Department of Molecular Genetics and Microbiology and Adjunct Professor in the Division of Rheumatology, University of New Mexico (UNM) Health Sciences Center, Albuquerque, New Mexico, USA. He has a BSc from Cornell University, a PhD from Johns Hopkins University, and was a faculty member at The Scripps Research Institute, La Jolla, California for two decades. He has been a member of multiple professional societies, journal editorial boards, and scientific boards, including co-Chair of The American Lupus Society Medical Advisory Board. At UNM he teaches immunology in the graduate school, the medical school, and for postgraduate physicians.

Professor Rubin has authored 82 original research studies and over 50 reviews and book chapters. His overall area of interest is autoimmune disease. He has devised numerous immunoassays for autoantibodies, including a recently developed rapid antinuclear antibody test for use at the clinical point-of-care. His basic research studies have centered on how failure of immune tolerance can lead to diseases such as systemic lupus erythematosus. Work on drug-induced lupus using patient samples, on drug metabolism pathways *in vitro*, and in mouse models have implicated aberrant central T-cell tolerance as the underlying cause of autoantibody production in lupus-like syndromes.



Professor Murray Urowitz, MD
 University of Toronto, Canada

Disclosures

Grants/Research

Support: GSK

Consultant/Advisor: BMS;
 GSK

Professor Urowitz is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the Lupus Academy's 6th 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 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 Krembil 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.

Biographies



Professor Ronald van Vollenhoven, MD, PhD

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Disclosures

Grants/Research

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

Consultant/Advisor:

AbbVie; Biotest; BMS; Celgene; Crescendo; GSK; Janssen; Lilly; Merck; Novartis; Pfizer; Roche; UCB; Vertex

Professor van Vollenhoven is a member of the Lupus Academy Steering Committee and has been involved in the planning and development of the Lupus Academy's 6th 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, 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 residency (specialty training) 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.

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Professor Ann Clarke, MD, MSc, FRCPC
University of Calgary, Alberta, Canada

Lupus and malignancy: The risk and the reasons

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Multiple cohort studies and meta-analyses have shown that patients with systemic lupus erythematosus (SLE) have a slightly increased overall risk of malignancy as compared with controls. The largest cohort study, from the Systemic Lupus International Collaborating Clinics (SLICC), reports a standardised incidence ratio (SIR) of 1.14 (95% confidence interval (CI) 1.05, 1.23).¹ The risk for haematological malignancies is particularly increased, with the SLICC cohort study reporting an SIR of 3.02 (95% CI 2.48, 3.63) for all haematological malignancies, and an SIR of 4.39 (95% CI 3.46, 5.49) for non-Hodgkin's lymphoma. The risk for thyroid, lung, hepatobiliary, vaginal/vulvar, and bladder cancers and for cervical dysplasia is also increased in most studies.¹ Conversely, the risk for breast cancer is consistently reduced across studies, with some studies also showing a trend for a reduced risk for endometrial, ovarian, and prostate cancers.¹ In childhood-onset SLE, although the samples are much smaller, the overall risk of malignancy and haematological malignancy appears to be increased, SIR 4.7 (95% CI 2.6, 7.8) and SIR 5.2 (95% CI 1.1, 15.2), respectively.²

The reasons underlying these altered susceptibilities are unclear. A case-cohort study nested within the SLICC cohort demonstrated a trend towards an increased risk of lymphoma in those exposed to cyclophosphamide (hazard ratio (HR) 2.80; 95% CI 0.87, 8.98), but there was no association between increased SLE activity and lymphoma (HR 0.68; 95% CI 0.36, 1.29).³ A nested

case-control study from Taiwan also demonstrated an association between a higher cumulative dose of cyclophosphamide and malignancy (odds ratio (OR), 1.09; 95% CI 1.04, 1.13); this study also showed an association between a lower hydroxychloroquine dose and malignancy (OR 0.93; 95% CI 0.90, 0.97).⁴ The increased risk of lung cancer has been associated with smoking; hepatobiliary and vaginal/vulvar carcinomas and cervical dysplasia have been postulated to be related to an increased risk of viral infections (i.e. hepatitis C and human papilloma virus) or impaired viral clearance; bladder cancer has been associated with cyclophosphamide. The decreased risk of breast, ovarian, and prostate cancer may potentially be partially attributable to lupus-related anti-DNA antibodies, which inhibit DNA repair or directly damage DNA, and are toxic to cancer cells with pre-existing defects in DNA repair.⁵

In summary, patients with SLE have an altered susceptibility to malignancy, which likely reflects a combination of dysregulated immune signalling and environmental insults, such as medication and viral exposures. Immunosuppressive therapy should be minimised, if possible, in those with a recent history of malignancy. Cancer screening should be tailored to the patient's risk profile. For patients with cyclophosphamide exposure, there should be consideration of more frequent pap smears and urine cytology screening, and for patients with a smoking history, there may be a role for low-dose CT screening.

Learning Objectives

- Describe the risk of different types of malignancy in adult and paediatric SLE
- Evaluate the association between immunosuppressive therapy and risk of malignancy in SLE
- Discuss the possible pathogenesis between SLE-related immune dysregulation and malignancy
- Review the evidence for a potential shared genetic susceptibility to SLE and malignancy
- Explore other factors influencing the risk of malignancy in SLE
- Provide recommendations regarding malignancy screening in SLE and choice of immunosuppressive therapy in patients with a previous malignancy

This image shows a single sheet of white paper with horizontal ruling lines. The lines are evenly spaced and run across the width of the page. There are no margins, text, or other markings on the paper.



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

The term 'mixed connective tissue disease' is archaic and should be replaced

References

1. Sharp GC, Irvin WS, Tan EM, et al. Mixed connective tissue disease — an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am J Med.* 1972;52:148–59.
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In the 1970s, Sharp and colleagues claimed to have described 'an apparently distinct rheumatic disease syndrome with clinical characteristics including a combination of features similar to those in systemic lupus erythematosus, scleroderma, and polymyositis.'¹ The patients were said to have mild disease with a low steroid requirement, no evidence of any lung or renal involvement, a strong association with antibodies to ribonucleoprotein (anti-RNP), and a good outlook. In 1980, Nimmstein *et al*, having reviewed the original 25 patients reported by Sharp, showed that the majority of patients had evolved into more distinct and recognisable autoimmune rheumatic

diseases.² It is evident that virtually all of the original claims for 'so-called mixed connective tissue disease (MCTD)' have simply not stood the test of time.³ While I would not deny the existence of a relatively mild form of undifferentiated autoimmune rheumatic condition, the term mixed connective tissue disease really should be abandoned.⁴ The fact that four sets of classification criteria have emerged for it over the past 30 years indicates that even those who do have some belief in 'MCTD' cannot even agree amongst themselves! It is time the term MCTD was confined to the dustbin of medical history.

Learning Objectives

- Discuss the clinical phenotype of anti-RNP antibodies
- Describe the arguments for/against classifying anti-RNP antibodies into a primary (distinct) entity
- Explain why MCTD is/is not correct terminology

[illegible]



Professor Andrea Doria, MD
University of Padova, Italy

Mixed connective tissue disease: “*Rem tene, verba sequentur*”

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Patients suffering from connective tissue diseases (CTDs) share several genetic traits, which may account for the presence of common clinical manifestations and even overlapping of CTDs. Among overlap syndromes, a new entity was described in the early 1970s that was characterised by the presence of shared features of the major CTDs (i.e. SLE, scleroderma, polymyositis) and was, therefore, named mixed connective tissue disease (MCTD).¹ Apart from the clinical features, the main distinguishing trait of MCTD is the presence of anti-ribonucleoprotein (U1RNP) antibody, which may be considered a red flag for the disease.²

MCTD has received several criticisms throughout the decades, due to the fact that it looked – and sometimes still looks – like a blurred entity, which sooner or later is likely to evolve into a definite CTD; nevertheless, many patients are still diagnosed with MCTD and several authors keep publishing on that topic.^{3–5}

Diagnostic uncertainty in rheumatology is common, therefore claiming MCTD does not exist, or is just

a prelude to a more definitive diagnosis, would leave a number of patients in an uncertain position; many patients with MCTD never develop SLE, scleroderma or polymyositis/dermatomyositis yet they remain ill, sometimes seriously ill. Admittedly, the current name (MCTD) is not the best one, but people are now confident with it, so why change it? Maybe we could – what about anti-U1RNP syndrome? However, what's new, what warrants a name change? Such actions would only result in confusion and the debate would still go on. The question is not the name, the point is believing whether or not MCTD exists.

Syndromes are a comfortable ‘hodgepodge’ in which physicians may accommodate complex entities that cannot be brought back to a unique disease. The term comes from the Greek *syndromos*, running together, which is exactly what happens with different symptoms converging on repetitive patterns of presentation that physicians are able to recognise. MCTD falls into this category and should be appreciated for what it is: maybe it is a misnomer but, nonetheless, it affects real patients.

Learning Objectives

- Patients with anti-RNP antibodies have a specific clinical phenotype?: Yes
- Patients with a clinical phenotype associated to anti-RNP antibodies could be classified as a distinct (primary) entity?: Yes
- Is ‘mixed connective tissue disease’ a correct term?: Yes

[illegible]

Abstracts

Plenary I: Biomarkers in SLE Update

Moderators: Ronald van Vollenhoven (Netherlands)
& Richard Furie (USA)



Professor David Pisetsky, MD, PhD

Duke University Medical Center, North Carolina, USA

dsDNA antibodies: New insights

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Antibodies to DNA (anti-DNA) are the serological hallmark of systemic lupus erythematosus (SLE) and are markers of diagnostic and prognostic significance. These antibodies can bind to sites on both single-stranded (ss) and double-stranded (ds) DNA, recognising charged determinants on the phosphodiester backbone. While anti-DNA are considered to have high avidity, the interaction of these antibodies with DNA depends on a mode of interaction called monogamous bivalency. In monogamous bivalency, both antibody Fab sites must contact determinants along the same piece of DNA since each Fab binding site has low affinity. As such, anti-DNA binding requires a piece of DNA sufficient to span both Fab combining sites. Some anti-DNA antibodies, however, require pieces of DNA hundreds of bases long, probably because the determinants recognised are not often present. Recent studies have suggested that the Fc portion of the anti-DNA also contributes to binding since F(ab')₂ fragments of IgG from patients with lupus

fail to bind to DNA, despite their ability to bind to other antigens such as tetanus or Epstein–Barr virus proteins. In general, studies on the properties of anti-DNA antibodies have utilised pure DNA as the antigen, although *in vivo* DNA probably exists in the form of nucleosomes in close association with histones. Furthermore, recent studies show that DNA can be a component of cellular microparticles. Microparticles are small membrane-bound vesicles released from dead and dying cells. Anti-DNA antibodies can bind to particles generated *in vitro*. Importantly, microparticles from patients with lupus have bound IgG, suggesting that particles rather than soluble antigen may be the basis of immune complex formation in lupus. Since current assays are based on pure DNA antigens, advances in the serology of SLE may benefit from analysis of DNA preparations that correspond more closely to the *in vivo* form of this molecule.

Learning Objectives

- Describe the binding of antibodies to ssDNA and dsDNA
- Describe the differences between assay format for detecting anti-DNA antibodies
- Describe monogamous bivalency as a mode of anti-DNA binding
- Describe the structure of microparticles
- Describe the evidence that microparticles are the target antigens of anti-DNA antibodies

[illegible]



Professor Anisur Rahman, PhD, FRCP
University College London, UK

Atherosclerosis biomarkers

References

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There is strong evidence for an increased risk of cardiovascular disease (CVD) and asymptomatic atherosclerosis in patients with systemic lupus erythematosus (SLE). The overall increase in CVD risk is between 5–10 fold and cannot be explained fully by standard risk factors such as smoking, hypertension, and diabetes.¹ In practical terms, this means that we know some of our patients with SLE will develop early CVD, but we are not able to identify which patients so that we can take preventive measures.

The availability of biomarkers would help in two ways. It would enable us to give more accurate advice to patients about their own personal risk of developing CVD, which could help them in deciding about how to modify factors such as diet, smoking, and exercise. The biomarkers could also provide clues about the biological reasons underlying increased risk of atherosclerosis in patients with SLE.

Several forms of cardiovascular imaging have been used in patients with SLE, but carotid ultrasound appears to be the most promising. There is evidence from Pittsburgh, USA that baseline intima-media thickness and presence of plaque both predict development of CVD over the next 8 years.²

Serological markers include antibodies, microparticles, and invariant natural killer T cells (iNKT cells). Both antiphospholipid antibodies and anti-apolipoprotein A1 antibodies have been studied. The latter are associated with the development of CVD in patients with rheumatoid arthritis and with disease activity in SLE, but have not been shown to be associated with CVD in patients with SLE. Endothelial microparticles are released from active or damaged endothelium, and their levels have been associated with abnormal endothelial function in active SLE. iNKT cells are stimulated by lipids. In a study comparing 36 SLE patients with atherosclerotic plaque and 64 with no plaque, the plaque group had altered number and phenotype of iNKT cells.³

Learning Objectives

- Discuss why there is an increased risk of atherosclerosis and CVD in patients with SLE and why this risk is not fully explained by conventional risk factors
- Describe how establishing biomarkers for atherosclerosis in SLE could help in managing this risk of atherosclerosis and CVD in patients with SLE
- Explain the value of vascular ultrasound identifying plaque, which predicts future CVD
- Describe why antibodies, microparticles, and invariant natural killer T cells are possible serological biomarkers for atherosclerosis in SLE

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Abstracts

Plenary I: Biomarkers in SLE Update

Moderators: Ronald van Vollenhoven (Netherlands)
& Richard Furie (USA)



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

Renal biomarkers

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Lupus nephritis represents one of the major unmet needs in the treatment of lupus. Complete response to induction therapy occurs in a minority of patients, and flares occur despite maintenance therapy. Metrics used to assess response to therapy are driven primarily by reductions in proteinuria, as changes in renal function are often not observed in the short-term and assessment of urinary sediment is influenced by observer experience. While a reduction in glomerular and interstitial inflammation is associated with

improvement in proteinuria, a reduction in glomerular filtration rate from damage, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or calcineurin inhibitors can also be associated with a reduction in proteinuria. Although renal biopsies may prove helpful in determining the response to therapeutic intervention, their performance presents logistic issues. Therefore, a non-invasive method to determine lupus nephritis activity is needed to help guide therapeutic interventions.

Learning Objectives

- Recognise the need for biomarkers in the treatment of lupus nephritis
- Describe potential lupus nephritis biomarkers
- Discuss results of a clinical trial with an experimental therapy that targeted a potential biomarker

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Dr Raquel Faria, MD
University of Porto, Portugal

CNS biomarkers

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Neuropsychiatric involvement in systemic lupus erythematosus (NPSLE) is complex, and includes heterogeneous manifestations involving both the central and peripheral nervous system, with disabling effects. The prevalence of NPSLE depends on which syndrome is present; after analysing which events can be attributed to SLE, only 6.1% are likely due to SLE itself.

For active SLE, there are several models that can improve NPSLE diagnosis when a neurological syndrome is present. The first challenge is to distinguish between neurologic vasculopathy, inflammation, or both, and then whether there are infections or comorbidities that could mimic NPSLE.

There are some established NPSLE biomarkers, but they lack sensitivity and specificity. These biomarkers are mainly cerebrospinal fluid analysis for white cells, protein and oligoclonal bands, serum high-disease activity parameters (complement and anti-dsDNA antibodies), anti-P ribosomal antibodies for psychosis, and anti-phospholipid antibodies (aPL) for vasculopathy syndromes. Several classical neuropsychometric evaluations are also validated and traditional magnetic resonance imaging and electroencephalogram are generally very useful.

In clear contrast to other systemic manifestations of SLE, the presence of vasculitis is not a prominent feature of NPSLE. Instead, growing evidence shows that blood–brain barrier (BBB) dysfunction may be essential to the development of NPSLE, allowing the passive diffusion of auto-reactive antibodies and cytokines, and facilitating the development of a pro-inflammatory environment. Self-reactive autoantibodies, such as anti-endothelial cell antibodies, aPL, and

anti-N-methyl-D-aspartate receptor can induce BBB disruption through endothelial cell binding, allowing passive diffusion of other autoantibodies into the cerebrospinal fluid (CSF). This interaction might induce the production of pro-inflammatory chemokines such as matrix metalloproteinase-8 (MMP-8) and plasminogen activator inhibitor-1, or cause endothelial cell dysfunction through the induction of the complement cascade.

Interferon α (IFN α) levels have been shown to be elevated in CSF (but not in serum) in NPSLE patients compared with SLE patients without neuropsychiatric manifestations.

Antiphospholipid antibodies have been rediscovered as pathogenic in NPSLE, in addition to their effect as inducers of thrombosis causing focal manifestations of NPSLE. It has been shown that through their interaction with endothelial cells they can induce BBB dysfunction, having a synergic effect with other antibodies; additionally, they may bind neuronal cells and induce neurotoxicity.

A subset of anti-dsDNA antibodies cross-react with a subunit of anti-N-methyl-D-aspartate and its receptor; these complexes have been related to mood disorders, acute confusional state (when in high titres), and cognitive decline including memory dysfunction. Another example is the cross-reactive binding of the anti-ribosomal P protein with neuronal surface antigens (neuronal growth-associated protein 43).

In the future, and as more data become available, we will hopefully be able to tailor the approach and management of NPSLE based on the clinical presentation, immunological phenotype, and genotype pattern.

Learning Objectives

- Discuss why NPSLE is a heterogeneous condition, and therefore why the discovery of broad CNS biomarkers would rarely be specific
- Explain why risk factors for brain blood barrier disruption seem to be among the main mechanisms for NPSLE
- Discuss why several antibodies and cytokines have been studied to be used as CNS biomarkers, but only few are validated for the clinical scenario

Notes

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Case Study Workshops

Saturday 6th May

Morning (11:00) Parallel Case Study Workshops

Moderator: Thomas Dörner (Germany)
 Lupus and the skin



Roger A. Levy (Brazil) &
 Ricard Cervera (Spain)

Moderator: David Isenberg (UK)
 Management of clotting issues



Munther Khamashta (UK/UAE) &
 Hannah Cohen (UK)

Moderator: Andrea Doria (Italy)
 Lupus and the heart and great vessels



Murray Urowitz (Canada) &
 Ronald van Vollenhoven (Netherlands)

Moderator: Bevra Hahn (USA)
 Lupus and the musculoskeletal system



Zahir Amoura (France) &
 Sandra Navarra (Philippines)

Afternoon (14:00) Parallel Case Study Workshops

Moderator: Thomas Dörner (Germany)
 Lupus and the skin



Roger A. Levy (Brazil) &
 Ricard Cervera (Spain)

Moderator: David Isenberg (UK)
 Management of clotting issues



Munther Khamashta (UK/UAE)
 Hannah Cohen (UK)

Moderator: Andrea Doria (Italy)
 Lupus and the heart and great vessels



Murray Urowitz (Canada) &
 Ronald van Vollenhoven (Netherlands)

Moderator: Bevra Hahn (USA)
 Lupus and the musculoskeletal system



Zahir Amoura (France) &
 Sandra 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 Thomas Dörner (Germany)

Presenters: Professor Roger A. Levy (Brazil) & Professor Ricard Cervera (Spain)

Lupus and the skin



Cutaneous manifestations occur in 70% of lupus patients. Acute, subacute, and chronic lesions are the most common, they vary in severity, and may or may not be associated with simultaneous systemic organ involvement. Many but not all are photosensitive and in these, photoprotection with sun screen and barrier methods is essential for improvement. Hydroxychloroquine is invariably indicated, but sometimes is not sufficient. It is important to identify the different forms of lupus skin involvement, since the treatment and prognosis varies between types. Sometimes the usual treatments with antimalarials, steroids in various forms, and immunosuppressive agents are not effective. This workshop will review three cases of B-cell inhibition with impressive improvement of refractory alopecia areata, and generalised acute and subacute annular lesions. It is also important to consider the differential diagnosis of lupus when there are skin manifestations, which may be photosensitive even with a positive antinuclear antibody test.

Professor Roger A. Levy, MD, PhD

Case 1: 16-year-old female presented with subacute skin lesions, alopecia, and polyarthritis

In 2011, a 16-year-old female presented with subacute skin lesions, alopecia, and polyarthritis. She was positive for antinuclear antibodies (ANA), anti-Sm antibodies, anti-Ro antibodies, anti-RNP antibodies, and Coombs, she also had low C4. In April 2013, she developed a skin rash despite complete photoprotection and was treated with prednisolone (1–2 mg/kg/day), hydroxychloroquine (400 mg/day) and azathioprine (2 mg/kg). In May 2014, she received a 3-day course of IV methylprednisolone (500 mg/day) and switched her azathioprine to mycophenolate mofetil (MMF, 3 g/day) in July 2014. In December 2014, she had received a 3-day course of IV methylprednisolone (500 mg/day) for the previous 3 months. In March 2015, MMF was stopped due to skin and oral mucosa infections and in June 2015, her skin disease worsened despite receiving 80 mg/day prednisolone, hydroxychloroquine, and MMF. Her subacute/necrotic skin lesions were refractory to high dose oral and IV methylprednisolone, plus hydroxychloroquine (400 mg/day), plus azathioprine 2 mg/kg or MMF 3 g/day. She was subsequently given a B-cell inhibitor and her skin disease began to improve over the next 9 months on azathioprine 100 mg/day, tapering prednisolone to 5 mg/day, and reduced azathioprine.

Professor Roger A. Levy, MD, PhD

Case 2: 32-year-old female, with skin manifestations plus haemolytic anaemia, rheumatoid arthritis-like polyarthritis

A 32-year-old female, diagnosed with systemic lupus erythematosus in 2004 at 19 years of age, presented with skin manifestations plus haemolytic anaemia, rheumatoid arthritis-like polyarthritis, and positive ANA and anti-Ro antibodies. In 2009, her skin disease had been difficult to control with methotrexate plus prednisolone, and in 2012 she developed serositis and nephritis and was enrolled in the Eurotrial. After the third month, she had a positive pregnancy test; at the time she was receiving prednisolone 10 mg/day, azathioprine, and hydroxychloroquine (400 mg/day). She had a Caesarean section at 40 weeks. In February 2014, she developed haemolytic anaemia (Htc = 11%) and her 24-hour urinary protein was 4 g; she received azathioprine (150 mg/day) and prednisolone 140 mg/day for 8 days (Htc = 20%) tapering. In May 2014, she developed bilateral hip osteonecrosis and her protein/creatinine was 1.63 mg/dL. In July 2014, on azathioprine 150 mg/day, prednisolone 10 mg/day, her protein/creatinine was 1.90 mg/dL and she had experienced a subacute skin rash for a week. In August she received MMF 2 g/day and her protein/creatinine was 0.40 mg/dL, which increased in September 2014 to 1.10 mg/day along with worsening of skin lesions. She did not respond to additional hydroxychloroquine over the subsequent 3 months. In March 2015, she had refractory subacute skin lesions, nephritis and osteonecrosis and was started on a B-cell inhibitor as well as receiving MMF 3 g/day, hydroxychloroquine 400 mg/day, and prednisolone 7.5 mg/day. Her renal response was good and skin response excellent.

Case 3: 44-year-old Caucasian female with fever and acute pain in the second finger of her right hand

The patient reported 6 days of fever (37–38°C), acute pain in the second finger of her right hand, and general malaise. Despite paracetamol treatment, she persisted with fever. Medications on admission included hydroxychloroquine 200 mg/day and aspirin 100 mg/day. The patient was otherwise normal. Physical examination revealed splinter haemorrhages in the second finger of her right hand and a mitral murmur.

Learning Objectives

- Recognise the different forms of lupus skin involvement
- Discuss how to make the patient understand the importance of proper treatment adherence
- Propose and discuss alternative treatment therapies for refractory cases
- Describe some of the major confounders of lupus skin disease

This image shows a single sheet of white paper with horizontal ruling lines. The lines are evenly spaced and run across the width of the page. There are no margins, text, or other markings on the paper.



Moderator: Professor David Isenberg (UK)

Presenters: Dr Hannah Cohen (UK) & Professor Munther Khamashta (UK/UAE)

Management of clotting issues



Professor Munther Khamashta, MD, PhD, FRCP

Case 1: Venous thromboembolism and thrombocytopaenia

A 65-year-old Caucasian female was diagnosed with systemic lupus erythematosus (SLE) in 2000 and was treated with low dose prednisolone. In 2003, she had an unprovoked left proximal deep venous thrombosis (DVT). She was treated initially with dalteparin and started on warfarin, target INR 2.5 (range 2.0–3.0). Antiphospholipid antibodies, lupus anticoagulant, and high positive IgG anti- β 2-glycoprotein 1 antibodies were persistently positive, consistent with a diagnosis of thrombotic antiphospholipid syndrome (APS), and a decision was made to continue warfarin long term. In 2003, she developed immune thrombocytopaenia with her platelet count, previously normal, $30 \times 10^9/L$. Haemoglobin was 110 g/L and white cell count was $5.6 \times 10^9/L$ with neutrophils $3.1 \times 10^9/L$. The warfarin was stopped. The prednisolone was increased to 60 mg/day resulting in a rise in her platelets after 2 weeks to $150 \times 10^9/L$. The prednisolone was titrated down and her thrombocytopaenia recurred. She was treated with rituximab followed by normalisation of her platelet count and the warfarin was resumed. In 2013, she was recruited to the RAPS (Rivaroxaban in APS) trial in which she was randomised to rivaroxaban 20 mg/day, which she tolerated well.

Discussion points:

Treatment of DVT associated with thrombotic APS

Treatment of immune thrombocytopaenia

Management of anticoagulation during thrombocytopaenia



Professor Munther Khamashta, MD, PhD, FRCP

Case 2: Arterial thrombosis and thrombocytopaenia

A 44-year-old Afro-Caribbean female presented with renal SLE in 2010. She had two children following uncomplicated pregnancies in 2004 and 2008. She was treated with low dose prednisolone, mycophenolate, and azathioprine. In 2012, she received a course of rituximab with cyclophosphamide for joint symptoms and high dsDNA, with a reaction during the second rituximab infusion: dyspnoea, pressure in her chest, and facial flushing. Antiphospholipid antibody testing showed persistent moderate positive IgM anti- β 2-glycoprotein 1 and anticardiolipin antibodies. In 2013, she developed neurological symptoms. An MRI brain scan showed foci of ischaemic cortical damage. She was started on long-term anticoagulation with warfarin, target INR 3.5. In January 2017 she was admitted as an emergency after a routine blood test showed a platelet count of $8 \times 10^9/L$. Haemoglobin was 105 g/L and white cell count $6 \times 10^9/L$ with neutrophils $3 \times 10^9/L$. The immature platelet fraction was raised at 19.1% (NR 0.8–7.3). Warfarin was stopped and following treatment which included IV methylprednisolone, IV immunoglobulin (IVIg), mycophenolate, and also ofatumumab, the latter in view of her previous reaction to rituximab, her platelets recovered to normal levels.

Discussion points:

Treatment of asymptomatic persistent antiphospholipid antibodies in SLE

Treatment of cerebral ischaemic lesions associated with thrombotic APS

Treatment of immune thrombocytopaenia

Dr Hannah Cohen, MBChB, MD, FRCP, FRCPath

Case 3: Microvascular skin ulcers, arterial thrombosis and thrombocytopaenia

A 41-year-old Caucasian female initially presented in 1991 with glomerulonephritis. In 2001 she developed a proximal lower limb deep venous thrombosis (DVT) following a long-haul flight. She was treated initially with dalteparin and long-term warfarin, target INR 2.5. Antiphospholipid antibody testing showed triple

positivity with high positive IgG anticardiolipin and anti- β 2-glycoprotein 1 antibodies. She was diagnosed with SLE in 2006 manifesting mainly as renal lupus, with a lupus flare in 2013 for which she received steroid treatment. She had two early miscarriages, in 2015 and February 2016.

In June 2016 she was admitted to hospital with an SLE flare associated with skin ulcers (over the right shin and dorsum of her right foot) and a blue second right toe. A skin biopsy showed microvascular thrombosis. Imaging showed right dorsalis pedis artery occlusion and a small mural thrombus of the right common iliac artery. She was treated with dalteparin, IV methylprednisolone, and rituximab. Her platelets fell from $150 \times 10^9/L$ to $<50 \times 10^9/L$ associated with a raised immature platelet fraction of 15% (NR 0.8–7.3) and received IVIg and plasma exchange (PEX). In August 2016, she was readmitted with necrotic skin ulcers. These were debrided, dalteparin was continued, and she was also treated with antibiotics, iloprost, rituximab, and IVIg. She had a small intracerebral bleed when her platelets were $70 \times 10^9/L$.

In December 2016, she was readmitted with worsening necrotic skin ulcers and platelets $50 \times 10^9/L$. She underwent skin debridement and was treated with iloprost, dalteparin, rituximab, methylprednisolone, IVIg, PEX, and antibiotics. Mycophenolate was added for her thrombocytopaenia. She underwent epidermal skin grafting in January 2017. In March 2017, she was readmitted with deterioration in the skin ulcers that had been healing. A biopsy showed spongiotic dermatitis thought likely to be due to a reaction to iodine. The ulcers were treated with flomazine and by the end of March 2017 had almost healed. Eltrombopag was added. Her platelets recovered to $120\text{--}130 \times 10^9/L$.

Discussion points:

Treatment of skin ulcers associated with APS

Treatment of immune thrombocytopaenia in the context of dalteparin and iloprost

Dr Hannah Cohen, MBChB, MD, FRCP, FRCPath

Case 4: Thrombotic thrombocytopaenic purpura

A 17-year-old Caucasian female was diagnosed to have juvenile SLE in January 2013 when she presented with lupus nephritis. She was treated with mycophenolate and prednisolone. In November 2013, she received rituximab, with a further course of rituximab in November 2014. In November 2016, she presented with an SLE flare and was admitted to hospital for treatment with IV methylprednisolone. On admission she had thrombocytopaenia, with a fall in her platelets from $214 \times 10^9/L$ to $87 \times 10^9/L$. Her platelets continued to fall to $24 \times 10^9/L$. Lactate dehydrogenase increased to 645 (N <214) IU/L and a blood film showed red cell fragmentation. ADAMTS13 (A Disintegrin And Metalloproteinase with Thrombospondin type-1 repeats 13) activity was <5.0 IU/dL. A diagnosis of thrombotic thrombocytopaenic purpura was made and she was treated with plasma exchange, rituximab, and aspirin 75 mg/day. Her platelet counts and ADAMTS13 activity returned to normal and she was discharged from hospital on tapering prednisolone, mycophenolate, and aspirin.

Discussion points:

Diagnosis of thrombotic thrombocytopaenic purpura

Treatment of thrombotic thrombocytopaenic purpura

Learning Objectives

- Recognise the spectrum of presentations of thrombotic APS in SLE, including:
 - Venous thromboembolism
 - Arterial thrombosis e.g. cerebral ischaemic lesions
 - Microvascular thrombosis e.g. skin ulcers
- Recognise appropriate therapeutic approaches for thrombotic APS
- Recognise causes of thrombocytopaenia in SLE, including:
 - Immune thrombocytopaenia
 - Thrombotic thrombocytopaenia purpura
- Recognise therapeutic approaches to thrombocytopaenia and management of anticoagulation in patients with thrombocytopaenia



Moderator: Professor Andrea Doria (Italy)

Presenters: Professor Murray Urowitz (Canada) & Professor Ronald van Vollenhoven (Netherlands)

Lupus and the heart and great vessels



Professor Murray Urowitz, MD, FRCPC

Case 1: An uncommon cause of cardiomyopathy in SLE

A 74-year-old female patient with a long history of systemic lupus erythematosus (SLE) and acute onset of heart failure will be discussed. Initial diagnosis was based on musculoskeletal and skin features, pericarditis, Libman-Sacks endocarditis, and neuropsychiatric involvement. The patient had been clinically and serologically inactive for many years under treatment with hydroxychloroquine and low dose prednisone. In 2014, she presented with acute heart failure. An initial echocardiogram showed new right bundle branch and left anterior hemiblock. Heart echocardiogram also demonstrated severe bi-ventricular hypertrophy and bi-atrial enlargement. Serum levels of troponin 1 (270 ng/L, normal <14 ng/L) and brain natriuretic peptide (1080 pg/L, normal <100 pg/L) were elevated. The patient was diagnosed with hypertrophic infiltrative cardiomyopathy, with the most possible causes including Fabry's disease, amyloidosis, and sarcoidosis. Extensive genetic testing for the former was negative. Cardiac MRI showed no late gadolinium enhancement and no evidence of significant inflammation. Endomyocardial biopsy demonstrated diffuse vacuolation of cardiomyocytes and myelinoid and lamellar inclusions that were pathognomonic for antimalarial-induced cardiomyopathy. Hydroxychloroquine was discontinued and the patient was treated with diuretics. After 2 years of follow up, she had significant regression of the cardiac hypertrophy and associated biomarkers. However, 1 year after hydroxychloroquine discontinuation, conduction system abnormalities persisted with new atrial fibrillation that required ablation. The possible associated factors of this rare cardiomyopathy will be discussed.



Professor Murray Urowitz, MD, FRCPC

Case 2a: Uncommon vasculitides in SLE

A 40-year-old female, diagnosed with SLE in 1996 with musculoskeletal and skin involvement, severe Raynaud's phenomenon, and positive antinuclear antibodies will be discussed. She had quiescent disease until October 2015 when she stopped her medications. After 6 months she presented to the emergency department of her local hospital with retrosternal chest pain. She was diagnosed with an ST-elevation myocardial infarction (STEMI) of the inferior wall. Coronary angiography was normal and she was managed conservatively. Her STEMI was attributed to coronary vasospasm. There was no concomitant clinical or serological activity and anticardiolipin antibodies were not found. She started hydroxychloroquine and amlodipine shortly thereafter. Four months later she developed acute pain over the left carotid artery. Doppler ultrasound and magnetic resonance angiography revealed severe inflammation of the left carotid artery wall. C-reactive protein was elevated, but other biomarkers were normal. Treatment with high doses of prednisone led to partial resolution of symptoms after 3 months.

Professor Murray Urowitz, MD, FRCPC

Case 2b: Uncommon vasculitides in SLE

A 30-year-old female marathon runner with clinically and serologically inactive disease presented with abrupt onset of unilateral (left) intermittent claudication at 50 metres. Arterial Doppler below the level of the common femoral artery was normal. Disease serology was active (decreased C3/C4, increased anti-dsDNA). Magnetic angiography revealed severe stenosis of the left common iliac artery and focal occlusion of the internal iliac artery. She was managed with balloon angioplasty and increased doses of prednisone and azathioprine. After 6 months, she was able to walk 1000 metres with no symptoms. Disease serology was partially improved (increasing C3).

Professor Ronald van Vollenhoven, MD, PhD

Case 3: Chest symptoms (e.g. pain, shortness of breath) in SLE

A number of cardiac manifestations of SLE must be considered in a patient with SLE who presents with chest symptoms (e.g. pain, shortness of breath). Lupus may be associated with inflammation in the pericardium or the myocardium itself, and in either case the clinical picture may be dominated by subjective symptoms, haemodynamic compromise, or both. The diagnosis must be made expeditiously and treatment should be initiated promptly to reduced inflammation, restore cardiac function, and prevent long-term sequelae.

Professor Ronald van Vollenhoven, MD, PhD

Case 4: Diffuse and non-specific symptoms in SLE

Patients with SLE may present with diffuse and non-specific symptoms and signs that are found to originate in the heart only after extensive evaluations. Therefore, patients such as the one presented here, who have fever, general malaise, and highly elevated inflammatory markers, must be evaluated thoroughly. If no immediate alternative explanation is found, investigation of the heart by imaging and/or functional testing must be considered in addition to physical examination. The prognosis of most patients with cardiac involvement in SLE is often good, but in some cases irreversible consequences may occur despite prompt treatment.

Learning Objectives

Case 1

- Cardiomyopathy in late stage SLE may have unusual causes
- Prolonged antimalarial intake may be associated with an infiltrative cardiomyopathy
- Elevated CK and elevated troponin and BNP levels are associated with antimalarial cardiomyopathy

Cases 2a & 2b

- Isolated large vessel involvement is uncommon in SLE
- Large vessel involvement may be due to spasm or vasculitis
- Vascular imaging can confirm diagnosis and lead to prompt treatment

Cases 3 & 4

- Recognise cardiac manifestations of SLE
- Identify appropriate diagnostic tests for cardiac manifestations of SLE
- Describe the proper therapeutic interventions for patients with SLE who have cardiac involvement

Notes



Moderator: Professor Bevra Hahn (USA)

Presenters: Professor Zahir Amoura (France) & Professor Sandra Navarra (Philippines)

Lupus and the musculoskeletal system



Professor Zahir Amoura, MD, MSc

Case 1: 40-year-old Caucasian female

A 40-year-old female of Caucasian origin was diagnosed with systemic lupus erythematosus (SLE) in August 2013 based on polyarthritis, malar rash, haemoglobin 9.6 g/dL with positive direct Coombs test (IgG), lymphopaenia (0.7 g/L), positive antinuclear antibody (ANA) (1/1280), positive anti-dsDNA, positive anti-Sm, positive anti-SSA, low C3. Hand X-rays were unremarkable. She was prescribed prednisone 20 mg/day with hydroxychloroquine 400 mg/day. She became asymptomatic 1 month later. In March 2014, she presented with fever, arthritis with synovitis of MCP/PIP II, III, IV joints and of wrists. Laboratory tests revealed: lymphopaenia (0.850 g/L), positive Farr assay (47 UI/mL; N <9), low C3 (0.65 g/L; N 0.69–1.34), increased CRP (15; N <5). She was treated with hydroxychloroquine (400 mg/day) and oral prednisone (5 mg/day).

Discussion points:

Step-by-step management of relapsing SLE arthritis

Management of SLE refractory arthritis



Professor Zahir Amoura, MD, MSc

Case 2: 33-year-old Afro-American female

A 33-year-old Afro-American female was diagnosed with SLE in 2005 based on polyarthritis, positive ANA, anti-DNA antibody (ELISA and Farr), positive SSA antibodies, and low C3 and C4 levels. She was treated with hydroxychloroquine (400 mg/day) and low dose of oral prednisone (15 mg/day). She had two pregnancies (in 2006 and 2011). After the first pregnancy, she underwent a moderate flare with Class II glomerulonephritis treated with moderated dose of oral corticosteroids. She had been asymptomatic between 2006 and 2014 under hydroxychloroquine and low dose prednisone (<10 mg/day). She underwent gastric band surgery in 2012 for obesity (BMI 36) followed by >30 kg weight loss. She presented in January 2016 for arthritis with synovitis of MCP/PIP II and III and progressive muscular weakness involving both shoulder and both upper arms. She had no muscle pain. She was taking hydroxychloroquine (400 mg/day) and prednisone (5 mg/day). Laboratory tests revealed: Farr assay >97 UI/mL (N <9), C3 0.44 g/L (N 0.69–1.34), CRP <5 (N <5), CK 420 UI/L (N 25–160). She had no proteinuria. Myopathic changes were found on electromyography detection studies.

Discussion points:

Differential diagnosis of myositis in a patient with SLE

Treatment of myositis in a patient with SLE

Professor Sandra Navarra, MD, FPCP, FPRA

Case 3: 35-year-old female with SLE and disabling polyarthritis

A 35-year-old nurse was diagnosed with SLE 12 years ago presenting as fever, alopecia, arthralgias, pericarditis, anaemia, leucopaenia, hypocomplementaemia, high titre ANA and strongly positive anti-dsDNA. Initially, she was treated with methylprednisolone pulses and was thereafter maintained on hydroxychloroquine (400 mg/day) and prednisone averaging 5 mg/day.

Five years ago, she developed painful arthritis involving the hands, wrists, elbows and knees. Assessment results included erythrocyte sedimentation rate (ESR) 83 mm/hr, CRP 48 mg/L, positive ANA 1:1280 (speckled), anti-dsDNA, anti-RNP, anti-Ro, and anti-cyclic citrullinated peptide (CCP) 101 U/mL (ULN 17); anti-La and rheumatoid factor were negative, serum complement levels normal. Radiographs were normal, musculoskeletal ultrasound showed findings consistent with active synovitis on the hand joints,

with moderate effusion on both knees. Because of persistent disabling polyarthritis despite intra-articular steroids and high daily prednisone, she was started on methotrexate 15 mg/week increased to 20 mg/week and given a dose of 1 g rituximab, but this resulted in only minimal improvement. She then decided to try a TNF inhibitor which resulted in dramatic resolution of the joint symptoms.

Discussion points:

Differential diagnoses and management approach to arthritis in SLE

Review the data on use of biologics for musculoskeletal involvement in SLE

Professor Sandra Navarra, MD, FPCP, FPRA

Case 4: 58-year-old female with SLE develops avascular necrosis of the hips and osteoporosis

A 58-year-old female was diagnosed SLE at 28 years of age, presenting with fever, malar rash, oral ulcers, arthritis pleuropericarditis, haemolytic anaemia, thrombocytopaenia, hypocomplementaemia, high titre ANA and positive anti-dsDNA, anti-RNP, and anticardiolipin. She initially received methylprednisolone pulses and was thereafter maintained on hydroxychloroquine and prednisone. Ten years later, her lupus was in remission and she was off all medications, however she developed bilateral hip osteonecrosis; she refused hip surgery and was lost to follow up.

She returned to clinic to consult regarding a bone densitometry test interpretation of osteoporosis with T-score -2.8 and Z-score -2.0 at the lumbar spine; vitamin D level is 28 ng/mL (LLN 30) and other laboratory tests are normal. Her most recent hip radiographs show Stage 4 avascular necrosis. The patient is nulligravid and had her menopause at 50 years of age; she does not smoke or drink alcohol and there is no family history of osteoporosis.

Discussion points:

Pathophysiology, risk factors and non-surgical management of avascular necrosis

Pathophysiology and treatment of glucocorticoid-induced osteoporosis

Learning Objectives

- Describe how to manage refractory arthritis in SLE
- Describe how to manage myositis in SLE
- Discuss the differential diagnoses and management approach to arthritis in SLE
- Discuss the efficacy data of biologic agents for musculoskeletal involvement in SLE
- Discuss the risk factors, pathophysiology, and management of avascular necrosis
- Discuss the risk factors, pathophysiology, and management of glucocorticoid-induced osteoporosis

Notes



Professor Robert Rubin, PhD

University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

Drug-induced lupus

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Drug-induced lupus (DIL) is a reversible idiosyncratic side effect of numerous, apparently unrelated medications in which symptoms and signs overlap with those of systemic lupus erythematosus (SLE). These features will be described in the context of guidelines for diagnosing DIL and for distinguishing it from SLE and from other types of adverse drug reactions. Several genetic factors predispose to DIL, but the slow drug acetylation phenotype has the most significance regarding its underlying etiology.

While rapid resolution of symptoms after discontinuing the implicated medication is the signature feature of DIL, it is unlikely that ingested drugs directly mediate the induction of autoimmunity. Their diversity in chemical structure and pharmacological action, yet capacity to produce similar clinical features after long-term administration, suggest that the sporadic appearance of reactive drug metabolites underlies induction of autoimmunity. In fact, all pharmacological classes of lupus-inducing drugs undergo oxidative transformation by myeloperoxidase released by activated neutrophils and/or by mitochondrial P450 hydroxylases, a process prevented by N-acetylation of the putative reactive molecular groups.

Mechanisms for DIL will be discussed. Of particular interest is the finding, using a mouse model system, that the presence in the thymus of procainamide-hydroxylamine resulted in the appearance of autoreactive T-cells and anti-chromatin autoantibodies. How an intra-thymic xenobiotic leads to disruption of central T-cell tolerance will be explained in a proposed scheme for DIL, which may have general ramifications in the normal establishment of T-cell tolerance. Finally, because DIL is a systemic autoimmune disease essentially indistinguishable from mild or early lupus, drug-induction of lupus-like disease may have more than incidental significance in the origin of idiopathic SLE as well.

Learning Objectives

- Describe guidelines for diagnosis of drug-induced lupus
- Differentiate between drug-induced lupus, other types of adverse drug reactions, and SLE
- Explain the importance of reactive drug metabolites in the etiology of drug-induced lupus
- Describe possible mechanisms of drug-induced lupus
- Explain abnormalities in central T-cell tolerance in development of lupus-like and other autoimmune diseases

[illegible]



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Optimising lupus management in pregnancy

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Systemic lupus erythematosus (SLE) affects women of child-bearing age and is commonly encountered in obstetric practice. Pregnancy poses an important challenge for doctors looking after these women. Knowledge about medication safety, the effect of pregnancy on the disease, and vice versa, together with pre-conception counselling and multidisciplinary team care, is important to provide the best obstetric and medical care to these women.

Women with SLE have increased risks of miscarriage, pre-term delivery, pre-eclampsia, fetal growth restriction, and disease flare in pregnancy. Risk factors for adverse pregnancy outcomes in SLE include lupus nephritis, particularly with chronic kidney disease Class 3–5, anti Ro/La antibodies, active disease, and antiphospholipid antibodies. The most important issues of delaying pregnancy until there is disease remission, ensuring continued remission by continuation of drugs that are safe in pregnancy, and adequately and promptly treating any flare of disease will be discussed. Adequate surveillance of the mother and fetus is imperative, but stratification of women is important to ensure that those with low-risk pregnancies are not over medicalised.

There is an understandable reluctance to prescribe drugs, particularly immunosuppressant drugs, in pregnancy and in breastfeeding mothers. However much harm can result if drugs are withdrawn, omitted, or the dose reduced inappropriately. There is evidence from many rheumatic conditions, but particularly rheumatoid arthritis, that active disease impacts adversely on pregnancy outcomes. It also has an adverse effect on female fertility and time to pregnancy.

Recently published guidelines from the British Society of Rheumatology and EULAR have reviewed the safety data for antirheumatic drugs in pregnancy. These publications include recommendations for which drugs are compatible with pregnancy and during lactation. It is hoped that these guidelines will reduce errors of omission where important medication for disease control is discontinued prior to or during pregnancy.

Learning Objectives

- Explain the importance of pre-pregnancy counselling for women with SLE
- Describe the risk factors for adverse pregnancy outcome in women with SLE
- Determine which medications are compatible with use in pregnancy and lactation
- Discuss the management of SLE in pregnancy

Notes

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Immunisation of patients with SLE

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Preventing infection is a major goal of management for patients with systemic lupus erythematosus (SLE), since one third die of infection, and their risk for infection is 10 times higher than the general population. Risk is increased for bacterial, viral, fungal, and parasitic infections. Risk is increased by active disease, frequent flares, low serum albumin, hypocomplementaemia, anti-dsDNA, neutropaenia, lymphopaenia, and immunosuppressive treatments (prednisolone [especially ≥ 20 mg daily for 2 weeks or more], azathioprine, mycophenolate, and particularly rituximab and cyclophosphamide). To date there is no evidence that belimumab is associated with any increase in infections. Antimalarials (hydroxychloroquine) probably reduce infection risk.

For physicians, three strategies are important: 1) increased awareness of the high risk for infection (clues favoring infection over disease flare include fever in a patient already treated for SLE, shaking chills, and hsCRP levels >6 mg/dL); 2) prophylactic antibiotics/antivirals to prevent pneumocystis (PCP) and herpes simplex infections, and treating latent tuberculosis before immunosuppression starts; and 3) keeping immunisations current. With regard to prophylaxis, PCP risk is reduced by two weekly doses of trimethoprim-sulfamethoxazole (TMP-SMX), and outbreaks of herpes simplex are reduced by daily acyclovir doses. A problem with some antibiotics in SLE include increased photosensitivity (tetracyclines, fluoroquinolones, sulphonamides) and three-times-higher-than-normal risk of allergic reaction (sulphonamides, penicillins, cephalosporins, erythromycin). Regarding immunisations, many studies have shown that influenza, pneumococcus, hepatitis B, tetanus (and anthrax) vaccines have a good

safety profile in SLE and do not increase flare rates. The safety of human papilloma virus vaccine is, however, controversial. In general, post-vaccine titres and T-cell reactions are reduced in SLE patients on immunosuppression, but the responses to standard doses are in the protective range in a large majority. Annual influenza vaccines reduce risk of death in SLE patients with flu by at least 50%. Standard immunisation approaches to adults in Portugal and elsewhere in Europe include annual influenza, and updates of pneumococcus vaccines, using either PCV23 (pneumococcal polysaccharide), PCV13 (adjuvant) or a combination (PCV13 first; PCV23 2 to 8 weeks later), and repeating PCV23 every 5 years. Patients with splenectomies for any reason are at high risk for sepsis with encapsulated organisms and should be vaccinated with pneumococcus, meningococcus and H. influenzae prior to surgery when possible, or 2 weeks later if surgery cannot be delayed. Adults with SLE, if previously inadequately vaccinated, should be vaccinated for hepatitis A and B, diphtheria, and tetanus (every 10 years). Some experts recommend human papilloma virus vaccination for women that are sexually active. Vaccinations with live vaccines are NOT recommended for immunosuppressed individuals (defined as ≥ 20 mg prednisolone daily and/or any additional immunosuppressive); this includes herpes zoster, measles, mumps, rubella, nasal spray influenza, and yellow fever. Herpes zoster is a particular problem since the prevalence in SLE is very high (approximately 20% of patients); currently it is difficult to know how to proceed, but a controlled trial of a few hundred patients is in progress, and new vaccines for zoster that are not live virus are being developed.

Learning Objectives

- Describe infection risk in patients with SLE
- Explain the key treatment strategies for managing infection risk in patients with SLE
- Discuss the prophylactic and immunisation approaches required for effectively managing infection risk in patients with SLE

[illegible]



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Where do new oral anticoagulants fit in SLE?

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The direct oral anticoagulants (DOACs) include dabigatran etexilate, a direct thrombin inhibitor, and apixaban, edoxaban, and rivaroxaban, direct factor Xa inhibitors. DOACs are established as therapeutic alternatives to warfarin and other vitamin K antagonists (VKAs), and becoming the standard of care for a wide range of indications. These include primary thromboprophylaxis for major lower limb orthopedic surgery, the treatment and secondary prevention of venous thromboembolism (VTE), the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation; and acute coronary syndromes.¹ DOACs, in contrast to VKAs, are prescribed at a fixed dose with a more predictable effect and, therefore, do not require regular anticoagulant monitoring in the majority of clinical settings. They also have a rapid onset of action, so bridging anticoagulation with low-molecular-weight heparin at the initiation of anticoagulation can often be eliminated. In addition, they are not affected by changes in diet and alcohol intake and have fewer drug interactions that affect anticoagulant intensity, which would be expected to result in improved quality of life for patients.

The main focus of studies of DOACs in systemic lupus erythematosus (SLE) is on comparison with warfarin in patients with thrombotic antiphospholipid syndrome (APS), in whom the current mainstay of treatment is anticoagulation with VKAs.² Approximately 15% of patients with SLE have thrombotic APS, which is a major adverse prognostic factor.³ Appropriate management of thrombotic APS is essential to minimise its deleterious impact. The RAPS (Rivaroxaban in Antiphospholipid Syndrome) trial randomised 116 APS patients, approximately 20%

of whom had SLE, on warfarin target INR 2.5 for previous VTE, to remain on warfarin, or switch to rivaroxaban 20 mg daily. The primary outcome was the percentage change in endogenous thrombin potential (ETP). When anticoagulation intensity was assessed by the ETP alone, rivaroxaban was inferior to warfarin. However, peak thrombin generation was lower with rivaroxaban and, therefore, the overall thrombogram indicated no difference in thrombotic risk. This conclusion was supported by concentrations of in-vivo coagulation activation markers being increased in only a few patients in both treatment groups, and the absence of new thrombotic events during 6 months of treatment. Quality-of-life assessment showed a significant improvement with rivaroxaban.^{4,5}

In summary, RAPS suggests that rivaroxaban offers an effective, safe and convenient alternative to warfarin in SLE patients with APS who have previous VTE and require standard intensity anticoagulation. Anecdotal clinical reports and case series suggest that recurrent thrombotic events with DOACs in APS/SLE patients mainly occur when DOACs are used for APS-related arterial thrombosis or in triple antiphospholipid antibody positive APS patients (of note, 28% of RAPS patients were triple positive). The RAPS results are not applicable to APS patients with VTE who require higher intensity anticoagulation (i.e. those with recurrent VTE while on standard intensity anticoagulation) or APS patients with stroke or other ischemic brain manifestations, or arterial thrombosis in other sites. Ongoing and future studies will clarify the role of DOACs in these APS patient subgroups with SLE, as well as in other SLE patients with or without antiphospholipid antibodies.

Learning Objectives

- Describe the potential benefits of direct oral anticoagulants compared with VKAs and considerations with regard to their use
- Discuss the data on the use of direct oral anticoagulants in APS patients with SLE
- Explain appropriate current use of direct oral anticoagulants in patients with SLE

Notes

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Immunopathology in SLE: The pathogenic engines

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Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease with an abnormal immune reaction against various autoantigens, including disturbances of lymphocyte activation, and innate immunity partly related to genetic predispositions as identified by genome-wide association study (GWAS) studies.

This presentation will address recent insights into:

- the role of type 1 interferon in SLE
- abnormalities of memory B-cell activation
- the role of impaired Treg functions
- the potential contributions of the autoreactive plasma cell compartment producing autoreactive IgG

While our understanding of the underlying mechanisms of SLE immunopathology has greatly advanced over the last decade, with insight into certain domains of the immune system, it remains to be shown whether a common abnormality is responsible for these immunological and clinical consequences.

Learning Objectives

- Describe the role of type 1 interferon in SLE
- Describe the abnormalities of memory B-cell activation
- Describe the role of impaired Treg functions
- Describe the potential contributions of the autoreactive plasma cell compartment producing autoreactive IgG

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Curbside Consults



Moderator: Munther A. Khamashta (UK/UAE)

Professor Munther Khamashta, MD, PhD, FRCP

St. Thomas' Hospital, London, UK & Dubai Hospital, Dubai, UAE

Panellists: Zahir Amoura (France), Ann Clarke (Canada), Anisur Rahman (UK), Sandra Navarra (Philippines)

Curbside consults: The experts tackle three short and challenging cases



Case 1: Acute lupus hemophagocytic syndrome

A 30-year-old female, diagnosed with systemic lupus erythematosus (SLE) at 22 years old, and Class IV lupus nephritis 5 years later, was admitted to hospital with 3-day history of fever (38.5°), sore throat, bilateral earache; and she was unable to walk unsupported. Her current medication included mycophenolate mofetil 1 g/BD and hydroxychloroquine 200 mg/BD.

Chest and abdominal examinations were normal, she had no meningeal irritations, no focal neurological deficit, no skin rash and no evidence of active arthritis. Laboratory tests revealed low Hb, WBCs, and sodium, and elevated ESR, urea, globulin, and LDH. She also had elevated anti-DNA, low complement (C3/C4), proteinuria, and Pr/Cr 1.125 g/day.



The patient was diagnosed with acute febrile illness of presumed infection and active lupus with nephritis, which responded (initially) to treatment with IV methylprednisolone succinate 500 mg/day for 3 days and IV antibiotics, before daily spikes in fever returned.

Sepsis workup included blood culture, urine culture, ASO titre, throat swab, and detailed viral serology including HBsAg, HBC antibodies, EBV, CMV serology, and malaria parasite.



CT with contrast (brain, chest, and abdomen) and echocardiogram were normal. She received potent IV piperacillin/tazobactam but with no improvement; she had progressive cytopaenias. Moreover, the acute phase reactant response showed CRP >120 and ESR 34 mm/hour, conversely her ferritin level was 14,179 ng/mL raising the possibility of hemophagocytosis. Other biochemical values of note included triglycerides 568 mg/dL (40–200 mg/dL).

Bone marrow examination confirmed the diagnosis of hemophagocytic syndrome and the patient received IV methylprednisolone succinate 500 mg/day for 3 days, and prednisolone 1 mg/kg/day thereafter. Two days prior to discharge from the hospital she received cyclosporine 1 mg/kg BD.

Discussion: *Why do some patients develop hemophagocytic syndrome?*

Would you consider hematopoietic stem cell transplantation in this situation?



Case 2. Disseminated TB in a patient with active lupus nephritis

A 27-year-old male with SLE develops prolonged fever, jaundice, and painful swelling of the elbow following the second dose of cyclophosphamide pulse therapy for active lupus nephritis; he was also on prednisone 40 mg/day.

Work-up revealed hepatic calcifications on abdominal ultrasound and normal chest radiograph. Synovial fluid aspirated from the elbow joint and urine specimens were positive for acid-fast bacilli, and eventually grew *Mycobacterium tuberculosis* (TB) on cultures. He was started on anti-TB therapy.

Discussion points:

How would you manage the active lupus nephritis?

What is your stand on TB prophylaxis for patients on chronic high dose steroid?

A 49-year-old patient had stable SLE for the past 22 years until she developed episodes of diffuse abdominal pains accompanied by alternating diarrhoea with constipation for 12 months; colonoscopy revealed rectal ulcers and abdominal CT scan showed colonic diverticulosis. Four months later, she was admitted to hospital with severe abdominal pain and worsening diarrhoea; laboratory tests disclosed thrombocytopaenia, hypocomplementaemia and high titre anti-dsDNA. There was dramatic resolution of symptoms with high dose corticosteroids and she was discharged following significant improvement. A few weeks later, while on tapering prednisone, she was re-admitted because of recurrence of profuse diarrhoea with severe electrolyte imbalance. Hospital course was marked by diarrhoea, severe hypoalbuminaemia with progressive anasarca requiring IV albumin infusions, and episodes of massive haematochezia requiring multiple blood transfusions. Colonoscopy showed ischaemic colitis with oedematous friable recto-sigmoid mucosa. She underwent abdominoperineal resection with ileal resection of necrotic intestinal segments; histopathology confirmed haemorrhagic gangrenous necrosis of the small intestine and colon, with small and medium vessel vasculitis and thrombosis.

How will you manage the severe gastrointestinal vasculitis?

Learning Objectives

- ## Notes

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Professor Ronald van Vollenhoven, MD, PhD

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Where are we now with blocking B-cell activating factors?

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2. Navarra SV, Guzman RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet.* 2011;377:721–31.

Despite intense biopharmaceutical development over the past decade, the only approved biological for systemic lupus erythematosus (SLE) to date remains belimumab, a monoclonal antibody targeting the B-lymphocyte stimulating cytokine Blys (BAFF). Belimumab was approved in 2011 on the strength of two large randomised trials demonstrating its efficacy and safety, and expectations ran high that this would herald a new era in the treatment for lupus.^{1,2} However, these expectations were not fulfilled for two different reasons: the uptake in practice and the clinical impact of belimumab have remained limited, and the development of other agents targeting B-cell activating factors did not succeed. Should we be disappointed?

There are important lessons to be learned, both for those who are involved in clinical trial design and for clinicians treating patients with SLE. One important point is that the way the (successful) clinical trial is done determines the formal approval, which in turn is used to guide

and direct physicians. However, in the case of belimumab the formal approval is strangely at odds with the way in which most rheumatologists practice. For example, the approval text refers to disease activity as though a clinician would look at a single point in time to make a treatment choice, without taking the entire history of the patient's disease into account. Another paradoxical fact is that the outcome used in the BLISS trials, the SLE Responder Index (SRI), has been chosen almost reflexively in several trials with other agents, despite a lack of evidence that it is better suited for this purpose, and the SRI now has the dubious honour of being the primary outcome for most failed lupus trials. Perhaps the most important lesson comes from the many studies conducted since the approval of belimumab, which have demonstrated the excellent safety of this agent, its steroid-sparing properties, and its retention in a segment of the patient population. These all suggest that belimumab is nonetheless an important therapeutic advance for a sizeable subset of patients with SLE.

Learning Objectives

- Explain that biologics targeting B-lymphocyte stimulating cytokines are a class of (potential) therapeutic agents for SLE
- Describe about the results in clinical trials of several biologics targeting B-cell stimulating cytokines
- Discuss the implications these results have for clinical trial design
- Explain learnings of the past 6 years with relevance for clinical practice

[illegible]

Abstracts

Plenary IV: Therapy Updates in SLE

Moderators: David Isenberg (UK), Peter Lydyard (UK) & Roger A. Levy (Brazil)



Professor Richard Furie, MD

Hofstra Northwell School of Medicine, New York, USA

Targeting the interferon pathway in SLE

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It has been known for several decades that the majority of patients with systemic lupus erythematosus (SLE) have an activated interferon pathway. Although an obvious target for drug development, the initial trials with monoclonal antibodies to interferon α were either unsuccessful or yielded modest results. However, the Phase II study with anifrolumab, a monoclonal antibody to the type 1 interferon receptor, yielded robust data and confirmed our initial hypothesis that inhibition of the type 1 interferon pathway could reduce disease activity. With heightened interest in this therapeutic strategy, many different approaches are being taken to developing drugs to inhibit the interferon pathway in SLE.

Learning Objectives

- Explain the role of type 1 interferons in SLE
- Describe strategic approaches to inhibiting the interferon pathway
- Discuss results of clinical trials with experimental therapies that target the interferon pathway

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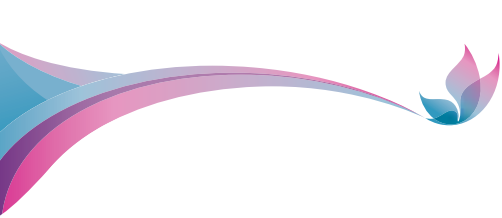
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