Lupus Academy
Eastern European Roadshow Meetings: Budapest

Abstract Booklet

Semmelweis University,
Budapest, Hungary
19th March 2016

LupusAcademy
Communicate. Educate. Treat.

Meeting organisation

The content for this activity has been developed under the control of the meeting Chairs: Professor Andrea Doria, Padova, Italy, and Professor Ricard Cervera, Barcelona, Catalonia, Spain, 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

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GlaxoSmithKline, UCB (Gold supporters) and
Bristol Myers Squibb (Bronze supporter).

Welcome

Dear Friends and Colleagues

On behalf of Lupus Academy, it is with great pleasure to welcome you to the **Lupus Academy's† Eastern European Roadshow Meeting at Semmelweis University, Budapest (19th March 2016)**. This meeting is being organised in collaboration with Professor György Nagy, to whom we are very grateful.

These are exciting times for lupus clinicians and scientists as we embark on new frontiers in the diagnosis, management and novel treatment targets for lupus. This meeting will include a half-day educational programme that reflects the key issues in lupus diagnosis, management and the challenges we face in clinical practice. The educational programme will be delivered through morning plenary sessions and afternoon interactive workshops held at the University.

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

We sincerely hope that this meeting will provide you with new ideas for your clinical work, enhanced enthusiasm for collaborative research, and fruitful discussions with your colleagues who have an interest in improving patient outcomes in lupus.

We look forward to meeting and talking with you in Budapest.

With kind regards,

Professor György Nagy and the **Lupus Academy Steering Committee**

Professor Ricard Cervera
co-Chairman 2016

Professor Andrea Doria
co-Chairman 2015

Professor Thomas Dörner, Professor Richard Furie, Professor Bevra Hahn, Professor David Isenberg, Professor Munther Khamashta, Professor Roger A. Levy, Professor Ronald van Vollenhoven, Professor Sandra Navarra, Professor Murray Urowitz, Professor Zahir Amoura

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

Programme

Saturday 19th March 2016			Page
09:45	**Opening Address**	György Nagy *(Hungary)*, Ricard Cervera *(Spain)* & Andrea Doria *(Italy)*	
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12:00	Discussion		
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13:30	*Moderator:* Ricard Cervera *(Spain)* Haematologic challenges: Cytopaenias	Emese Kiss *(Hungary)*	20
15:00	**Meeting Close**		

Biographies

Professor Ricard Cervera, MD, PhD, FRCP

Hospital Clinic, Barcelona, Catalonia, Spain

Disclosures

Consultant/Advisor:
GSK

Professor Cervera is a member of the Lupus Academy Steering Committee, co-Chairman of the Lupus Academy (2016) and has been involved in the planning and development of the Lupus Academy Eastern European Roadshow Meeting programme and materials.

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

Professor Cervera is an Associate Editor of the journal *Lupus Science & Medicine* and is on the Editorial Boards of 20 medical journals. He is coordinator of the European Forum on Antiphospholipid Antibodies and of the European Working Party on Systemic Lupus Erythematosus (SLE) (Euro-Lupus Group). He is Chairman of the Medical Advisory Board of the Catalan Association of Lupus Patients and Medical Advisor to Lupus Europe. He chaired the 6th and 8th International Congresses on Autoimmunity, the 1st and 2nd Latin-American Congresses on Autoimmunity, the 5th Meeting of the European Forum on Antiphospholipid Antibodies and the 8th European Lupus Congress.

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

Professor László Czirják, MD, PhD

Department of Rheumatology and Immunology, University of Pécs, Hungary

Disclosures

None

László Czirják is Professor of Rheumatology and Medicine and Chief of the Department of Rheumatology and Immunology in the University of Pécs in south-western Hungary. He is involved in teaching rheumatology and clinical immunology to medical students (in Hungarian and English), and is also a regular speaker on postgraduate courses.

In 2005, as a Councillor of the European scleroderma association (EUSTAR), Professor Czirják organised the first EUropean League Against Rheumatism (EULAR)/EUSTAR educational course on scleroderma in Budapest. Between 2007 and 2011, he was the general secretary of EULAR and from 2010 to 2013 he was the secretary of EUSTAR. He is a member of the Editorial Board of *Annals of Rheumatic Diseases, Clinical Experimental Rheumatology* and the *Journal of Scleroderma and Related disorders*.

Between 2009 and 2014, Professor Czirják was the co-Chairman of the Immunological Committee of the Hungarian Academy of Science. He is the Vice President of the Hungarian Society of Rheumatology and a Member of the Hungarian National Pharmacological Therapy Committee.

Professor Czirják's research interests predominantly focus on the investigation of the clinical and immunological aspects of systemic sclerosis. His research group performs studies on the survival, disease activity and other clinical-epidemiological aspects of systemic sclerosis. He is both participant and organiser of several international multicentre follow-up observational studies in patients with scleroderma. He is also performing both experimental and clinical systemic lupus erythematosus (SLE)-related research, including the investigation of the role of complement factors in lupus. He was involved in the international task force developing "treat-to-target" recommendations for patients with SLE.

Biographies

Professor Andrea Doria, MD

University of Padova, Italy

Disclosures

Consultant/Advisor:
GSK

Professor Doria is a member of the Lupus Academy Steering Committee, was co-Chairman of the Lupus Academy (2015) and has been involved in the planning and development of the Lupus Academy Eastern European Roadshow 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 up to now. He is also a member of American College of Rheumatology (ACR).

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

Professor Doria is on the Editorial Boards of several rheumatology and immunology journals, including *Lupus, Autoimmunity, Clinical and Experimental Rheumatology, Autoimmunity Reviews, Journal of Autoimmunity, Experimental Biology and Medicine, Rheumatology Reports, 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 in 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.

Associate Professor Emese Kiss MD, PhD

Department of Rheumatology and Immunology, Semmelweis University, Budapest, Hungary

Disclosures
None

Emese Kiss is Associate Professor of Medicine, Rheumatology and Clinical immunology at Semmelweis University, Budapest, Hungary.

Professor Kiss is currently the Head of the Clinical Immunology, Adult and Paediatric Rheumatology Department at the National Institute of Rheumatology and Physiotherapy, Budapest, Hungary.

Graduating from the Medical School of the University of Debrecen, Hungary she worked at the 3rd Department of Internal Medicine, Medical and Health Sciences Centre, University of Debrecen.

Professor Kiss completed her PhD thesis on "The importance of complement receptor 1 expressed on lupus erythrocytes". After passing her "habilitation" examination in 2004, with a thesis entitled "Chronic organ damage and co-morbidities in systemic lupus erythematosus", she became an examiner, reviewer and consultant for PhD theses, and now actively participates in graduate and postgraduate education. She has worked in her current position since 2007.

In 2014, after successfully defending her thesis on "Clinical and experimental experiences in systemic lupus erythematosus (SLE)" focusing on accelerated atherosclerosis, associating antiphospholipid syndrome (APS), osteoporosis and malignancies in SLE patients, Professor Kiss became a Doctor of the Hungarian Academy of Sciences.

Her research activities are related to clinical aspects and molecular mechanisms of systemic autoimmune disorders, especially SLE, APS and vasculitides. She has published 178 full text articles and 38 book chapters, and has 370 impact factors, 2582 citations and 14 grants to date.

Professor Kiss is a member of the jury of the Hungarian Scientific Research Fund and also of the Evaluation Committee of the Bólyai Scholarship. She is member of the Editorial Boards of two national medical journals, a reviewer of some international papers, General Secretary of the Hungarian Reproductive Immunology Society, Secretary of the Hungarian Association of Rheumatologists, and Board member of the Hungarian College of Clinical Immunology and Allergology. Professor Kiss has participated in EULAR/ESCISIT lupus projects, and also in the work of the EURO PHOSPHOLIPID Project Group. Possessing a Good Clinical Practice certificate, she has been Principal Investigator in several clinical trials.

Associate Professor László Kovács, MD, PhD

Department of Rheumatology, University of Szeged, Hungary

Disclosures
None

László Kovács is Associate Professor and Director of the Department of Rheumatology at University of Szeged, a regional centre of systemic autoimmune diseases and inflammatory rheumatic diseases in south-east Hungary. Graduating from the University of Szeged in 1991, he went on to specialise in internal medicine, rheumatology, clinical immunology and nephrology during his clinical career at the 1st Departments of Internal Medicine and Rheumatology at University of Szeged, and in the County Hospital in Székesfehérvár, Hungary.

Professor Kovács completed his PhD thesis on autonomic nervous system dysfunction in Sjögren's syndrome in 2004. His major current clinical interests are systemic lupus erythematosus (SLE) and systemic vasculitides. His research activities relate to T-cell dysfunction in SLE and predictors of long-term response to biological therapies in rheumatoid arthritis. The Department of Rheumatology in Szeged is a member of the PRECISESADS European multinational consortium for the research on a detailed characterisation of the molecular pathogenesis of systemic autoimmune diseases.

Biographies

Associate Professor György Nagy MD, PhD, DSc

Department of Rheumatology and Immunology, Semmelweis University, Budapest, Hungary

Disclosures

None

György Nagy is Associate Professor of Medicine, Rheumatology and Immunology at Semmelweis University, Budapest, Hungary.

Professor Nagy is currently the Secretary General of the Hungarian Association of Rheumatologists and a member of the EUropean League Against Rheumatism (EULAR) Standing Committee on Investigative Rheumatology. He is also a member of the Faculty of 1000 Medicine/Clinical Immunology and Rheumatology Board and is editorial board member of several international and Hungarian scientific journals. He has been the Principal Investigator or co-Investigator of many Hungarian and international research grants and has served as abstract reviewer for numerous international meetings including the American College of Rheumatology (ACR) and EULAR. In addition, he has co-organised several national and international meetings, including the Congress on Controversies in Rheumatology & Autoimmunity (CORA), the European Workshop for Rheumatology Research (EWRR), the European Society for Clinical Investigation (ESCI) and the Semmelweis Symposium.

Professor Nagy's research interests focus on molecular mechanisms of autoimmune diseases, with a special interest in the role of nitric oxide and reactive oxygen intermediates. He also studies the role of extracellular vesicles in the pathogenesis of various autoimmune diseases. He has co-authored more than 150 scientific publications.

Notes

Abstracts

Plenary I: Pathogenesis, Diagnosis and Treatment of SLE and APS

Moderators: Professor Ricard Cervera (Spain) & Professor Andrea Doria (Italy)

Associate Professor György Nagy MD, PhD, DSc
Department of Rheumatology and Immunology, Semmelweis University, Budapest, Hungary

The pathogenesis of SLE, novel data

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by production of antinuclear autoantibodies and multifarious clinical manifestations. Both genetic and environmental factors are believed to influence the development of SLE. Overproduction of pro-inflammatory cytokines, reactive oxygen intermediates (ROIs) and nitric oxide play a central role in the pathogenesis of SLE. The increased expression of type I interferon (IFN)-regulated genes is well known in lupus and IFN may represent new therapeutic target. T-lymphocytes of patients with SLE have been shown to be activated *in vivo* and provide help to autoreactive B-cells. T-helper 17 cells and CD4+CD25–Foxp3+ regulatory T-cells have also been implicated in SLE. Altered expression of signalling molecules and mitochondrial dysfunction may contribute to the altered T-cell activation. The presentation reviews recent achievements in the understanding of the molecular mechanisms of SLE and highlights the development of novel therapies.

Learning Objectives

At the end of the presentation, participants will be able to:

- Recognise the environmental and genetic factors that influence the development of SLE.
- Understand the roles of various inflammatory mediators in the pathogenesis of SLE.
- Discuss the potential of IFN and T-cell subtypes as therapeutic targets in SLE.
- Discuss the recent development of novel therapeutic strategies for SLE.

Notes

Abstracts

Plenary I: Pathogenesis, Diagnosis and Treatment of SLE and APS

Moderators: Professor Ricard Cervera (Spain) & Professor Andrea Doria (Italy)

Professor László Czirják, MD, PhD
Department of Rheumatology and Immunology, University of Pécs, Hungary

Diagnostic challenges in SLE and APS

Systemic lupus erythematosus (SLE) is highly variable, systemic autoimmune disease characterised by variable, multisystem organ involvement and inflammation. Confirming the diagnosis of SLE is often challenging as we lack diagnostic criteria for SLE. The currently available classification criteria are useful as a basis for diagnosis, although a careful clinical judgement is mandatory to make appropriate diagnosis and treatment decisions. The most frequent clinical symptoms include polyarthritis, variable skin symptoms, photosensitivity, serositis, antiphospholipid syndrome, lymphadenomegaly, nephritis and neuropsychiatric symptoms. Leukopaenia, direct Coombs antibodies and decreased complement levels also contribute to the clinical presentation of SLE. Detection of anti-dsDNA and other antibodies (anti-phospholipid, -Sm, -SS-A) helps in diagnosis and defining clinical subsets. Other connective tissue diseases, infections and certain malignancies are important in the differential diagnosis of SLE. Early diagnosis and risk assessment is also important, because there are substantially different clinical subsets with variable outcomes. The prognostic subsets of patients depend on the presence of organ manifestations, age, gender, ethnicity and social circumstances. The treatment strategy may be different, and some well-defined subsets require long term treatment.

Antiphospholipid syndrome is not a rare disease, it is the most common acquired thrombophilia with a wide spectrum of clinical presentations. Venous and arterial thrombotic events and morbidity during pregnancy are the most important symptoms, and deep vein thrombosis is the most commonly reported venous manifestation. Other manifestations (cognitive impairment, mood disorders, decreased platelet count, etc.) can also be present. Diagnostic screening algorithms which include the detection of the different antiphospholipid autoantibodies, and risk assessment in the different forms of disease are important. Classification criteria are available and useful, although we lack diagnostic criteria, so a careful clinical judgement is mandatory to make appropriate diagnostic and treatment decisions.

Learning Objectives

At the end of the presentation, participants will be able to:

- Recognise that SLE is a highly variable, multisystem disorder.
- Understand that early diagnosis and risk assessment are important, because there are substantially different clinical subsets depending on organ manifestation, age, gender, ethnicity and social circumstances.
- Identify antiphospholipid syndrome, venous and arterial thrombotic events and morbidity in pregnancy as the most important symptoms.
- Understand that deep vein thrombosis is the most common venous manifestation.
- Appreciate that whilst classification criteria are available, we lack diagnostic criteria, therefore careful clinical judgement is mandatory to make appropriate diagnostic and treatment decisions.

Notes

Abstracts

Plenary I: Pathogenesis, Diagnosis and Treatment of SLE and APS

Moderators: Professor Ricard Cervera (Spain) & Professor Andrea Doria (Italy)

Professor Andrea Doria, MD
University of Padova, Italy

New trends in the treatment of SLE

Survival of patients with systemic lupus erythematosus (SLE) has improved dramatically over the last few decades; however, patients with SLE still display a four-to-five fold higher standardised mortality rate compared with the general population.[1] Persistent disease activity and drug side effects, especially with corticosteroids, are responsible for increased organ damage, which in turn is predictive of more damage and death.[2] Accordingly, reducing disease activity and sparing corticosteroid use are unmet needs in the management of SLE patients.[3]

In meeting these needs, new biologic agents are proving to be very promising, since when added to the standard of care they appear to reduce disease activity and spare the need for corticosteroids. Belimumab is currently the only biologic agent approved for SLE, following successful completion of two randomised controlled trials (RCTs) in which it met the primary end points and was well tolerated.[4,5] Post-hoc analyses revealed that patients with higher disease activity, and musculoskeletal and skin manifestations are the best responders to belimumab.[6] However, these indications are not sufficient for optimal use of the drug. Thus, further data coming from clinical practice settings are welcome. Conversely, the biologic rituximab was not approved for SLE due to the failure of two RCTs. However, due to its effectiveness in open-label studies and registries, rituximab continues to be used in daily clinical practice in SLE patients with severe and refractory manifestations.

In order to optimise disease outcomes, we can also use new therapeutic strategies. Treat-to-target seems to be very promising, with major targets including disease remission and low disease activity. We know that remission and low disease activity are associated with better outcomes and prolonged survival.[2,7] However, no widely accepted definitions of remission and low disease activity are available to date.

From a clinical perspective, we can define clinical remission as the absence of signs and symptoms or urinary and haematological abnormalities due to the immune pathways involved in the disease in patients who are corticosteroid free and in clinical-serological remission. In other words, complete remission can be defined as clinical-serological healing in patients who are free of any treatment. However, complete remission is often hard to accomplish for the majority of patients with SLE, whereas clinical remission without corticosteroids or with a minimal dose of corticosteroids could be acceptable alternative targets. Low disease activity, even with low dose steroids, may also be a reasonable target in order to minimise development of organ damage.[8]

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2. Zen M, Bassi N, Nalotto L, et al. Disease activity patterns in a monocentric cohort of SLE patients: a seven-year follow-up study. *Clin Exp Rheumatol* 2012; 30(6): 856-63.

3. Doria A, Gatto M, Iaccarino L, Punzi L. Value and goals of treat-to-target in systemic lupus erythematosus: knowledge and foresight. *Lupus* 2015; 24(4-5): 507-15.

4. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011; 63(12): 3918-30.

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7. Zen M, Iaccarino L, Gatto M, et al. Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. *Ann Rheum Dis* 2015; 74(12): 2117-22.

8. Doria A, Gatto M, Zen M, Iaccarino L, Punzi L. Optimizing outcome in SLE: treating-to-target and definition of treatment goals. *Autoimmun Rev* 2014; 13(7): 770-7.

Learning Objectives

At the end of the presentation, participants will be able to:

- Recognise that persistent disease activity and drug side-effects are the two main determinants of organ damage in SLE, and that damage is predictive of more damage, worse prognosis and death.
- Understand the effectiveness of belimumab in daily clinical practice and recognise the most appropriate patients for belimumab treatment.
- Understand the effectiveness of rituximab in daily clinical practice and recognise the most appropriate patients for rituximab treatment.
- Recall the different definitions of clinical, or clinical and serological (complete) remission, being aware that prolonged clinical and serological remission remain very difficult to achieve.
- Understand that clinical remission or even low disease activity with minimal corticosteroid intake is recommended.
- Appreciate that a tight balance between therapeutic harm and benefit has to be provided and that corticosteroid withdrawal should be prompt.

Notes

Abstracts

Plenary I: Pathogenesis, Diagnosis and Treatment of SLE and APS

Moderators: Professor Ricard Cervera (Spain) & Professor Andrea Doria (Italy)

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

New trends in the treatment of APS

Currently, there is consensus on treating patients with antiphospholipid syndrome (APS) and thrombosis with long-term oral anticoagulation, and to prevent obstetric manifestations with the use of aspirin and heparin. These recommendations are based on randomised controlled trials and observational studies. Despite this body of evidence, there are grey areas where knowledge is scarce or does not exist. In other words, there is a subset of patients whose APS is difficult to manage. Some examples include patients with "seronegative" APS, those who do not display formal (clinical or laboratory) classification criteria for APS, and those with recurrent thrombotic events despite optimal anticoagulation. In addition, there are those patients with clinical manifestations that are not included in the current classification criteria, such as haematologic manifestations (thrombocytopaenia and haemolytic anaemia), neurologic manifestations (chorea, myelitis or multiple sclerosis-like lesions), nephropathy and heart valve disease associated with antiphospholipid antibodies, and those selected cases of thrombotic APS where anticoagulant treatment is withdrawn when antiphospholipid antibodies have become persistently negative.

Learning Objectives

At the end of the presentation, participants will be able to:

- Recognise the main unmet needs in the management of the APS.
- Describe the current recommendations for the treatment of thrombotic and obstetric manifestations of APS.
- Discuss the alternative options for the management of difficult APS cases.
- Discuss new trends in research on new therapies for APS.

Notes

Notes

Case Study Workshops

Saturday 19th March 2016

Parallel Case Study Workshops		
Moderator: Andrea Doria *(Italy)* Lupus glomerulonephritis		László Kovács *(Hungary)*
Moderator: Ricard Cervera *(Spain)* Haematologic challenges: Cytopaenias		Emese Kiss *(Hungary)*

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.

Case Study Workshop

Moderator: Professor Andrea Doria (Italy)

Presenter: Associate Professor László Kovács (Hungary)

Lupus glomerulonephritis

Case study 1

A 28-year-old female, whose symptoms started with convulsions, subsequently developed pleuritis, subfebrility, polyarthritis and pancytopaenia. Immunoserology showed anti-dsDNA positivity. She was started on medium-dose corticosteroids, but pleuritis persisted and nephrotic syndrome developed. Renal biopsy revealed diffuse global proliferative lupus nephritis, with wire-loop lesions, cellular crescent, loop-necrosis and full-house immune deposits including anti-C1q positivity. She was treated with high dose IV methylprednisolone and IV cyclophosphamide, after which the nephritis went into complete remission. The subsequent course was, however, complicated by frequent relapses of pleurits, polyarthritis and general weakness, and therefore the maintenance immunosuppressive treatment was changed from azathioprine to mycophenolate mofetil. She continued to be asymptomatic with mycophenolate therapy, and the corticosteroid dose was tapered to 8 mg/day. After 1 year in remission, mycophenolate was gradually tapered off and as disease activity did not recur, she was able to embark pregnancy on chloroquine and low-dose corticosteroid therapy. Although a minor relapse occurred during pregnancy, which responded promptly to an increase of the corticosteroid dose, she successfully delivered a baby and is doing well now.

Case study 2

A 31-year-old female presented with diffuse peripheral oedema, pericardial and pleural effusion, hypoalbuminaemia and anaemia. Somewhat surprisingly, no significant proteinuria was detected, and the cause of the severe hypoalbuminaemia was identified to be protein losing enteropathy, confirmed by albumin scintigraphy. Anti-dsDNA, -SSA and -SSB positivity and hypocomplementaemia confirmed the diagnosis of systemic lupus erythematosus (SLE). Corticosteroid and IV cyclophosphamide therapy resulted in the normalisation of the serum albumin level and the resolution of the symptoms. After repeated minor relapses on maintenance azathioprine treatment, proteinuria of 1.0-1.7 g/day, microscopic haematuria, cylindruria, and moderate renal function impairment (eGFR: 42 mL/min) was noted. Renal biopsy revealed diffuse segmental endocapillary proliferative glomerulonephritis, which is not typical of SLE by itself, but the presence of IgG, IgM, C3 and C1q, and the exclusion of an infectious background led to the diagnosis of lupus nephritis. She was given IV methylprednisolone, followed by oral corticosteroid and mycophenolate mofetil therapy. Subsequently, the renal parameters and the extrarenal manifestations have shown gradual improvement.

Case study 3

A 26-year-old female had been treated for SLE for 8 years. Her previous manifestations included photosensitive rash, polyarthritis, pleuritis, pericarditis, Raynaud's phenomenon and fibrosing interstitial lung disease. She was positive for anti-dsDNA, anti-Sm and anti-U1RNP antibodies, and had very low levels of complement-3 and -4. Her past medical history was notable for Little's disease, hepatitis-C carrier state (without active hepatitis) and bronchial asthma. In 2009, she developed nephrotic syndrome in association with microscopic haematuria, cylindruria and rapidly deteriorating renal function. Kidney biopsy revealed diffuse global proliferative lupus nephritis with fibrocellular crescents. She was treated with IV methylprednisolone and cyclophosphamide (corrected for renal function), but kidney function initially continued to worsen and dialysis became necessary. She was dialysed for the next 6 weeks, while corticosteroid and cyclophosphamide treatment was continued, and the gradual improvement in renal function allowed subsequent cessation of dialysis. She was switched to azathioprine and her subsequent disease course was free from relapses. Her kidney function parameters improved to the border of normal range.

Case study 4

A 50-year-old female was admitted for polyarthritis, Raynaud's and proteinuria of 1.2-2.7 g/day, microscopic haematuria and mild renal insufficiency (eGFR: 45 mL/min). She was known to have psoriasis for 13 years, and had been previously treated with methotrexate, cyclosporin and anti-TNF agents. Her son had lupus nephritis and lives with a transplanted kidney. Her kidney biopsy disclosed membranous glomerulonephritis with interstitial fibrosis, full-house immune deposits, and PLA2R positivity, the latter suggesting membranous nephropathy secondary to an underlying disease. She was seropositive to anti-dsDNA and anti-Annexin-V antibodies. She was also treated with high-dose IV methylprednisolone, followed by oral corticosteroid and IV cyclophosphamide pulses (cumulative dose: 4700 mg). In parallel with the tapering of the corticosteroids, her psoriatic skin lesions became rather active and widespread. Her proteinuria decreased to below 0.5 g/day, and her kidney function returned to normal. As a common therapy for both active psoriasis, and membranous lupus nephritis, cyclosporine treatment was initiated. Her lupus has remained inactive, but psoriatic lesions have shown only moderate improvement. In a further effort to control both diseases, and knowing that anti-TNF is not advised in SLE, she was prescribed ustekinumab, an IL-12/23 receptor blocker that has had favourable first results in Phase I and II trials with SLE, and is currently licensed for the treatment of psoriasis. Her skin symptoms have improved substantially, and her lupus has remained inactive.

Learning Objectives

At the end of the workshop, participants will be able to:

- Know how to manage lupus before and during pregnancy.
- Understand the differential-diagnostic work-up of conditions with generalized oedema in lupus.
- Understand how to potentially restore kidney function even from dialysis-dependent advanced renal failure.
- Govern the treatment of lupus in the presence of the co-morbidity of a common disease, psoriasis.

Notes

Case Study Workshop

Moderator: Professor Ricard Cervera (Spain)

Presenter: Associate Professor Emese Kiss (Hungary)

Haematologic challenges: Cytopaenias

Case study 1

A 25-year-old female patient presented with lymph node enlargement and fever in 2004. Combined *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infection was diagnosed, and IgA deficiency was also evident. The patient responded well to macrolide antibiotic therapy. Two years later she presented with convulsions requiring carbamazepine treatment. After developing polyarthritis, alopecia, leucopaenia, antinuclear antibodies (ANA), anti-dsDNA and anti-C1q antibodies, as well as lupus anticoagulant (LAC) positive, her disease was classified as systemic lupus erythematosus (SLE) in 2007. Low dose methylprednisolone was prescribed. Her LAC became constantly positive without any thrombotic or obstetric complications. Due to persistent leucopaenia (WBC 1.5-3.0 g/L) glucocorticoid treatment could not be omitted; otherwise the patient was well. During her pregnancy in 2010, low-molecular-weight heparin (LMWH) was given, together with aspirin. Enormous lymph node conglomeration appeared at the beginning of the second trimester and persisted throughout her pregnancy. Infections were excluded with appropriate examinations and her spleen and liver were normal size. Histopathology confirmed immune reactive lymphadenopathy, and excluded lymphoma. The patient responded well to low dose glucocorticoid treatment and gave birth, by Caesarean section, to a girl weighing 3280 g at the 40th week of gestation. In 2012 she consulted for generalised lymphadenopathy with increased lactate dehydrogenase (LDH) and a high titre of anti-dsDNA, which was induced by Parvovirus B19, and resolved spontaneously. Histology findings were similar to previous ones. In December 2014, after an upper airway infection treated with cephalosporin, the woman required urgent hospitalisation with profuse epistaxis, and vaginal and gastrointestinal bleeding as a consequence of severe thrombocytopaenia. Her platelet count was 5 g/L. During the first week, she received 2 mg/kg parenteral glucocorticoid, supportive therapy and 3x4 Unit platelet suspension. When her platelet count started to increase, glucocorticoid was slowly tapered and azathioprine was introduced. Red blood cell transfusion was not required. She was able to stop steroids within 3 months, and azathioprine within 6 months, but she had to restart azathioprine one year later due lupus flare resulting in polyarthritis, fatigue and highly active serology findings. She continues to take azathioprine, vitamin D and, for short periods, low dose glucocorticoid, and is in remission.

Points to be discussed:

Differential diagnosis of lymph node enlargement (lupus activity, infection, lymphoma at present).

Adequate therapy during pregnancy in antiphospholipid-antibody-positive patients without previous incidents or clinical manifestations (aspirin+ prophylactic dose LMWH). Risk stratification in aPL Ab positive patients.

Possible causes of leucopaenia in SLE (lupus activity, infection, and carbamazepine therapy at present).

Causes of thrombopaenia in SLE, causes of secondary immune thrombocytopaenic purpura (ITP) and treatment of acute ITP.

Case study 2

A 55-year-old woman presented in October 2010 with widespread purpuras as her first presentation of severe thrombocytopaenia (platelet 8G/l). Acute infection was initially excluded, but a urea breath test disclosed *H. pylori*. Immune serology findings indicated the presence of ANA, anti-dsDNA, anti-cardiolipin (IgG) and anti-SS-A autoantibodies. Secondary ITP was diagnosed and the patient started pulse i.v. methlyprednisolone (500 mg for 5 days) immediately, with supportive therapy including 8U platelet concentrate. The appearance of malar rash confirmed the diagnosis of SLE. Glucocorticoid was tapered and 2 mg/kg bodyweight of azathioprine was initiated. As the ITP relapsed on less than 10 mg of glucocorticoid, within 3 months immune suppression was changed to 3 mg/kg bodyweight of cyclosporin A in March 2011. This regimen proved to be effective, and the glucocorticoid dose was reduced to

as low as 5 mg glucocorticoid per day, after which cylosporin A was reduced by 50%. Platelet count (and LDH level) fluctuated from 60 to 250 g/L. Haemorrhagic complication was not reported. However, immune serology data (ANA, adsDNA, aSS-A, and aCL, ab2GP) indicated continuous activation of the immune system requiring long-standing treatment. In November 2013, 3 years after first admission, and with 2 years remission on low dose methylprednisolon plus cyclosporine A, the woman required urgent hospitalisation due to severe relapse resulting in fast decline of platelets from 260 to 27 g/L. As an acute treatment, she received 1 mg/kg bodyweight i.v. glucocorticoid in combination with 2 g/kg bodyweight i.v. immunoglobulin. Fast and significant short-term efficacy was observed, leading to switching back to the previous combination of glucocorticoid and cyclosporine A. A lupus flare was identified in June 2015 based on polyarthritis, thrombocytopaenia with purpuras, and immune serology findings (ANA, adsDNA, aCL, ab2GPI, aSS-A positivity). The flare responded well to an increased dose of steroid. Cyclosporin A was replaced by 2 g/day mycophenolate mofetil, which seems to be an effective and well-tolerated maintenance therapy.

Points to be discussed:

Standardised definitions and terminology for persistency and severity of ITP.
International Working Group criteria for therapeutic response.
Therapeutic possibilities in chronic secondary ITP (high dose intravenous immunoglobulin, rituximab).

Case study 3

A 31-year-old female presented with facial erythema in August 2003. The dermatologist diagnosed a mycotic lesion, pityriasis rosea, but surprisingly it responded well to topical steroids. She was referred to a tertiary rheumatology centre, where ANA, and aCL (IgG and IgM) were detected in immune serology. Undifferentiated connective tissue disease was diagnosed and careful follow-up indicated. Anti-SS-A appeared in December 2003, ab2-GPI together with aCL and ANA in February 2004, when the disease met the classification for antiphospholipid syndrome (APS). During a sunny May 2003 she observed malar rash and photosensitivity, and was positive for LAC and anti-dsDNA complicated with hypocomplementaemia. SLE with associated APS was diagnosed. Aspirin and chloroquine were prescribed, but the latter was withdrawn due to concerns of retinal toxicity. Direct antiglobulin tested positive in 2007, without signs of haemolysis. Despite having three types of aPL antibodies and also being positive for anti-SS-A, her pregnancy with aspirin + LMWH therapy was not problematic, and as a result, a boy weighing 2640 g was born at the 38th week of gestation. The patient was in clinical remission, free from any immune suppressive therapy, although immune serology showed persistent activity. In June 2013 she was admitted to the intensive care unit in unconscious state with hypotension due to severe anaemia (Hgb 40 g/L). Increased LDH and reticulocyte count, indirect hyperbilirubinaemia and direct antiglobulin positivity pointed to autoimmune haemolysis. Therapy included a 2-litre plasma exchange, 200 mg dexamethasone and 200 mg cyclophosphamide infusions for 5 days, and 1 g/kg bodyweight i.v. immunoglobulin. She had become better despite of tapering steroid, and laboratory results reflected her improved clinical condition. Unfortunately, *Clostridum* toxin and enterohemorrhagic-*Escherichia coli*-negative diarrhoea complicated the situation leading to dramatic decline in haemostasis, and also to CNS symptoms, such as irritability, hallucinations and feelings of inadequacy. Diffuse vascular demyelination was detected with MRI. Renal function and haemostasis parameters were normal. Six units of appropriately prepared red blood cell suspension was transfused, and rituximab was introduced. After four cycles of rituximab, she started with azathioprine as maintenance therapy. Until now, neither side effects, nor loss of efficacy have been observed.

Points to be discussed:

Initiative phase of SLE (autoantibody production, fore-running APS).
SLE classification criteria (without redundancy, only DAT positivity or AIHA can be pointed).
Various forms of haemolytic anaemias, treatment of AIHA (warm haemaglutinin).

Case study 4

The woman's SLE started with pleuritis and pericarditis at the age of 25. Symptoms included polyarthritis, ANA, anti-dsDNA and mild leucopaenia. She had given birth to her baby prematurely. Between 1985 and 2008 she received only glucocorticoid therapy and her first admission to our centre continued treatment. Immune serology was also similar. Osteoporosis had developed, so azathioprine was introduced and steroid dose reduced. Between 2008 and 2012 she was quite well, but suffered from fluctuating polyarthralgia and headache associated with fluctuating antibody titres. She was enrolled to

Continued over

Case Study Workshop

a double-blind, placebo-controlled randomised study in July 2012. In January 2013 as her symptoms disappeared, and a declining activity was observed, she continued to participate in the open label extension period of the trial. Two weeks later after a local trauma a haematoma appeared. It increased and spread, involving various parts of her body. Complete blood count, including platelets, was normal, but C-reactive protein increased. Ultrasound could not differentiate between fasciitis and haemorrhage. The elongation of partial thromboplastin time was proven, which was corrected by the addition of normal human plasma. Fibrinogen was normal and anti-dsDNA was positive in high concentration. Specialised haemostasic examinations disclosed factor VIII deficiency (the activity was below 1%, 19 Bethesda Units of inhibitor) as the consequence of antibody to factor VIII. Rescue therapy consisted of NovoSeven (rfVII), Humafactor 8 (fVIII) and cyclophosphamide in combination with i.v. 2 mg/kg bodyweight prednisolone. Complete haematologic recovery was reached within a short period of time. Maintenance factor supplementation has net been required. Glucocorticoid was highly reduced then omitted. Despite not taking immunosuppressive therapy, the lupus has not flared. No bleeding complications were observed.

Points to be discussed:

Mild lupus with one severe flare.

Differences between bleeding complications.

Lupus anticoagulant versus clotting factor deficiency.

Learning Objectives

At the end of the workshop, participants will be able to:

- Identify the most important forms and cytopaenias occurring in SLE.
- Distinguish mild and severe complications.
- Discuss potential associated diseases.
- Discuss adequate treatment modalities.
- Govern the treatment of lupus in the presence of the co-morbidity of a common disease, psoriasis.

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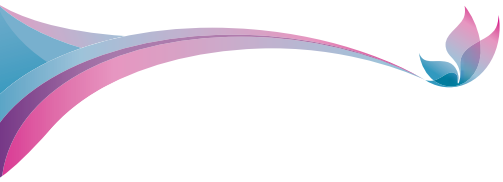

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