

The 13th Medinterna International Meeting: New Avenues in Autoimmunity

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The 13th Medinterna Meeting, which took place in Porto, Portugal on 12–14 February 2015, was a great success. Approximately 300 people attended, with speakers from 11 countries presenting lectures and roundtables on the most important issues.

WHAT DID WE LEARN ON FEBRUARY 12?

The first day was devoted to autoimmunity and began with João Viana (Lisbon, Portugal) who lectured on the predictive power of diagnostic tests. Defined through interactive exercises, sensitivity and specificity alone can give misleading diagnostic predictions. The predictive power of a test can be calculated through a *likelihood ratio* and expressed by ROC curves in integral graphs, the predictive power of a test being as strong as the area under the curve deviations from 0.5.

Yehuda Shoenfeld (Tel Aviv, Israel) spoke about autoimmunity, the Hygiene Theory, and how helminths can be implicated in new immunomodulating drugs. According to the Hygiene Hypothesis, there is an inverse relationship between the eradication of infectious agents and the emergence of different autoimmune diseases. The appearance of type 1 diabetes mellitus and multiple sclerosis in Sardinia following malaria eradication was given as a paradigmatic example. Parasitic worms have been implicated in the treatment of autoimmune diseases, e.g., *Trichuris suis* therapy for active ulcerative colitis and Crohn's disease. Ongoing research is exploring the effects of tuftsin and phosphorylcholine compounds on the treatment of lupus nephritis, colitis and rheumatoid arthritis (RA) in experimental models.

José Alves (Amadora, Portugal) discussed how immunogenicity reduces the efficacy of biological therapy. Sharing some data from his research group, he described the idiotypic/anti-idiotypic network, which may explain why patients with RA develop antibodies against anti-tumor necrosis factor (TNF) before starting anti-TNF therapy. He emphasized that any biological drug may induce immunogenicity. Anti-drug antibodies can neutralize or increase drug clearance, thereby reducing plasma biological drug concentrations. They can also be associated with adverse events such as infusion reactions or thrombosis. Etanercept is the biotechnological anti-TNF drug with fewer reports of anti-drug antibodies.

Dr. Alves provided evidence that immunogenicity can be reduced with the concomitant use of other immunosuppressors, namely methotrexate.

An autoimmune 'dance' was led by Jan Damoiseaux and Jan Tervaert (Maastricht, The Netherlands), in their "Rumba of autoimmune renal diseases." They presented a case report of a patient with de novo nephrotic syndrome, negative for anti-PLA2R, in the presence of antinuclear antibodies and decreased C3. The differential diagnosis of C3 hypocomplementemia as well as renal autoimmune diseases was reviewed. Since the electrophoresis of the patient revealed no M protein, the kinetics of free light chains was debated. Finally, monoclonal gammopathy of renal significance (MGRS) was described as a novel entity and proliferative glomerulonephritis with monoclonal immunoglobulin G deposits was disclosed as the diagnosis.

At the first roundtable of the afternoon, on rheumatic diseases (RA), Georg Schett (Erlangen, Germany) described how RA is characterized by local and systemic bone loss, as inflammation induces osteoclast differentiation and bone resorption by means of inflammatory cytokines (e.g., TNF). Bone erosion is worsened as autoantibodies against citrullinated proteins effectively induce osteoclast differentiation and trigger bone loss before the onset of RA. In addition, he explained how immune complexes such as rheumatoid factor can induce osteoclast differentiation and bone loss via FcR binding (osteoclasts express Fc receptors), and how the sialylation status of autoantibodies affects Fc-receptor binding, which in turn determines bone structure in RA.

Carlo Selmi (Milan, Italy) highlighted how psoriatic disease is not simply a systemic disease with two exclusive phenotypes, and that one should always consider the "one disease into another" bias. The genetic basis of psoriatic arthritis (PsA) disease is complex, with several HLA associations (HLA-B13, HLA-B27, HLA-B38, HLA-B57, HLA-DRB1). Environmental factors, not yet established, can possibly trigger the PsA, and infection, gut microbiota and metabolomics were considered. He emphasized that there are gender differences in treatment which are under study at the present time. New treatments should be mechanism based and biomarkers of PsA should be a priority for early diagnosis, progression prediction and treatment allocation.

Ian Giles (London, UK) talked about unplanned pregnancy and systemic rheumatic diseases, how pregnancy affects disease and, in turn, how disease and treatment may affect the pregnancy. After reviewing normal physiological changes in inflammation markers during pregnancy, he explained the importance of pregnancy planning, and how disease features and activity, ongoing treatment, postpartum risk of flare and breastfeeding should be taken into account in patient management. He said that during pregnancy, although RA and PsA may subside and ankylosing spondylitis remains identical, systemic lupus erythematosus, antiphospholipid syndrome (APS) and systemic sclerosis pregnancies bear particular risks, complications and therapeutic challenges. Accidental exposure to some immunosuppressant drugs should be managed based on benefits and risks in an individualized fashion.

At the second roundtable, the link between blood vessels and bone was demonstrated by three research projects. Diana Carmona-Fernandes (Lisbon, Portugal) proposed that the relative expression of interleukin (IL)-1 and IL-6 cytokines might explain the link between atherosclerosis and osteoporosis; and that RANKL relative expression is also related to bones and arterial wall atheromatosis, suggesting that in a disease context it might explain atherosclerotic plaque ossification. Sofia Barreira (Lisbon, Portugal) discussed how patients with hyperhomocysteinemia have lower bone mineral density, regardless of gender, age and significant cardiovascular risk factors. Alice Castro (Lisbon, Portugal) estimated the incidence of cardiovascular events in women with RA to be in the order of 7 per 1000 patient-year, suggesting that inflammation and endothelial activation contribute significantly to cardiovascular events.

Ahmet Güll (Istanbul, Turkey) then spoke about Behçet's disease, a multisystem disorder whose immunologic and clinical features resemble autoinflammatory syndromes despite the involvement of innate and adaptive immune responses. Different pathological mechanisms were discussed: significant host predisposing (familial aggregation, geographic distribution, HLA-B51), non-HLA related polymorphisms (ERAP1, KLRC4, MEFV, NOD2, TLR4, CCR1, FUT2) and the association with IL-10 and IL-23R/IL-12RB2 expression. Therapeutic trials for Behçet's disease with anti-TNF, anti-IL17, anti-IL1, abatacept and apremilast are presently ongoing.

Finally, the day ended with a case report presented by Carolina Ourique (Oporto, Portugal) of a young woman with tip of the nose necrosis, focusing cryoglobulinemia and antiphospholipid syndrome (APS), who is being treated successfully with immunosuppressants and anticoagulation.

WHAT DID WE LEARN ON FEBRUARY 13?

The morning of the second day was devoted to vasculitis and started with Cees Kallenberg (Groningen, Netherlands) talking about the relationship between systemic vasculitis and

infection. Highlighting that certain viral infections induce vasculitis, Dr. Kallenberg presented several case reports, such as subacute bacterial endocarditis and invasive amebiasis with positivity to antineutrophil cytoplasmic antibodies (ANCA), proteinase 3 (PR3) and myeloperoxidase (MPO). Additionally, bacterial infections can modulate the expression of various vasculitides, with the example of *Staphylococcus aureus* carriage being associated with relapse and persistence of ANCA positivity in granulomatosis with polyangiitis (GPA). These microbial factors should be taken into account when designing therapeutic regimens.

The hot topic at this year's meeting was Neurology, with a session dedicated to Neuroimmunology and the new avenues in diagnosis and treatment in nervous system involvement. Pedro Abreu (Porto, Portugal) spoke about primary neurological involvement in autoimmune diseases, focusing on multiple sclerosis, a major disease in neurologic autoimmunity. The etiology is still unknown, but there may be a relation with environmental, genetic and infectious factors. The disease can manifest in several phenotypic forms, and signs/symptoms can develop in days or months and vary in severity. The diagnosis is grounded on the Revised McDonald criteria, based on final clinical findings and ancillary tests (magnetic resonance imaging and cerebrospinal fluid study). Although there is still no definite cure for the disease, there is a growing number of disease-modifying drugs that alter and slow disease progression, resulting in the patient being highly incapacitated but usually not dying of the disease. Therapies with the intent to promote remyelination such as the anti-LINGO show promise. Joana Guimarães (Porto, Portugal) described secondary neurological involvement in autoimmune diseases, focusing the discussion on neuromyelitis optica (NMO), a pathology with transverse myelitis and optic neuritis as cardinal manifestations. Since 2004, with the discovery of IgG antibodies targeting aquaporin 4, the nomenclature has been widened to NMO Spectrum Diseases. More than 20 autoimmune diseases were described in patients with NMO and NMO-IgG seropositivity, the most common being Sjögren's syndrome, systemic lupus erythematosus (SLE) and myasthenia gravis. It is recommended that NMO-IgG be measured in patients with autoimmune diseases with signs or symptoms suggestive of NMO Spectrum Diseases. Filipe Palavra (Coimbra, Portugal) provided a more practical approach to central nervous system dysfunction in autoimmune diseases. The speaker stressed that the involvement of white matter is quite frequent and that many of the cognitive and behavioral manifestations of autoimmune diseases have an organic explanation, such as grey matter involvement. Therefore, exclusion of primary CNS disorders is critical and there is a need for a change in diagnostic criteria and biomarkers in order to facilitate the differential diagnosis. An interesting and unusual clinical report was presented of a patient with aortitis and systemic manifestations,

where all the exhaustive studies were negative. The patient vomited, yielding some *Ascaris*; all the clinical manifestations resolved with administration of albendazol.

Christopher Denton and Gerry Coghlan (London, UK) discussed new findings in pulmonary hypertension (PAH), stating that this clinical manifestation is common and complex in systemic sclerosis, but a treatable vasculopathy in most cases, with outcome-based studies confirming the value of treatment. Prognosis is similar to idiopathic PAH if optimally managed. The prevalence of PAH in SLE is much lower (around 1%), with excellent control of the disease appearing to be the key to its management. Non-invasive testing can be used to screen patients with connective tissue diseases at risk of PAH, but these tests miss some patients who subsequently develop this complication. The lecturers presented the DETECT score, which reduces this risk by suggesting right heart catheterization in some of these patients.

At the first session of the afternoon, Marcos Gattorno (Genoa, Italy) spoke on how not to miss an autoinflammatory disease, describing this disorder as “experiments in nature” that increase our understanding of the mechanisms regulating the inflammation. The study of cryopyrin-associated periodic syndromes (CAPS) shed light on the function of NLRP3-inflammasome (which may be considered the paradigm), and that other monogenic diseases might be the approach to identify novel pathways of activation of inflammation. Interferonopathies were presented as the new frontier of study, and diseases related to proteasome deficiency were stressed for their lack of response to IL-1 blockade.

The subject of the next roundtable was antiphospholipid syndrome (APS) and pregnancy, discussed by Maria José Sousa (Lisbon, Portugal), Angela Tincani (Brescia, Italy) and Jaume Alíjotas (Barcelona, Spain). Seronegative APS (SNAPS) was addressed in clinical cases without the presence of antiphospholipid antibodies (aPL). In some cases, we see positivity to anti-phosphatidylethanolamine antibodies (aPE), anti-acid phosphatidic antibodies (aPI), anti-phosphatidylserine antibodies (aPS) and antivimentin/cardioliipin antibodies. In the field of obstetric APS, the speakers directed the focus at various unclear and controversial situations, not unusual in these women. There is a need to focus on this group of “aPL carriers” in order to protect maternal and fetal health. The “syndrome of obstetric morbidity associated with APS” (OMAPS) was defined, comprising women presenting a clinical obstetric/biologic picture resembling that of fulfilled full-blown Sydney criteria, but with incomplete criteria. This definition includes women with laboratory criteria and histories such as two early miscarriages, three or more non-consecutive miscarriages, late-onset or puerperal preeclampsia, fetal growth restriction

at term, premature birth at 34–37 weeks gestation, placental hematoma, abruptio, recurrent implantation failure, and premature rupture of membranes.

David Isenberg (London, UK) lectured on the latest developments in clinical assessment of SLE. In the past 25 years reliable and validated activity indices to assess SLE patients have been developed, the principle indices now in use being the British Isles Lupus Assessment Group (BILAG) Index and the SLE Disease Activity Index (SLEDAI). Other available instruments include the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC-ACR) Damage index and the SLE Quality of Life (QOL) Questionnaire. Attempts are being made to establish more lupus-specific quality of life indices.

The day ended with Carlo Perricone (Rome, Italy) guiding the audience through the genetics of SLE through examples, such as the increased genetic predisposition to infection in these patients. The production of autoantibodies is genetically determined and environmentally triggered, and it is the combination of these various factors that determine the disease onset and clinical manifestations. Dr. Perricone concluded with the intriguing comment: “in autoimmunity everything is a combo of bad luck, genes and infections.”

FEBRUARY 14, THE LAST DAY

The topics included the Expanding spectrum of IgG4-related disease (presented by David D’Cruz), and New biologics in lupus (by Anisur Rahman from London). Autoinflammatory diseases – clinical management, old and new treatment, and some aspects of autoinflammation were presented at a roundtable by José Hernandez-Rodriguez and Juan Arostégui (Barcelona) and Alessandra Soriano (Rome), chaired by Ricard Cervera and Jordi Yague (Barcelona). The subject of the last lecture was Management of cardiovascular risks in SLE, by Ian Bruce (London).

Next year the 14th Medinterna Meeting on Autoimmune Diseases will be held at Fundação Cupertino de Miranda, Porto, on 4–6 February. An exciting scientific program is being prepared and an excellent group of international and national speakers will present their most recent and controversial work. Immunologists, rheumatologists, internists and lab specialists are invited to attend the meeting and visit the UNESCO Heritage City of Porto.

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“Art is not a pastime but a priesthood”

Jean Cocteau (1889-1963), French writer, designer, playwright, artist and filmmaker