

11th Medinterna International Meeting: What Did We Learn?

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The Medinterna International Meeting took place in Porto, Portugal, on 6–9 February 2013. This annual conference is organized by the Medinterna Association and sponsored by São João Hospital Centre. Different topics in Autoimmunity were discussed over the four days. The first day of the meeting, February 6, was dedicated to arthritis, specifically rheumatoid arthritis cardiovascular risk factors in RA, and the relationship between bone, cartilage and osteoporosis.

WHAT DID WE LEARN ON FEBRUARY 7?

Vasculitis was the topic of the day. M. Eric Gershwin (Davis, USA) began with a lecture on the relationship between environment and autoimmunity. The importance of this association and the balance between genetic and environmental factors in the

development of autoimmune diseases were demonstrated by the example of primary biliary cirrhosis. The already known increased risk in first-degree relatives of PBC patients and the high concordance in monozygotic compared to dizygotic twins associated with bacteria, viruses, xenobiotics or chemical compounds (e.g., drugs like acetaminophen) have the potential to modify host proteins to render them more immunogenic. Chemical xenobiotic modification of the lipoyl domain of the E2 component of pyruvate dehydrogenase complexes is sufficient to break self-tolerance, allowing the production of pathognomonic anti-mitochondrial autoantibodies.

Elizabeth Jury (London, UK) spoke of the importance of regulatory B cells in autoimmunity and the interaction between these cells and invariant natural killer T cells. Systemic lupus erythematosus iNKT

cells are numerically and functionally impaired because of a decreased expression of CD1d on immature B cells. This abnormal interaction was reversed in patients responding to rituximab treatment.

Yehuda Shoenfeld (Tel Aviv, Israel), in his talk on vaccination and autoimmune diseases, summarized the most consistent associations between infecting agents and autoimmune diseases [Table 1]. As we know, several infections can induce the production of autoantibodies. He demonstrated that the burden of Epstein-Barr virus in peripheral blood mononuclear cells was more than 15-fold greater in SLE patients than in healthy control individuals; that high levels of anti-*Saccharomyces cerevisiae* (produced after exposure to alcoholic beverages, rice, vaccine adjuvant) were found in 57.5% of patients with active SLE vs. 8.5% of healthy controls; that *Helicobacter pylori* eradication raised the platelet count in idiopathic thrombocytopenic purpura; and that malaria infections may exert a protective effect against autoimmune nephritis in SLE. Finally, vaccination with phosphorylcholine compounds was discussed as a future therapy for prophylaxis of autoimmune diseases.

In the first roundtable discussion of the day, on systemic vasculitis, Cees Kallenberg (Groningen, The Netherlands) presented identifying risk and predictive factors in ANCA-associated vasculitis. Silica, some drugs such as propylthiouracil, and *Staphylococcus aureus* nasal carriage were identified as risk factors, while PR3 and persistence of ANCA after induction were con-

RA = rheumatoid arthritis

PBC = primary biliary cirrhosis
iNKT = invariant natural killer T

Table 1. Most consistent associations between infecting agents and autoimmune diseases

1. Epstein-Barr virus (MS, SLE, RA, Sjögren's syndrome)
2. Cytomegalovirus (SLE, atherosclerosis, diabetes mellitus, systemic sclerosis, IBD)
3. *Helicobacter pylori* (ITP, SSC, Crohn's disease, GBS)
4. *Chlamydia pneumoniae* (atherosclerosis, MS)
5. Parvovirus B19 (SSc?)
6. *Escherichia coli* (RA)
7. *Proteus mirabilis* (RA)
8. *Yersinia enterocolitica* (IBD)
9. *Campylobacter jejuni* (GBS)

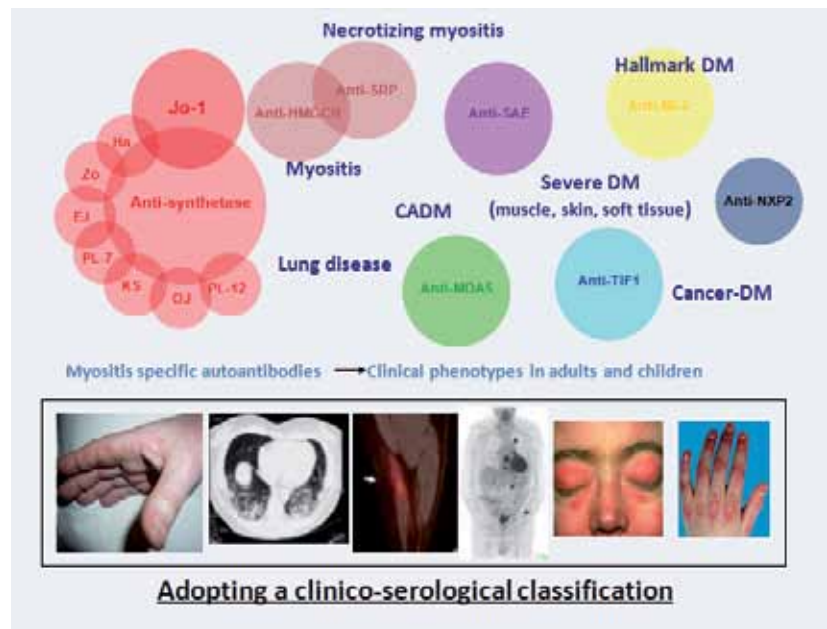
MS = multiple sclerosis, SLE = systemic lupus erythematosus, RA = rheumatoid arthritis, IBD = inflammatory bowel disease, ITP = idiopathic thrombocytopenic purpura, SSC = systemic sclerosis, GBS = Guillain-Barre syndrome

SLE = systemic lupus erythematosus

sidered predictive factors for relapsing disease. The new classification of vasculitis was also discussed. Lisa Willcocks (Cambridge, UK) presented a brief review on vasculitis treatment (current and new therapies). For induction, intravenous pulse cyclophosphamide was shown to induce remission, as did a daily oral regimen with fewer side effects; for maintenance, azathioprine was shown to be superior to mycophenolate mofetil. Rituximab treatment in vasculitis (RITUXIVAS and RAVE) was also effective as an alternative to cyclophosphamide mainly in refractory disease. Remission was achieved in a higher percentage when rituximab was administered every 6 months for 2 years. Jan Willem Tervaert (Maastricht, The Netherlands) spoke about vasculitis complications, particularly increased cardiovascular risk. Accelerated atherosclerosis in large vessel vasculitis is well documented, and it was found that the criteria for metabolic syndrome in small vessel vasculitis were met by a higher number of patients compared to healthy controls. These findings could be associated with therapy (steroids in high doses – prednisolone or equivalent > 7.5 mg/day; B cell depletion) and high myeloperoxidase levels. In large vessel vasculitis, preventive treatment with low dose aspirin was encouraged and it was demonstrated that the use of statins will likely be effective in reducing cardiovascular risk. The need for randomized control trials was reinforced.

The subject of the second roundtable discussion was idiopathic inflammatory myopathies. Ingrid Lundberg (Stockholm, Sweden) highlighted the importance of CD28^{null} T cell, Jo-1 and high mobility group chromosomal protein 1 in the inflammation of muscles. Some of them may be potential targets for therapy. Hasha Gunawardena (Bristol, UK) spoke of the clinical relevance of and differences between the specific and non-specific autoantibodies in idiopathic inflammatory myopathies [Figure 1]. Finally, Jiri Vencovsky (Prague, Czech Republic) reviewed current treatments. Glucocorticoids remain the first choice (1 mg/kg/day); if effective, start a gradual reduction after 4 weeks, if not,

Figure 1. Autoantibodies in idiopathic inflammatory myopathies



DM = diabetes mellitus

check the diagnosis and add immunosuppressive drugs (methotrexate or azathioprine). In refractory disease rituximab may be effective, intravenous immunoglobulin has mixed results, and anti-tumor necrosis factor therapy is not recommended.

In the roundtable on hepatobiliary and pancreatic autoimmune disorders, Diego Vergani (London, UK) led a discussion on the basic science of autoimmune hepatitis. Susana Lopes (Porto, Portugal) showed that hepatobiliary involvement in inflammatory bowel disease (more commonly primary sclerosing cholangitis and autoimmune hepatitis) do not correlate with disease activity. It was also reinforced that some drugs used in their treatment (e.g., anti-TNF α agents) could induce autoimmune hepatitis. Pedro Pereira (Porto, Portugal) distinguished between the two subtypes of autoimmune pancreatitis and reviewed the HISORT criteria and the therapeutic options in these diseases. Steroids are the main therapy, with azathioprine and rituximab being used in refractory disease (20%–40%).

TNF α = tumor necrosis factor-alpha

After Ducla Soares (Lisbon, Portugal) lectured on the interaction between the autonomic nervous system and autoimmunity, David D’Cruz (London, UK) presented a review on relapsing polycondritis. The diagnosis of this disease requires two major criteria (auricular chondritis, nasal chondritis, laryngotracheal chondritis) or one major plus two minor criteria (ocular symptoms, hearing loss, vertigo, seronegative polyarthritits). The first clinical assessment is based on an otolaryngological, ophthalmological, cardiovascular and pulmonary evaluation (pulmonary function tests and dynamic inspiratory/expiratory computed tomography examination). Since no randomized control trials have been published, it was proposed that non-steroidal anti-inflammatory drugs, colchicine, dapsone, inhaled or topical steroids be used for mild disease; that steroids and immunosuppressive drugs (rituximab, azathioprine, mycophenolate mofetil, cyclosporin) be used for moderate disease; and intravenous methylprednisolone, intravenous cyclophosphamide, IVIG and plasma exchange for severe disease (life-threatening).

IVIG = intravenous immunoglobulin

The day finished with a very interesting case report presented by Marco Alba and Gerard Espinosa (Barcelona, Spain) describing mixed cryoglobulinemia. Conventional immunosuppressive therapy was used without response. A small B cell clone was later identified allowing the experimental and successful use of bortezomib.

WHAT DID WE LEARN ON FEBRUARY 8?

Srini Kaveri took us on a time travel through the history of IVIG. He described the many theories developed over the years to explain the mechanism of IVIG, from the Fc receptor blockade in the 1980s, to the idiotyp theory, the cytokine network in the 1990s and the Th1/Th2 balance theory in the late 1990s. Subsequent papers theorized that IVIG also could influence dendritic cells and T regulatory cells. Although much has been written, there is still much to discover about IVIG.

Jan Damoiseaux and Jan Tervaet (Maastricht) talked about cryoglobulinemia, reminding us that this possible diagnosis should always be suspected and that it is mostly associated with hepatitis C virus infection, although there are exceptions. We also learned that while corticosteroids are the main treatment, there are promising results with rituximab and interleukin-2.

The scientific program moved on with Athol Wells (London, UK) who spoke about lung involvement in systemic sclerosis. Since this is the most common cause of death in this condition, severity staging is crucial, although there are as yet no perfect tools. When assessing a patient and when in doubt as to the severity of the disease, one should treat vigorously using immunosuppression to prevent progression.

Luc Mouthon (Paris, France) spoke of scleroderma renal crisis, which is associated with high mortality. It is mainly a clinical diagnosis, so a renal biopsy is not mandatory. He spoke of the role of corticosteroids in inducing this condition and that the prior use of angiotensin-converting enzyme inhibitors may be associated with higher mortality in patients who actually

develop SRC. The search for new therapeutic targets continues. Recent papers indicate that endothelin 1 may be an answer as it was found to be overexpressed in glomeruli and arterioles in SRC.

Maria José Leandro (London, UK) then discussed IL-6 inhibition as a treatment for rheumatoid arthritis. Tocilizumab is indicated when there is inadequate response or intolerance to disease-modifying anti-rheumatic drugs or TNF antagonists. It can be used in both monotherapy and combination therapy. Studies have also shown tocilizumab to be more effective than adalimumab monotherapy. This IL-6 inhibitor has been shown to arrest progression of structural damage and improve quality of life after 24 weeks of treatment.

Gerry Coghlan (London) spoke about pulmonary hypertension in systemic sclerosis, reporting that survival has improved but that pulmonary arterial hypertension must be recognized in our patients. Newer and more sensitive tools are emerging to improve the diagnosis.

The next subject was vaccination, with David Fedson (SergyHaut, France) speaking on anti-pneumococcal vaccination and its vital role in reducing pneumococcal invasive disease. Pneumococcal disease is still an important health problem for older adults and the vaccine has proven to be clinically and cost-effective in reducing severity and rate. It has been shown that the antibody response to polysaccharide pneumococcal vaccination, protecting against invasive disease, may last up to 10 years. Much work has still to be done but one must “celebrate the extraordinary progress that has already been made in the control of pneumococcal infection with vaccination.”

Saraiva da Cunha (Coimbra, Portugal) spoke about herpes zoster infection, a frequent infection in older adults, with post-herpetic neuralgia as its most common complication. The herpes zoster vaccine is now used to reduce severity of disease and occurrence of post-herpetic neural-

gia and is recommended for people over age 50 years. Many questions have still to be answered with regard to the optimal timing for vaccination or the duration of the antibody response, but some vaccination protocols for rheumatoid arthritis and inflammatory bowel disease already mention this option. It is hoped that it will be recommended for other autoimmune diseases.

The day went on with Dr. Isabel Almeida and Dr. Ivone Silva (both from Porto) demonstrating the burden of digital ulcers in scleroderma that lead to a high degree of disability and high risk of recurrence. It was also claimed that effective prevention is the best treatment and that lifestyle modifications as well as pharmacological treatment are essential.

Carmen Siméon, from Barcelona, then spoke of the need for pre-scleroderma classification criteria as a way to increase early diagnosis. A high degree of suspicion is necessary when a patient presents with Raynaud phenomenon, puffy fingers and antinuclear antibody – “red flags” for early scleroderma. Dr. Siméon also spoke of the importance of a thorough patient screening program in order to diagnose internal organ involvement early. Therefore, all patients with suspected early scleroderma must complete an esophageal manometry, echocardiogram and lung function tests.

The theme of systemic sclerosis continued with Carles Tolosa Vilella (also from Barcelona) who reviewed the therapeutic tools available. For the cutaneous lesions, recent studies have shown that MMF and rituximab are promising. As for interstitial lung disease, the progression and severity of the illness must dictate therapeutic choice – thus, in induction therapy, cyclophosphamide may be used in severe disease and MMF in moderate disease; maintenance therapy may use MMF or azathioprine and in refractory therapy rituximab can be used. In digestive disease only symptomatic treatment should be given, such as proton pump inhibitors or prokinetics.

SRC = scleroderma renal crisis
IL = interleukin

MMF = mycophenolate mophetil

A patient with Raynaud phenomenon and/or digital ulcers may use calcium channel blockers, prostacyclins, endothelin inhibitors and phosphodiesterase inhibitors, as well as undertaking lifestyle modifications and preventive measures. In pulmonary hypertension immunosuppressants are usually not required, patients being treated with calcium channel blockers if vasoreactivity is present, or prostacyclins, endothelin inhibitors and phosphodiesterase inhibitors if there is no vasoreactivity. In scleroderma renal crisis, angiotensin-converting enzyme inhibitors should be titrated and, if needed, calcium channel blockers or

alpha-blockers added. In extremis, dialysis must be initiated.

Carlos Selmi (Milan, Italy) ended the day with a session on Epigenetics in Autoimmunity. He demonstrated that DNA methylation determines gene expression and that such methylation is affected by environmental factors. His work on monozygotic twins thus showed that these twins are discordant in the frequency of autoimmune diseases, which may be attributed to differences in DNA methylation in several genes. The fact that certain autoimmune diseases have a geographical distribution also shows that the environment can affect gene expression.

Finally, on February 9, the last day of the meeting, we heard several lectures dedicated to antiphospholipid syndrome. In particular, the problems related to pregnancy and APS (by Monika Ostensen), the mechanisms of thrombosis in APS (Anisur Rahman), and the difficulties diagnosing seronegative APS (Roger Lévy, from Brazil).

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APS = antiphospholipid syndrome

Capsule

Detecting and targeting tumor relapse by its resistance to innate effectors at early recurrence

Tumor recurrence represents a major clinical challenge. Kottke et al. show that emergent recurrent tumors acquire a phenotype radically different from that of their originating primary tumors. This phenotype allows them to evade a host-derived innate immune response elicited by the progression from minimal residual disease (MRD) to actively growing recurrence. Screening for this innate response predicted accurately in which mice recurrence would occur. Premature induction of recurrence resensitized MRD to the primary therapy, suggesting a possible paradigm shift for clinical treatment of dormant

disease in which the current expectant approach is replaced with active attempts to uncover MRD before evolution of the escape phenotype is complete. By combining screening with second-line treatments targeting innate insensitivity, up to 100% of mice that would have otherwise relapsed were cured. These data may open new avenues for early detection and appropriately timed, highly targeted treatment of tumor recurrence irrespective of tumor type or frontline treatment.

Nature Med 2013; 19: 1625

Eitan Israeli

Capsule

Distinct fibroblast lineages determine dermal architecture in skin development and repair

Fibroblasts are the major mesenchymal cell type in connective tissue and deposit the collagen and elastic fibers of the extracellular matrix (ECM). Even within a single tissue, fibroblasts exhibit considerable functional diversity, but it is not known whether this reflects the existence of a differentiation hierarchy or is a response to different environmental factors. Using transplantation assays and lineage tracing in mice, Driskell and co-researchers show that the fibroblasts of skin connective tissue arise from two distinct lineages. One forms the upper dermis, including the dermal papilla that regulates hair growth and the arrector pili muscle, which controls piloerection. The other forms the lower dermis, including the reticular fibroblasts that synthesize the bulk of the fibrillar ECM,

and the pre-adipocytes and adipocytes of the hypodermis. The upper lineage is required for hair follicle formation. In wounded adult skin, the initial wave of dermal repair is mediated by the lower lineage and upper dermal fibroblasts are recruited only during re-epithelialization. Epidermal β -catenin activation stimulates the expansion of the upper dermal lineage, rendering wounds permissive for hair follicle formation. These findings explain why wounding is linked to formation of ECM-rich scar tissue that lacks hair follicles. They also form a platform for discovering fibroblast lineages in other tissues and for examining fibroblast changes in aging and disease.

Nature 2013; 504: 277

Eitan Israeli

“What I like in a good author isn’t what he says, but what he whispers”

Logan Pearsall Smith (1865-1946), American-born British essayist and critic