3rd CENTRAL EUROPEAN CONGRESS OF RHEUMATOLOGY

Second Announcement and Call for Papers

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Rheumatology highlights — Rheumatoid arthritis — Therapy of rheumatoid arthritis

WHAT BRINGS EULAR TO RHEUMATOLOGY ?

T.L. Vischer
Division de Rhumatologie
University Hospital, Geneva

EULAR, an umbrella organisation incorporating national rheumatological societies, social leagues with patient organisations and allied health professionals interested and working in the field of Rheumatology, is representing rheumatology in Europe and in ILAR. For many persons, it is still a remote organisation, with elderly statesmen uttering wise words. Europe has changed these last years and so has EULAR. Its role is to stimulate research, to improve the training of both professionals working in rheumatology and patients, define standards in all fields of rheumatology and to lobby. I will explain how EULAR is working and how you can participate in its activities.

Gender and Autoimmunity: Insights into Pathogenesis. Robert G. Lahita M.D., Ph.D., New York Medical College, Saint Vincent's hospital.

Most of the autoimmune diseases are common to women. In fact, the disease systemic lupus erythematosus (SLE) affects women some ten to fifteen times more frequently than it affects men. The reasons for the high female prevalence of autoimmune diseases remain unknown. We have tried to explain the differences in several ways. First, there are metabolic changes related to both estrogen and androgen that are found in both men and women with lupus. Women with lupus have an increase in the oxidation of androgens at C-19 in contradistinction to men. This forms the basis for androgen replacement as therapy for autoimmune diseases like lupus. For example, both mice and humans with lupus have benefited from the use of dehydroepiandrosterone (DHEA). Estrogens are of particular importance to patients with autoimmune diseases and the direction of estrone hydroxylation is related to the extent of disease and possibly even cytokine profiles. Molecular studies of hormone action on immune cells such as lymphocytes and macrophages indicate that specific receptors exist in these cells. However, alterations of cell functions and numbers are not related to pathogenesis. Studies of essential cellular functions in the murine model would indicate that apoptosis is regulated in part by sex hormones. Moreover, enhanced apoptosis might be a mechanism whereby sex steroids influence functions as fundamental as antigen presentation. This might have some part in the overall pathogenesis of diseases like lupus, but it is clearly not the only operative mechanism. Human female gonadal pathology could be related to the above mentioned effects on apoptosis. Such changes such as ovarian cysts and endometriosis might be a reflection of hormone effects on specific cell populations within an organ system like the ovary.

THE ULTIMATE EVIDENCE FOR AUTOIMMUNITY IN ATHEROSCLEROSIS:
Adoptive Transfer of ß2 Glycoprotein I (ß2GPI)-Reactive Lymphocytes Enhances Atherosclerosis in LDL Receptor Deficient Mice

Jacob George*, Boris Gilburd*, Arnon Afek‡, Aviv Shaish§, Dror Harats§, Yehuda Shoenfeld*

*** Research Unit of Autoimmune diseases, Department of Medicine 'B', ‡. Institute of Pathology, §. Institute of Lipid and Atherosclerosis Research, Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Israel.**

***Background*: It has been proposed that autoimmune factors can influence the progression of atherosclerosis. We have previously shown that immunization of LDL-receptor deficient (LDL-RD mice) with ß2 glycoprotein I (ß2GPI); a principal target of 'autoimmune' anti-phospholipid antibodies) enhances early atherosclerosis. In the current study we tested the hypothesis that adoptive transfer of ß2GPI reactive T-cells can accelerate atherogenesis in LDL-RD mice.**

***Methods and results*: LDL-RD mice were immunized with human ß2GPI. An additional group of mice were immunized with ß2GPI and boosted with the same antigen 3 weeks later. Control mice with immunized with human serum albumin (HSA). Lymphocytes obtained from the draining lymph-node cells or from splenocytes of ß2GPI or HSA immunized mice were stimulated *in-vitro* with ß2GPI or with the mitogen Concavaline A, respectively. The cultured lymphocytes were transferred intraperitoneally to syngenic LDL-RD mice and fed for 5 weeks a high fat 'Western' diet until sacrifice. Mice injected with lymphocytes from draining lymph nodes or spleens of ß2GPI-immunized animals displayed larger atherosclerotic lesions as compared to those induced by control treated animals. T-cell depleted splenocytes from ß2GPI were unable to promote lesion formation in the mice. Lymphocytes that mediated lesion enhancement displayed a predominant T helper 1 phenotype evident by increased secretion of interferon-Gammaγ upon *in-vitro* priming with ß2GPI.**

***Conclusion*: This is the first direct evidence for a role of antigen (ß2GPI)-reactive T cells in promoting atherosclerotic lesions in mice.**

ANTIPHOSPHOLIPID SYNDROME: CURRENT CONCEPTS

Ricard Cervera. Systemic Autoimmune Diseases Unit, Hospital Clínic, Barcelona, Catalonia, Spain.

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses, often multiple, and recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, in the presence of antiphospholipid antibodies, namely lupus anticoagulant, anticardiolipin antibodies, or both. False-positive tests for syphilis may be present in some of these patients. Other autoantibodies have also been detected in many patients with an APS, such as anti-β2 glycoprotein I, antimitochondrial, antiendothelial cell, antiplatelet, antierythrocyte, and antinuclear antibodies.

The APS can be found in patients having neither clinical nor laboratory evidence of another definable condition (primary APS) or it may be associated with other diseases. Systemic lupus erythematosus is the disorder in which a secondary APS is most commonly associated.

Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations. Any combination of occlusive events may occur in the same individual and the time interval between them also varies considerably from weeks to months or even years. Rapid chronological occlusive events, occuring over days, have been termed the "catastrophic" APS.

Recently, attention has been focused on a group of other microangiopathic syndromes which have been described in patients with this syndrome. The predominant disturbance is on small vessels as opposed to large veins and arteries, which are mainly involved in the majority of patients with APS. These microangiopathic syndromes include, in addition to the "catastrophic" APS, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and HELLP syndrome.

FEVER: THE RESPONSE OF THE CENTRAL NERVOUS SYSTEM TO OXIDATIVE STRESS

Walter Riedel

Max-Planck-Institute for Physiological and Clinical Research, W.G. Kerckhoff-Institute, D-61231 Bad Nauheim, Germany

Fever is entirely an integrated response of the central nervous system and starts within minutes after bacterial endotoxin (LPS) enters the vascular space. The interaction of LPS with the cells of the reticulo-endothelial system induces formation of oxygen radicals, followed by release of cytokines which are considered as the putative endogenous pyrogens. Because neither exogenous nor endogenous pyrogens are able to cross the blood brain barrier, the true signal which is transmitted to structures inside the blood brain barrier to elicit fever is still uncertain. We found recently that pretreatment with methylene blue, which totally abolished oxygen radical formation following LPS, completely blocked the febrile response. These results suggested that the brain is able to sense oxidative stress and it became evident that vicinal thiol groups of the redox-modulatory site of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor-channel complex may function as the receptive structure. This is supported by the finding that systemic application of the disulfide reducing agents dithiothreitol (DTT) or of α-lipoic acid, which both penetrate the blood-brain barrier, induce within minutes dose-dependently the full pattern of heat loss responses associated with a fall of core temperature, indicating a lowering of the thermoregulatory setpoint. The immediately induced antipyresis following systemic application of DTT or α-lipoic acid, when given in the febrile state, supports this concept. Since pretreatment with N^G-nitro-L-arginine methyl ester augmented α-lipoic acid or DTT elicited heat loss effector responses, the results conform to the hypothesis that nitric oxide exerts physiologically a negative feedback on NMDA mediated activities, most likely by acting as an oxidant of redox-modulatory thiol groups of NMDA receptors. Since methylene blue also augmented the heat loss response to DTT and α-lipoic acid, we conclude that this drug prevented fever by preventing oxidation of the redox-modulatory site of the NMDA receptor. The redox state of thiol groups, especially of NMDA receptors, thus, seems to be essentially involved not only in fever generation, but apparently plays a key role also in normal thermoregulation.

PATHOGENESIS OF RHEUMATOID ARTHRITIS: IDENTIFYING NEW TARGETS IN THE CYTOKINE NETWORK

Wlodzimierz Maslinski
Department of Pathophysiology and Immunology
Institute of Rheumatology, Warsaw 02-637, Spartanska 1, Poland

Despite enormous research efforts, the cause of rheumatoid arthritis (RA) is still unknown. Existing theories, not always exclusive, link very early stages of the disease with activation of T-cells, or dendritic cells or B-cells, that via secreted cytokines activate many other cell types including monocytes/macrophages, synoviocytes type A and B, mast cells, granulocytes, platelets, endothelial cells, chondrocytes, osteoclasts, osteoblasts etc. These cells in turn release more pro- than anti-inflammatory cytokines and mediators of inflammation. For more than a decade it has been postulated that this unbalanced production of cytokines creates a self perpetuating network of proinflammatory cytokines that have been described to operate as a cascade. TNF-α and IL-1β, due to their place on the top of this cascade, have been identified as the main targets for immuno-intervention. Several years of tests in vitro, in vivo on animal models, and in the clinic, proved that indeed, manipulation with the cytokine network, even without knowing the cause of RA, is achievable and results in amelioration of many symptoms of this disease. Despite these encouraging results, especially in neutralization of TNF-α using either neutralizing Abs or soluble receptors or IL-1β (IL-1R antagonist), none of these treatments cured the disease. Therefore, it is likely that cytokines or factors other than TNF-α and IL-1β also participate in the induction/expansion of proinflammatory cytokine cascade. IL-15 has recently been identified as one of these candidates. It is present in high quantity in synovial fluids and serum of RA patients. Moreover, by showing that IL-15 triggers TNF-α production, this cytokine has been placed at or near the top of the cytokine cascade. In addition IL-15, but not TNF-α, induces production of proinflammatory cytokine IL-17 by memory T-cells present in synovium. Since high concentrations of IL-17 are present in RA synovial fluids, the latter finding stresses that T-cells are not mere bystanders unable to produce any cytokine (as other T-cell derived cytokines are hardly present in the joints) but actively participate in the pathogenesis of this disease. Based on these data two groups recently tested the effects of neutralization of IL-15 on collagen induced arthritis (CIA). Transient (using soluble IL-15R alpha chain) or permanent (using mutant IL-15 protein exerting IL-15R antagonistic effects) inhibition of incidence and severity of CIA observed in these experiments prove that IL-15 plays a key role in the induction of arthritis in this animal model. Inhibition of several immune/cytokine parameters including reduced number of infiltrating T-cells, decreased expression of TNF-α, IL-1β and IL-17 indicate that blocking biological effects of IL-15 may present another target for the treatment of RA.

Interfering with proliferation and secretion of proinflammatory cytokines by fibroblast-like synoviocytes (synoviocytes B) that were shown to invade and contribute to cartilage degradation, may represent another target for therapy. These goals have been successfully achieved in our laboratory using taurine chloramine, a physiologic factor generated in activated neutrophils from amino acid taurine by the myeloperoxidase-H_2O_2-chloride system. Whether this biologically active compound will exert its immunosuppressive activities in vivo, is currently tested on CIA model in mice.

Our recent findings that select isoforms of protein kinase C (PKC) are critical for signaling events leading to the production of proinflammatory cytokines in human monocytes, may add also these enzymes to the list of target molecules that should be tested in further studies.

In summary, in addition to the successful interference with the cytokine cascade by blocking TNF-α and IL-1β, studies of the interrelations between cytokines have identified several new targets for the treatment of RA. The experiments testing these targets are currently explored in animal models of RA and already resulted in better understanding of the cytokine network operating in this disease.

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EARLY RHEUMATOID ARTHRITIS (ERA); DIFFICULTY IN DIAGNOSIS

A.Filipowicz-Sosnowska, M. Przygodzka
Rheumatology Clinic, Institute of Rheumatology
Warsaw, Poland

The diagnosis of rheumatoid arthritis (RA) is based on ACR criteria, which are clinical, radiological and immunological. During the first month after onset the diagnosis is often difficult because of a frequent "atypical" presentation and a lack of radiological changes. Rheumatoid factor has low specificity and is often negative in ERA. The other non-rheumatological disorders (viral infection, neoplastic and endocrine diseases) may also in the early stage present with RA – like symptoms.

The objective of this study was to precise the preliminary diagnosis of ERA on the basis of clinical examination for successful treatment.

During the last two years (1998-99), 457 RA patients (according ACR criteria) were hospitalised in Rheumatology Clinic (Institute of Rheumatology Warsaw). In this group 56 (12%) patients were admitted with the preliminary diagnosis ERA. All patients in this group fulfilled the first four clinical ACR criteria. The duration of the disease was varied from 3 to 9 months (x - 6,7±1,7). All patients were carefully examined, according number of painful and swollen joints and their localisation, presence of RF and radiological erosions. In cases of doubtful RA diagnosis other needful examinations were done.

The diagnosis of ERA was established in 32 (57%), but in 24 (43%) ERA was excluded. ERA patients were predominantly women, symmetrical polyarthritis of the hands was presented in 30 (94%), RF in 18 (56%), radiological erosions were found in 5 (15%). In group of patients with excluded ERA the following diagnosis was established; osteoarthritis 9 (37%), RA-like (nonclassified) 7 (29%), reactive arthritis 2 (8%), hepatitis viral infection 2 (8%), neo 2 (8%), hypothyreosis 2 (8%). In this group of patients polyarthritis of the hand was frequently asymmetrical, RF was presented in 12% and no radiological erosions were found.

Conclusion: 1) The diagnosis of ERA should be established by specialists 2) ACR criteria are not sufficient in ERA 3) The appearance of symmetrical polyarthritis is more specific for ERA.

EXTRAARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

J.Lukáč, J. Rovenský, P.Poprac, Š. Kopecký
Research Institute of Rheumatic diseases, Piešťany, Slovakia

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovitis, joint erosions and extraarticular manifestations. Inflammatory process can involve multiple organ systems. About 10 % of the patients show an intractable rapidly progressive course associated with severe extraarticular manifestations. Survival od RA patients is shorter than expected. Systemic form of RA contributes to the increased mortality of RA patients directly and indirectly – by adding the immobility, infections, and drug side effects. Systemic symptoms of RA - rheumatoid nodules, serositis and vasculitis - are the most frequent extraarticular manifestations. RA patients with extraarticular manifestations have more often increased concentrations of IgA RF and higher percentage of CD4+CD45RO+T cells.

Rheumatoid nodules occured in about 20% of RA patients with positive rheumatoid factors, predominantly at the sites of local presure and trauma but internal nodules are predominantnly in pulmonary parenchym, pericardium and tendon sheats. In authopsy of heart, nodules occur in 10 % of specimens. Patients with nodules are significantly more likely to have vasculitis and more severe extraarticular disease, faster radiographic progression and a greater likehood of rheumatoid factor and antinuclear antibody production.

Rheumatoid vasculitis occurs in about 23 % of post mortem specimens, histopathologic findings are often similar to polyarteritis. There is a higher frequency of HLA-DRB1 alleles, particularly B1*0401 homozygotes in patients with rheumatoid vasculitis than other patients with RA. The most frequent is nail-fold microinfarcts, leg ulcers, digital gangrene and sensory neuropathy. Rheumatoid vasculitis is associated with high titers of rheumatoid factor, low serum complement, antinuclear antibodies, cryoglobulins and circulatory immune complexes. In RA patients with vasculitis, a higher frequency of the pANCA antibodies was found.

Rheumatoid serositis- pleuritis and pericarditis is rather common in clinicaly inaparent form. Pleural and pericardial involvement occurs in a 50 % of authopsy specimens of patients with RA.

Pulmonary involvement manifests as a pleurisy, parenchymal nodules, interstitial pneumopathy and airway disease. Rheumatoid pulmonary vasculitis is rare, rheumatoid lung disease occurs more frequently in men who have long-standing rheumatoid disease, positive rheumatoid factor and subcutaneous nodules.

Pleural involvement is the most common manifestation of lung disease in RA.

The clinical features and course of pulmonary fibrosis in RA are similar to these of idiopathic pulmonary fibrosis. Bronchiolitis obliterans organizing pneumonia has been describes in RA patients. The histological pattern correspond to proliferative bronchiolitis in the airway and organizing pneumonia in the alveoli.

Cardial involvement. Echocardiographic evidence of some valve involvement can be detected in about 30 % of patients with RA. Diffuse myocardial lesions and myocarditis, left ventricular diastolic dysfunction are uncommon anf often in clinicaly inaparent form.

Ocular involvement. The most frequent is keratoconjuctivitis sicca which occurs from

10 to 35 % of RA patients. Episcleritis correlates with RA activity. Scleritis is less common than episcleritis. It is associated with vasculitis and can progress to scleromalacia. Another forms of ocular involvement are uveitis, episcleral nodulosis and corneal ulcers.
Neurologic complications. Nerve compression syndromes can involve n. medianus, n. ulnaris, n. tibialis posterior. Cervical myelopathy is caused by atlantoaxial subluxation. Central nervous system involvement (CNS vasculitis manifestation by stroke, seizures), meningitis and dural and extradural rheumatoid nodules are rare.
Muscular invelvement The most frequent is secondary muscle atrophy, inflamantory myopathy is rare. In some cases polymyositis can be caused by D-penicilamine.
Renal involvement The most frequent is tubulointerstitial nephropathy combined etiology, but mild membraneous or mesangial glomerulonephritis, vasculitis and secondary amyloidosis can occur too. In some patients with RA and necrotizing glomerulonephritis, cANCA antibodies may occur as a kidney-limited form of rheumatoid vasculitis.
Hepatopathy is the most frequent in Felty's syndrome (65% of patients) but elevated liver enzymes may occur in active RA or as side effect of drug therapy.
Hematologic abnormalities Anemia in RA is multifactorial and its degree correlates with clinic activity. Thrombocytopenia and leucopenia is mostly related to Felty's syndrome. Thrombocytosis is associated with active RA.
Complications of RA are: amyloidosis, drug induced side effects, infections and secondary osteoporosis.
Extraarticular involvement is a serious symptom of RA that contributes to shortened survival of RA patients. There is important to recognize unfavorable clinical and prognostic factors, early stages and subclinical forms of extraarticular manifestations to introduce adequate therapy and prevent serious consequences of extraarticular manifestations.

RHEUMATOID ARTHRITIS - OUTCOME DIMENSIONS FROM IMPAIRMENT TO QUALITY OF LIFE

L. Hodinka

National Institute of Rheumatology and Physiotherapy, Budapest, Hungary

The outcome continuum in rheumatology covers domains of impairment, functional capacity, socioeconomic state and quality of life. There is a rich armamentarium of instruments measuring the different aspects of outcome in rheumatoid arthritis including generic and disease-specific questionnaires.These are listed and evaluated regarding their value in the clinical practice, drug trials and meta-analytic studies.

Results obtained from the Hungarian validation and cost-utility studies using the EuroQoL 5D and the RAQoL instruments are presented.It is concluded that these are suitable to measure and reflect the "burden of the disease" in rheumatoid arthritis patients.

ANALYSIS OF REASONS FOR TERMINATING DMARD THERAPY IN A COHORT OF 1200 PATIENTS WITH RA

K.Pavelka, A.Pavelková, Š. Forejtová, K.Bulíř, J.Rovenský*/, H. Tuchyňová*/,
Institute of Rheumatology Prague, Czech Republic, */Research Institute of Rheumatology Piešťany, Slovak Republic

Objective: Most of the data on efficacy and safety of DMARDs comes from short and middle-term studies or metaanalysis and also guidelines „how to treat RA" mostly cover the window of 1-2 years. To fulfil „black hole" in our knowledge, we have analysed the big cohort of patients with RA from the point of view of termination of the treatment with DMARDs in clinical practise.
Methodology: We have constructed questionnaire for analysis of interruption of either monotherapy or combination of DMARDs. The questionnaire was fulfilled by investigators using the official patients documentation in 22 centres in Czech and Slovak Republic.
Results: 1168 treatment episodes of DMARDs of 764 patients were analysed. The mean duration of treatment with 1 DMARD was 26,0 ± 41,7 months, ranging from 39,4 (cyclophosf.) to 9,2 (cyclosp.) months. The correlation of treatment duration with other variables (disease and patient related) was performed by regression summary variables. There was a high correlation of treatment duration to type of DMARD ($p<0,01$), education ($p=0,0096$), presence of extraarticular RA manifestations ($p=0,04$), but no correlation was found to age, sex, rheumatoid factor positivity and corticosteroid therapy.
Conclusion: The mean treatment duration with DMARD was longer than expected. The reasons for interruption of DMARD therapy are not influenced only by individual DMARDs but also by other factors. There are also considerable differences in DMARDs strategies between geographically different regions.

A HERBAL REMEDY, HYBEN VITAL REDUCES OSTEOARTHRITIC PAIN AND STIFFNESS IN A GROUP OF PATIENTS SUFFERING FROM SEVERE OSTEOARTHROSIS

O. WARHOLM, S. SKAAR, H.M. MØLMER, E. HEDMAN, L. ELK

Department of Orthopaedic Surgery, Vestfold Central Hospital, 3116 Tønsberg, Norway

Purpose: **Hyben Vital, a standardized powder produced from seeds and shells of Rosa Canina, has been reported to inhibit certain leukocyte functions of relevance to the cell injury seen in osteoarthrosis and rheumatoid arthritis. The aim of the present study, thereforee, was to test the impact of Hyben Vital on pain and stiffness of the hip and knee, in a large group of patients with osteoarthrosis.**
Methods: **One hundred patients, all with an X-ray verified dianosis of osteoarthrosis of the hip or knee, and all on the waiting list for hip or knee surgery, participated in a randomized, placebo-controlled, double-blind study. Fifty of the patients were given 5 Hyben Vital capsules twice daily for 4 months and the other 50 were given identical placebo capsuled in the same dosage for the saame time. Pain was assessed by the patient on a scale of 0—4 and stiffness of the hip or knee was estimated by measuring the degree of flexion on a scale during passive flexion (made by the investigator) and active voluntary flexion. Energy, quality of sleep and motivation for daily activities were recorded on a separate sheet.**
Results: **Pain in the group treated with Hyben Vital significantly declined as compared to placebo, $p<0.035$ (Mann—Whitney). In addition, stiffness estimated as the change in the degree of flexion of the hip, significantly declined. This was shown by an improvement in passive flexion of the hip of aproximately 4 degrees in the active treated group, as compared with less than 1 degree in the placebo group, $p<0.033$ (Mann—Whitney). A similar, significant change in favour of Hyben Vital was also observed after active flexion. Pain in the knee joint was also relieved by Hyben Vital, but flexion of the knee showed improvement on both theraples, with no significant changes between them.**
Conclusion: **The present data indicate that Hyben Vital, a standardized herbal remedy produced from Rosa Canina, reduces osteoarthritic pain in the hip and knee joint, when tested in a double-blind, placebo-controlled design. The patients also reported a statistically significant improvement in energy, motivation for their daily activities and sleep during active therapy.**