Wednesday May 10, 2000 Posters

THE MECHANISM OF TAURINE CHLORAMINE INHIBITION OF CYTOKINE (IL-6, IL-8) SYNTHESIS BY RHEUMATOID ARTHRITIS FIBROBLAST-LIKE SYNOVIOCYTES.

E. Kontny[1], K. Szczepańska[1], J. Kowalczewski[2], M. Kurowska[1], I. Janicka[1], J. Marcinkiewicz[3], and W. Maśliński[1]
[1]Department of Pathophysiology and Immunology, [2]Clinic of Orthopaedy, Institute of Rheumatology, Warsaw, Poland; [3]Department of Immunology, Jagiellonian University Medical College, Cracow, Poland

Objective. Proinflammatory cytokines play critical role in the pathogenesis of rheumatoid arthritis (RA). TNF-α and IL-1β, originated from monocytes, induce synthesis of IL-6 and IL-8 in fibroblast-like synoviocytes (FLS). Therapeutic approaches to damp this cytokine "cascade", although effective, do not cure the disease. Taurine chloramine (Tau-Cl), formed in activated neutrophils by chlorination of free amino acid taurine (Tau), was shown to possess some antiinflammatory properties. We found that Tau-Cl blocks production of IL-6 and IL-8 by FLS isolated from RA patients (Arthritis Rheum 1999;42 (12):2552). The aim of present study was to elucidate the mechanism of Tau-Cl action, via testing the effect of this compound on: *(i)* the transcription of genes encoding IL-6 and IL-8, and *(ii)* on the activity of NFκB and AP-1 transcription factors.

Methods. FLS, isolated from the synovial tissue of RA patients, and cultured in vitro for 3-6 passages, were stimulated with the recombinant human IL-1β (1 ng/ml) in the presence of either Tau or Tau-Cl, added simultaneously with the stimulus at 250 μM or 500 μM concentrations. The relative expression of IL-6 and IL-8 mRNAs was evaluated after 4 hours of stimulation, using competitive reverse transcriptase assisted polymerase chain reaction (RT-PCR). The DNA-binding activity of NFκB and AP-1 was examined 30 min or 2 hours after cell stimulation, respectively, using electromobility gel-shift assay (EMSA).

Results. IL-1β triggered significant raise of the activity of transcription factors (NFκB and AP-1), followed by the elevation of cytokine (IL-6 and IL-8) mRNAs expression. Tau-Cl, but not Tau, reduced IL-1β-triggered cytokine mRNAs expression. This compound inhibited more potently the expression of IL-6 than IL-8 mRNA. Importantly, Tau-Cl diminished also the activity of NFκB, and to a lesser extent the activity of AP-1 transcription factor.

Conclusion. We report that Tau-Cl inhibition of IL-6 and IL-8 synthesis by FLS of RA patients results from the ability of this compound to reduce the activity of major transcription factors (NFκB, and AP-1) and consequent inhibition of transcription of these cytokine genes.

TAURINE CHLORAMINE AFFECTS PROLIFERATION OF RHEUMATOID ARTHRITIS FIBROBLAST-LIKE SYNOVIOCYTES.

E. Kontny[1], J. Kowalczewski[2], I. Janicka[1], M. Kurowska[1], J. Marcinkiewicz[3], and W. Maśliński[1]
[1]Department of Pathophysiology and Immunology, [2]Clinic of Orthopaedy, Institute of Rheumatology, Warsaw, Poland; [3]Department of Immunology, Jagiellonian University Medical College, Cracow, Poland

Objective. Hyperplasia of the synovial lining cell layer and damage to articular cartilage are major consequences of rheumatoid arthritis (RA). The activation and proliferation of fibroblast-like synoviocytes (FLS) contribute to pannus formation, production of pro-inflammatory cytokines and tissue degrading enzymes which, acting in concert, lead to joint destruction. Proliferation of FLS is supported by growth factors (e.g. platelet-derived growth factor, PDGF) present in the inflamed joints. Therapeutic approaches to inhibit an excessive growth of these cells are not satisfactory. The aim of present study was to investigate the effect of a dominant free amino acid, taurine (Tau), or its chlorinated derivative formed in activated neutrophils, taurine-chloramine (Tau-Cl) on PDGF-triggered proliferation of cultured FLS isolated from RA patients.

Methods. FLS, isolated from the synovial tissue of 11 RA patients, and cultured in vitro for 3-6 passages, were stimulated for 72 hours with the recombinant human PDGF (10 ng/ml). Tau, or Tau-Cl, were added at 125 μM-500 μM concentrations, either simultaneously, before or after the stimulus. Proliferation of the cells was determined by an assessment of DNA synthesis in FLS, based on the incorporation of ^{3}H-thymidine (2 μCi/ml)

Results. The rate of spontaneous proliferation of FLS was low (mean ± SEM 1614 ± 490 cpm), while PDGF increased it significantly (10,002 ± 1834 cpm; P=0.0001). Tau-Cl, but not Tau, inhibited proliferation of FLS in a dose-dependent manner. Both spontaneous and PDGF-triggered response was reduced by ≈ 70% in the presence of 250 μM, and it was almost completely blocked (by >90%) in the presence of 500 μM concentration of Tau-Cl, when this compound was added simultaneously with PDGF. Tau-Cl exerted similar inhibitory effect on the cells, which were either *(i)* once stimulated, or *(ii)* precultured and subsequently restimulated with PDGF. In contrast, pretreatment of FLS with Tau-Cl for 24 hours before stimulation was less effective.

Conclusion. We report that Tau-Cl, a physiologic factor originated from activated neutrophils, successfully blocks proliferation of RA FLS. We also suggest that Tau-Cl might affect the early signaling event(s) that trigger cell proliferation (e.g. expression of proteins regulating cell-cycle progression).

SERUM IFN-γ AND TNF-α IN HISTOLOGICAL VARIANTS OF RHEUMATOID ARTHRITIS

Piotr A. Klimiuk[1], Stanislaw Sierakowski[1], Robert Latosiewicz[2], Bohdan Cylwik[3], Jan Skowronski[2].
[1]Department of Rheumatology and Internal Diseases; [2]Department of Orthopedic Surgery; [3]Department of Pathology, Medical University of Bialystok, Bialystok, Poland

Histological heterogeneity of rheumatoid arthritis (RA) was reported to correlate with synovium cytokine transcription. The aim of present study was to determine whether serum concentrations of interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) are predictive of the morphological appearance of the disease. Tissue and serum samples were obtained from 25 patients with active RA and 25 with osteoarthritis (OA).

Histological analysis distinguished two types of rheumatoid synovitis among synovial specimens. In 16 samples diffuse lymphocyte infiltrates without any additional microanatomical organization were found. Lymphocytic aggregates with germinal center-like structure formation characterized remaining 9 biopsies. Serum concentrations of IFN-γ and TNF-α were measured using ELISA method.

Both histological types of RA synovitis shown unique serum cytokine profiles. IFN-γ was found in lower concentration in serum of RA patients as compared with OA patients, served as a control group (p=0.002). The lowest serum levels of IFN-γ characterized follicular synovitis in comparison with diffuse (p=0.049). Different pattern was observed in the case of TNF-α. Serum of RA patients demonstrated high concentrations of this cytokine in comparison with OA patients (p=0.001). TNF-α was a dominant serum cytokine among RA patients with follicular synovitis (p=0.010), compared to those with diffuse. Serum profile of analyzed cytokines could clearly identify patients with two different histological types of rheumatoid synovitis and with OA. The analysis of clinical data suggests that the activity of the rheumatoid disease among patients with follicular synovitis was more severe than in those with diffuse infiltrates.

The correlation between distinct histological appearance of rheumatoid synovitis with specific serum cytokine profile and diverse clinical activity of disease seems to confirm its heterogeneity. It also suggests the possibility of patient's varied responses to treatment regiments.

ON HISTOMORPHOLOGICAL VARIATION OF RHEUMATOID SYNOVITIS

Piotr A. Klimiuk[1,4], Jörg J. Goronzy[1], Johannes Björnsson[2], Robert D. Beckenbaugh[3], Cornelia M. Weyand[1]
[1]Division of Rheumatology, Departments of Medicine; [2]Laboratory Medicine and Pathology; and [3]Orthopedic Surgery, Mayo Clinic and Foundation, Rochester, Minnesota, USA; [4]Department of Rheumatology and Internal Diseases, Medical University of Bialystok, Bialystok, Poland.

Rheumatoid arthritis (RA) is a chronic inflammatory disease with tissue destructive potential. Tissue infiltrates are composed of T cells, macrophages and B cells which acquire defined organizations in the synovial membrane. Mechanisms controlling the topographical arrangement of the synovial lesions are not known, nor is it understood how distinct types of synovitis differ in their functional and pathological properties.

To address these questions, synovial tissue from 21 consecutive patients with active RA was collected. In 7 of these tissues, typical follicular structures resembling germinal centers were identified. In four tissues, granuloma formation was detected. The remaining 10 tissues lacked a defined spatial organization but were characterized by a diffuse infiltrate. Tissue extracts from all 21 samples were analyzed for the expression of T cell and macrophage derived cytokine mRNA by semiquantitative RT-PCR.

Granulomatous synovitis was correlated with high concentrations of IFN-γ and IL-4 specific transcripts. Macrophage activation was indicated by high amounts of IL-1β mRNA but IL-10 was distinctly low. A different profile of tissue cytokines emerged for specimens with germinal centers. IFN-γ was present in high and IL-1β in intermediate concentrations. Characteristically, IL-4 mRNA was virtually absent but IL-10 transcription was high. Diffuse synovitis was associated with low levels of IFN-γ, IL-4, IL-1β and IL-10 mRNA synthesis.

We conclude that the phenotypic heterogeneity of RA correlates with unique patterns of T cell and macrophage derived cytokines and the formation of anatomical structures in the synovial tissue. Distinct cellular compositions and cell-cell interactions are operational in rheumatoid synovitis suggesting that multiple pathomechanisms can determine the synovial inflammation.

ANTIKERATIN ANTIBODIES – DIAGNOSTIC MARKER AND PROGNOSTIC FACTOR

Wagner E., Strasser R., Fabian B.*, Lapin A.°, Temml C.°, Dunky A., Feyertag J., Bayer PM.*
5th Internal Department, Wilhelminenspital, A-1171 Vienna;
Central Laboratory, Wilhelminenspital, A-1171 Vienna;
° Health Screening Program, City of Vienna, Austria

Introduction: Serum IgG antibodies that label the stratum corneum of rat esophagus epithelium (antikeratin bodies, AKA) are reported to be the most specific serologic criterion for the diagnosis of rheumatoid arthritis (RA). It is presumed that their presence is associated with a worse prognosis. The goal of this study was to evaluate the diagnostic sensitivity and specificity in a large population including health controls, and to determine the value of AKA as a prognostic factor in RA.
Patients and methods: Outpatients consulting a Rheumatologic Outpatient Clinic (80 with seropositve RA, 23 with seronegative RA, 194 with miscellanous rheumatic diseases) and a group of healthy controls (n=203), were screened for antikeratin antibodies using indirect immunofluorescence. To evaluate AKA as an independent prognostic factor we compared the results of the Health Assessment Questionnaire (HAQ-score) at the time of blood sampling between AKA positive and AKA negative RA-patients.
Results: The overall diagnostic sensitivity of AKA was 40 %, specificity 93 % including healthy controls and patients with rheumatologic diseases other than RA for comparison. The sensitivity of AKA in seronegative RA-patients was 13 %. 3 of 7 patients with early undifferentiated arthritis could be classified correctly by the presence of AKA (confirmed by follow-up).
The mean HAQ-score in patients with AKA positive RA was 1.21 versus 0.87 in AKA negative RA. Both groups had a comparable disease duration. In the unpaired t-test the difference in mean HAQ was not statistically significant (p=0.21).
Conclusions: The results of our investigation show high specificity of AKA in RA. They possess a high diagnostic value in seronegative cases, especially in early arthritis. The value of AKA as a prognostic factor is not established, as there was only a trend towards worse outcome in AKA positives.

SOLUBLE CD44 VARIANT ISOFORM v5 (sCD44v5) IN PATIENTS WITHRHEUMATOID ARTHRITIS (RA) UNDERGOING METHOTREXAT TREATMENT (MTXT)

Fevertag J, Haberhauer G, Kittl EM*), Skoumal M, Bauer K*), Dunky A

Fifth Department of Internal Medicine (Rheumatology), Wilhelminen-Hospital Vienna, Austria, Montleartstr. 37, A-1171 Wien.
*) Central-Laboratory, Danube-Hospital, Vienna, Austria, Langobardenstr.122, A-1220 Wien.

Objective: sCD44v5 has been described in patients with erosive, IgM rheumatoid factor positive RA and in patients with longstanding psoriatic arthtitis. It has been proposed to be an easily available serum assay to follow immun activation in the clinical course of disease.
Methods: Serum levels of sCD44v5 were measured in 21 patients with RA (Steinbrocker stages II-IV, duration of disease >2 years) undergoing MTXT . Follow up measurements of sCD44v5, additionally to routine laboratory monitoring and clinical assessment of the disease status (28-swollen joint count,SJC) were performed after 6 months. Commercially available ELISA-tests, developed by Bender-MedSystems-Vienna were used. The ELISA-tests were performed according to the manufacturers instructions. According to MTXT the patients were devided into two groups: (A) 14 patients with preexisting and follow up MTXT, (B) 7 patients with initiation of MTXT after the first measurement.
Results: In group (A) patients' clinical parameters (SJC: 3,4 and 4,5) and sCD44v5 levels (61,5 and 62,9 ng/ml) remained within narrow limits. In group (B) a significant decrease of the SJC (11,0 to 6,5; $p<0,02$) and sCD44v5 levels (90,7 to 55,5 ng/ml; $p<0,05$) at the second measurement was noted.
Discussion: Our results indicate the efficiacy of MTXT in patients with RA+. Longterm determination of sCD44v5 serum levels seems to provide an opportunity to follow immune activation serologically in the course of patients with RA+ undergoing MTXT. Further studies have to confirm our preliminary results.

(supported by " Vienna Bürgermeister-Fond" No.1452)

Methotrexate reduces expression of intercellular adhesion molecule-1 and acute phase reactions in patients with rheumatoid arthritis

KULLICH W., Ch. CZERWENKA, G. PÖLLMANN, G. KLEIN
Ludwig Boltzmann Institute for rehabilitation of internal diseases
Saalfelden, Austria

Methotrexate is one of the most prescribed disease modyfying antirheumatic drugs (DMARD's) in the treatment of rheumatoid arthritis (RA). Adhesion molecules are crucial components in the immunoreactions and inflammatory processes. Studies demonstrate that there is increased expression of adhesion molecules in RA. Intercellular adhesion molecule-1 (ICAM-1), a member of the immunoglobulin superfamily, plays an important role in the leucocyte transendothelial migration and the cell-cell contact necessary for a variety of immunologic responses in RA. MTX could exert its effect of inhibiting cell proliferation by influencing these cellular and molecular interactions.
We studied 39 patients under therapy with Methotrexate who fullfiled the ARA-criteria for the diagnosis of a definite or classic RA and compared this group to 29 RA-patients without any DMARD-therapy. Additionally on 54 patients with RA the effects of therapy with low dose Methotrexate was monitored during a 4 weeks inpatient stay on a rehabilitation centre.
For the detection of ICAM-1 and serum amyloid A (SAA) levels we used quantitative enzyme immunoassays.
In the present study lower levels in the expression of ICAM-1 were found under the treatment with MTX compared to the group of RA patients without DMARD-therapy. It was interesting that the mean ICAM-1 serum levels decreased significantly from 326 to 264 ng/ml under low dose Methotrexate in those RA patients who had an 4 weeks inpatient stay in a rehabilitation centre.
Since some studies have been indicating that serum amyloid A (SAA) is a sensitive marker of inflammatory processes and SAA has an effect on the adhesion of macrophages and lymphocytes, we investigated SAA parallel to C-reactive protein (CRP) measurements. As leucocytes depend on adhesion molecules to enter the site of inflammation, our observations with reduced ICAM-levels under MTX-therapy and the parallel decrease of the acute phase proteins SAA and CRP suggests that the antiinflammatory effects of MTX may, in part, be dependent on the down regulation of adhesion molecules.

THROMBIN MODULATES THE PRODUCTION OF PROINFLAMMATORY CYTOKINES: IL-8, TNF-α AND IL-15 IN CULTURED WHOLE BLOOD ISOLATED FROM RHEUMATOID ARTHRITIS PATIENTS

A. Koc, M. Ziółkowska, G. Łuszczykiewicz, K. Księżopolska-Pietrzak, W. Maśliński,
Institute of Rheumatology, Warsaw, Spartańska 1, Poland

Objective: Activation of coagulation and fibrinolysis have been suggested to play an important role in the pathogenesis of rheumatoid arthritis (RA). Thrombin, an important factor of the coagulation cascade, also stimulates the production of many proinflammatory mediators (e.g. IL-8, IL-1, TNF-α, PDGF and prostaglandins). The aim of this study was to compare the effects of thrombin and LPS on the production of IL-8, TNF-α and IL-15 in culture of whole blood samples isolated from RA patients and healthy individuals.
Methods: 21 patients with RA and 17 healthy individuals (as a control group) were included in this study. Blood was collected into tubes containing two anticoagulants acting by different mechanisms: EDTA or heparin. Whole blood, diluted 1:4 in RPMI 1640, was cultured with or without thrombin (10U/ml) or LPS (5μg/ml) for 24 hours. Specific ELISA's were used to measure the concentrations of IL-8, TNF-α and IL-15 in culture supernatants.
Results: LPS stimulated significant production of IL-8 and TNF-α in both studied groups. However, cytokine production was markedly higher in the cultures of whole blood collected in heparin than in EDTA. There were no differences between levels of IL-8 production in blood samples from RA patients and healthy individuals. In contrast, TNF-α production was lower in cultures of blood isolated from RA patients than from control group. The effects of thrombin on cytokine production was even more complex: this factor stimulated high production of IL-8 and low of TNF-α. In contrast, thrombin reduced the basal level of IL-15 in culture of whole blood in both studied groups. In healthy individuals thrombin-stimulated IL-8 production was higher in culture of heparinized blood. On the contrary, in RA patients the higher production of IL-8 was observed in the cultures of whole blood collected in EDTA. Moreover, independent on anticoagulant, reduction of IL-15 levels by thrombin was stronger in healthy individuals than in RA patients (~50% and 24%, respectively). These results may be related to abnormalities of the clotting system in RA patients.
Conclusion: Our study indicate that thrombin, by modulation of proinflammatory cytokines production, may be involved in the pathogenesis of rheumatoid arthritis.

IL-17 ENHANCES THE EXPRESSION OF BOTH CYCLOOXYGENASES (COX-1 AND COX-2) IN HUMAN SYNOVIOCYTES ISOLATED FROM RHEUMATOID ARTHRITIS PATIENTS

M.Kurowska[1], E.Kontny[1], M.Zubiaur[3], J.Sancho[3], J.Kowalczewski[2], W. Maśliński[1]
[1]Department of Pathophysiology and Immunology, [2]Clinic of Orthopaedy Institute of Rheumatology, Warsaw, Poland,
[3]Department of Cellular Biology and Immunology, Instituto de Parasitologia Y Biomedica, Granada, Spain.

OBJECTIVE. Recent data indicate that IL-17 plays a role in the pathogenesis of RA. This cytokine, produced by abundant in inflamed synovium CD4+CD45RO+ memory T cells stimulates fibroblast-like synoviocytes (FLS) to release several mediators of inflammation including IL-6, IL-8, GM-CSF and PGE2. The critical enzymes in prostaglandins (PGs) synthesis are two cyclooxygenases: constitutively expressed in many cell types COX-1 and inducible COX-2. The selective inhibition of the latter COX isoform is believed to be crucial for controlling many symptoms of inflammation. **THE AIM** of this study was to test the hypothesis that IL-17 triggers not only COX-2 but also COX-1 expression in human synoviocytes. **METHODS**: Synoviocytes, isolated from synovial tissue of RA patients undergoing knee synovectomy, and cultured in vitro for 3-6 passages, were stimulated with IL-17 (5, 10, 20 ng/ml) or TNF-α (10 ng/ml) or IL-1β (1 ng/ml) for 30 min, 1h, 2h, or 4h. The RNAs isolated from these cells were used as templates in Quantitative Reverse Transcription Polymerase Chain Reaction (RT-PCR). **RESULTS:** As expected IL-17 strongly enhanced, in a dose-dependent manner, expression of mRNA encoding COX-2. Increased COX-2 message, visible as early as 30 minutes after stimulation, peaked at 2 hours and began to diminish by 4 hours. More interestingly, we have found that IL-17 significantly raised the levels of COX-1 message 4 hours after stimulation. **CONCLUSIONS:** IL-17 enhances the expression of mRNA encoding both COX-1 and COX-2 isoenzymes. Further experiments evaluating the potency of selective versus non-selective COX-2 inhibitors in blocking IL-17 triggered PGE2 production by human synoviocytes will determine the contribution of COX-1 expressed in these cells to the inflammation of synovium.

RHEUMATOID ARTHRITIS AND PURINE METABOLISM

A. B. Zborovsky, V. F. Martemyanov, M. Y. Stazharov, E. E. Mozgovaya, T. P. Chernykh, S. A. Bedina
Research Institute for clinical and experimental Rheumatology, Volgograd, Russia

Objective: the improvement of the pathological process activity diagnostics in Rheumatoid arthritis (RA) patients.

Material and methods: 142 RA patients were under observation. The mean age of the patients – 45.3 ± 3.6 years. The mean duration of the disease – 10.4 ± 3.3 years. I degree of RA activity was determined in 41, II – in 85, III – in 16 observationes. Adenin deaminase (AD), Adenosin deaminase (ADA), AMP-deaminase (AMPDA), Guanin deaminase (GDA), 5-Nucleotidase (5-NT), Xanthine dehydrogenase (XDG), Xanthine oxidase (XO) activities, ADA, XDG isoenzymes were determined in blood serum.

Results: The increase of GDA, 5-NT, XDG, XO activities, ADA-2, XDG-2 isoenzymes, the decrease of AD, AMPDA activities were observed in RA patients with I degree of activity at hospitalization. Increased AD, AMPDA, GDA, 5-NT, XO activities, ADA-2, XDG-2 isoenzymes and decreased ADA activity were revealed in II degree of RA activity; increased AD, GDA, 5-NT, XO activities, ADA-2, XDG-2 isoenzymes and decreased ADA, AMPDA, XDG activities – in III degree of RA activity. The reliable enzymatic differences were revealed in patients with the various degree of pathological process activity.

Conclusion: The determination of Purine metabolism enzymes activity indices promote to specification of the disease activity degree.

NITRIC OXIDE PRODUCTION AND MUD PACK THERAPY

S.Bellometti, P.Richelmi*, C.Gregotti*

P.d'Abano Research Centre, Padova-ITALY; *Department of Pharmacology, University of Pavia-ITALY

Introduction: recently some investigators have proposed nitric oxide (NO) as an important mediator in the loss of cartilage (Grabowski et al, 1997) and it has been demonstrated that serum levels of NO correlates with disease activity of rheumatoid arthritis and other inflammatory arthritis (Ueki Y et al, 1996). No is very important in the metabolism of the activated chondrocytes and is able to induce predominant catabolic effects on the cartilage, included the inhibition of proteoglycan and collagen synthesis as well as the activation of metalloproteases (Amin AR et al, 1995; Sakurai H et al, 1995). Several cytokines included IL1 (Hickery MS et al 1998) stimulate NO production and some cytokines production is influenced by NO (Taylor-Robinson AW et al, 1994).
Objective: several line of evidence indicate that mud pack therapy influences the mainly cytokines involved in the cartilage degradation and inflammation (Bellometti S et al, 1997, 1998), we have explored if NO is involved, or not, with the mechanism of action of this natural anti-inflammatory product.
Methods:we enrolled 37 osteoarthrosic patients, randomized in tnwo groups and collected blood samples before and after the treatments. Group A underwent a cycle of mud pack therapy; group B underwent thermal bath (control group). NO serum levels was determinedby colorimetric, non-enzymaticassay for determination of total nitrite.

Results:

	NO serum values (μM/ml)		
	Before	after	CV
group A	54,2±35	20,5±19,7	-62%
group B	50,2±31,8	25,7±15,3	-48%

In both the groups the intra-group differences are statistically significant ($p<0,05$), while the inter-group differences are not statisticalliy significant.
Conclusions: this trial shows a statistically significant decrease of NO serum levels in both groups. Our study suggests that this inflammatory mediators (NO) may be involved in the mechanism of action of MPT. There are strong body of evidence suggesting that MPT exerts beneficial effects on cartilage, favouring its homeostasis.

ASSESSMENT OF PULMONARY CHANGES IN RHEUMATOID ARTHRITIS PATIENTS

H. Garwolińska, M. Rell-Bakalarska.
The Institute of Rheumatology, Warsaw, Poland.
M. Korzeniewska-Kosel, J. Kuś, M. Pirożyński, L. Pawlicka, J. Kowalski, S. Wesołowski, D. Maziarski.
The Institute of Pulmonology, Warsaw, Poland.

In general 34 patients were studied (24 female and 10 male) aged 40 to 80 years (mean age 62 years) in whom rheumatoid arthritis was diagnosed on the basis of diagnostic criteria.
Mean duration of rheumatoid disease was 14,7 years. In 11 patients I/II stage of radiological changes (acc. to Steinbrocker) in peripheral joints was found and in 23 patients stage III/IV.
Pulmonary studies were performed in patients in whom effort dyspnoea cough and auscultation changes were found or in the patients in whom chest X-ray suggested presence of pathological changes. Clinical examination revealed in 38,2% of the patients effort dyspnoea, cough in 41,1% and in 32,4 patients on physical examination mild crepitations and dry rales in lower segments of lungs were found. Impairment of breathing mechanism was found in 55,0% of the patients and in 23,5% lowering of DCLO was observed (measurement of pulmonary diffusion volume for carbon oxide).
Laboratory studies showed high activity of inflammatory process (mean BSR 64,4 after 1 h, CRP 47, mean WBC 8,4). Waaler-Rose test was positive in 22 patients and latex agglutination text in 30 patients.
HRCT imaging allowed to diagnose: pulmonary fibrosis in 7 patients (20,6%), rheumatoid nodules joining with pleura in 3 patients (8,8%) and bronchiectasis in 6 patients (17,6%).
The above signs are the signs considered to occur during the course of rheumatoid arthritis and occur in 47% of the patients. Additionally emphysema was observed in 5 patients (14 7%). Neoplasmatic changes were found in 2 patients (5,8%) - they did not accept proposed surgical treatment.
Chronic inflammatory changes and signs of previous TBC infection were seen in 6 patients (17,6%). In one case (2.9%) mycobacteriosis caused by Mycobacterium kansasii was diagnosed.
Broncho-alveolar lavage was done only in one case of interstitial disease (lack of patients consent to proposed examination).

Conclusions:

1. Functional examination of lungs, DCLO and HRCT allow to detect and in some cases determine the character of pulmonary changes in rheumatoid arthritis patients.
2. In rheumatoid arthritis patients occurrence of clinical signs like: effort dyspnoea, cough, mild crepitations and dry rales on auscultation (not related to concurrent infection) must be treated with appropriate attention as they may indicate involvement of respiratory system in rheumatoid process.

The Proteus mirabilis antibodies levels in patients with Rheumatoid arthritis

Ushakova M.A., Muravijuv U.V., [1]Vaneeva N.P., [1]Jastrebova N.E., [1]Maslov I.I., Zacharova I.E.
Institute of Rheumatology RAMS, [1]Institute of Vaccina and Serum named by Mechnikov I.I, Moscow Russia .

The etiology of Rheumatoid arthritis (RA) is still unknown. The microorganisms of gut are also supposed as well as external factors.

The elevation of IgG and IgM antibody (AB) activity to antigens of Proteus mirabilis (P.m.) was noted by Ebringer A. and co-authors in 1985 in patients (pts) with RA, so we undertook the same investigation.

Serum samples of 27 RA pts ,correspondent to ARA criteria, were examined in ELISA with P.m. strain F-181 (from the Mechnikov's Institute collection) in order to indicate IgG and IgM AB activity. Serum from 100 health persons was taken as negative control.

The middle age of the pts was 50,9 +/- 5,3 years, the continuance of the disease was 9,9 +/- 9 years, the relation female: male was 8:1.RF was revealed in 23 (85%) pts. RA activity was of 2 stage in 33,3% and 3 and 4 stages in 29,6% accordingly and only in 7,4% of the 1 stage. In 9 pts the aseptic necrosis of different location were noted on roentgenogramms.

The elevation of activity of IgM in 51,8% (n=14) and IgG in 25,9 (n=7) AB to P.m. was more than in control group ($p<0.0001$).6 patients (54,5 %) with aseptic necrosis and RF-positive RA were found in the group of positive by IgM AB to P.m. and RF –positive patients (n=11).Those 6 patients formed 42,8% among the pts with high levels of IgM AB to P.m. (n=14).

So, the elevation of P.m. antibodies in RA patients indicate on the possible participation of Proteus mirabilis in RA pathogenesis and also in formation of aseptic necrosis in RA. The supplementary investigations are necessary to confirm this idea.

RHEUMATOID VASCULITIS: NITROGEN OXIDE AND IMMUNOLOGIC PARAMETERS ASSOCIATION

V.V. Chopyak[1], O.V. Synenkyy
Medical University[1], Regional Medical Centre for Clinical Immunology and Allergology, Lviv

The aim of study was to evaluate the specificity of L-arginine metabolism and immunologic parameters in patients with Rheumatoid Arthritis (RA) with signs of vasculitis.

There were 49 RA patients monitored, 19 of them had immunological and morphological signs of vasculitis. There were 40 males and 9 females, mean age 32±3,1 years, in disease during 5,3±1,8 years. Spectral photometry was utilised to evaluate L-arginine metabolism. It allowed to assess its arginase and NO-synthase metabolism alterations. Immunologic parameters were assessed by $CD3^+$, $CD22^+$, $CD4^+$, $CD8^+$, $CD16^+$, $CD25^+$, CD-HLA^+ lymphocytes levels, RF, CIC, C3, C4 complement components, crioglobulines, IgM, IgG, IgA, myeloperoxidase as well as proteases and phagocytes.

It was detected that CIC, crioglobulines levels were increased in patients with Rheumatoid Vasculitis, C3 complement component level lowered, increased number of $CD25^+$ lymphocytes and myeloperoxidase positive polynuclears. Besides that in these patients was detected depressed NO dependent L-arginine metabolism. We conclude that Rheumatoid Vasculitis includes the involving of endothelial-neutrophil mechanisms. It has to be mentioned in pathogenetical treatment of RA patients.

PULMONARY NECROBIOTIC NODULES IN RHEUMATOID ARTHRITIS

Orlovská M., Šimová L., Fabianová M

Research Institute of Rheumatic Diseases, Piešťany, Slovak Republic

Pulmonary involvement is one of the extra-articular manifestations of rheumatoid arthritis (RA). It includes pleurisy, parenchymal nodules, interstitial involvement and diseases of the airway. The presence of a solitary nodule in a patient with RA poses difficult problems in differential diagnosis, particularly when it precedes the articular disease.

Two cases of pulmonary involvement in the course of RA are presented:

- A 49-year old woman suffering from RA for 13 years. The onset of a solitary parenchymal nodule with a central cavity was asymptomatic. The new pulmonary nodule was noted on a preventative chest x-ray. Later, her state was complicated by spontaneous pneumothorax and pleuritis.
- A 5l-year old man with arthritis and a solitary parenchymal nodule discovered at the onset of RA.

In each case, the diagnosis was verified by open biopsy in order to distinguish it from tuberculosis, pneumoconiosis or pulmonary carcinoma.

RHEUMATIC SYNDROMES IN HYPOTHYROIDISM

J. Duda
NsP Michalovce, Slovakia

Primary hypothyroidism may be accompained by different rheumatic syndromes as neuropthy, myopathy, and arthropathy. 51 cases of untreated primary hypohyroidism / 45 F, 6 M with a median age of 54 yrs / presented different rheumatic syndromes. 10 pts /19%/ had erosive arthropathy of the PIP joints resembling RA or erosive OA. Destructive lesions of the knee respectively of the arm / 1 F, 1 M / were seen in two pts. 5 pts had recidiving synovitis of the knees /4/ and the arm /1/. Synovial fluid was extremely viscous in nature with a low white cell count. 60% of pts had polyarthralgias. The myopathy was present with wide spectrum of muscle complaints as pain, stiffenes and hypertrophy in 57%. Carpal tunel syndrome have been detected in 70% of the series. Another important feature of hypothyroidism included weakness /12%/, muscle cramps /8%/. 5 pts /10%/ had attacks with CaPPi crytals in some synovial fluid. Rheumatoid factor was positive in 9 pts /25%/. The radiographs of the hands showed narrowing of the PIP joints or erosive changes or severe erosive arthopathy of the knee /1 M/ and the arm /1 F/. The most frequent misdiagnosis on admision was rheumatoid arthritis. Improvement followed hormonal therapy has confirmed that hormonal imbalance could by responsible for this particular rheumatic condition. 2 pts more with early strumectomy in child age /12yrs M, 8yrs F/ of unknown cause resulted in delay in maturation of epiphyses. The overall picture resembled multiple epiphyseal dysplasia.

A PATIENT WITH RHEUMATOID ARTHRITIS AND NON-HODGKIN'S LYMPHOMA (CASE REPORT)

Bacova M., Kohout A., Soukup T., Bures J., Hrncir Z.
2nd Department of Internal Medicine and Fingerland Institute of Pathology, Charles University Hospital, Hradec Kralove, Czech Republic

Introduction: Non Hodgkin's lymphoma (NHL) has been reported in association with a number of autoimmune diseases, including rheumatoid arthritis (RA).

Case report: 78 years old man with longstanding IgM-RFs seropositive RA according to ACR (1987) criteria developed large cell lymphoma of B cell phenotype with high grade malignancy situated on stomach. He had a 22-year history of RA, treated with parenteral gold (in 1977), Prednisone (average dose 10 mg daily for many years), sulphasalazine (3 years) and azathioprine (7 years with cumulative dose 250 g). In 1991 interstitial pulmonary fibrosis with reduction of diffuse lung capacity was diagnosed. In 1992 paraprotein IgA kappa in serum was find and between 1992 and 1999 serum level of paraprotien was in range 10.5 g/l to 16.5 g/l. No evidence of malignant plasmocytoma was proved. This patient presented in May 1999 with a weight loss (17 kg within 6 months), dysphagia and abdominal pain. Ultrasonography and gastroscopy revealed a mass in gastric body with pathologic lymfadenopathy in superior retroperitoneum. Histologic analysis revealed the large cell lymphoma with B cell phenotype. Chest CT and bone marow biopsy showed no evidence of lymphoma. There was started chemotherapy regimen of cyclophosphamide, vincristine and methyl-prednisolone. After three cycles he was admitted with diarrhoea and fever. In the course of 3 days breathlesness with necessity of oxygen therapy was developed and patient died after 5 days in progredient respiratory insuficiency (in sputum Candida species and Acinetobacter was find).

Discusion: The possibility link between RA and lymphomas was raised by a lot of autors with the relative risk from 2.7 to 26. The relative risk of developing of NHL increases with duration of RA (in our case 23 years), the histologic type is often of B cell origin and extranodal localisation (as in our case). There is little evidence to suggest a major risk of NHL caused by immunosupresive drugs in usually doses, i.e. azathioprine.

Conclusion: In 78 year patient with longstanding RA the abdominal symptomatology with weight loss was a early manifestation of non Hodgkin lymphoma of B cell phenotype and gammapathy IgA kappa of undetermined origine.

INTERLEUKIN-1 RECEPTOR ANTAGONIST POLYMORPHISM IN PATIENTS WITH JUVENILE SPONDYLARTHRITIS.

K. Jarošová, D. Němcová[1], Š. Růžičková, Z. Cimburek, J. Vencovský.

Institute of Rheumatology, Prague, Czech Republic and [1]Dept. of Pediatrics, 1st Medical Faculty, Charles University, Prague, Czech Republic.

Introduction. A five-allele polymorphism exists for the interleukin-1 receptor antagonist (IL-1Ra) gene. It is based on the variable number of copies of an 86-basepair tandem repeat in intron 2 of the gene. Associations of this polymorphism with several inflammatory diseases have been recently reported. **Aims.** To determine the frequency of individual alleles of IL-1RN gene in a subgroup "arthritis with enthesitis (AE)" of juvenile idiopathic arthritis (JIA) patients and relate this to the development of disease severity. **Methods.** Polymorphic region of the IL-1Ra gene was amplified by PCR. Individual alleles were detected by gel electrophoresis. Patients with JIA (n=158) assigned to individual subgroups were investigated and compared with healthy controls (HC). **Results.** The most commonly found allele in all groups was IL-1RN*1. Allele IL-1RN*2 was found in 26.2 % in JIA patients and in 15.5% in HC (n=171; p<0.001). Within the individual subgroups of JIA patients the significant differences were found in AE patients (n=46; 32.6%; p<0.001) and in extended oligoarthritis (n=17; 50%; p<0.001). In AE patients who progressed either in juvenile ankylosing spondylitis (JAS) or in juvenile undifferentiated spondylarthritis (JSpA) (radiographic changes in sacroiliac joints) the skewed representation of IL-1RN*2 was found.

Group (n)	IL-1RN*2 (%)	Significance
HC (171)	15.5	
JIA (158)	26.2	p<0.001
AE(46)	32.6	p<0.001
- JAS (20)	37.5	p=0.002
- JSpA (14)	32.1	p=0.034
-persistent AE (12)	25.0	NS

Conclusions. IL-1Ra gene polymorphism may constitute a common genetic susceptibility factor for several forms of arthritis, which may be additive to HLA based susceptibility. The role for IL-1RN*2 is not known. This can be related to altered IL-Ra production, be in linkage disequilibrium with other gene(s) or have some unknown role for IL-1Ra, e.g. for its intracellular form.

Supported by grants NE/4879-3 from IGA of the Czech Ministry of Health.

USEFULNESS β-NAG (N-acetylo-β-glucosaminidase) AS AN EARLY NEPHROPATHY MARKER IN CHILDREN WITH JCA.

A.Korobowicz, E.Tuszkiewicz-Misztal, M.Piotrowski
Dept. Of Rheumatology, Children University Hospital, Lublin, Poland

Chronic renal insufficiency is a frequent complication of JCA. Diagnosis of the subclinical stage of nephropathy would modify the treatment and reduce the risk of late complications. Increased β-NAG urinery excretion is regard as a proof of renal tubular dysfunction. **The aim** of the study was to evaluate urinary of excretion: β-NAG, microalbumin and albumin in JCA patients without clinical symptoms of nephropathy. The **study** comprised 48 JCA patients (F-35, M-13). In all patients USG of kidney has been performed as well as assessment of urea, creatinine and electrolytes serum levels and urinanalysis. All results were normal. In all children there was no history of urinary tract infections. At the time of evaluation, duration of disease ranged from 3 months to 9 years (mean 2,84 years) and age of the children ranged from 4 to 17 years (mean 11,5). The onset of the disease was pauciarticular in 16 children (33,3%), polyarticular in 24 children (50%) and systemic in 8 (16,6%) children. Rheumatoid factor was present in 16 (33,3%) patients. The controls were 14 healthy children. **Methods.** Urine samples were taken from the first morning void and were stored in –20°C until analyses were performed. β-NAG was measured by colorimetry, microalbumin and albumin by nephelometry and other biochemical analyses by routine laboratory methods. Statistical analyses were done using *Statistica* program.

RESULTS (mean)

VARIABLE	STUDY GROUP	CONTROLS	P
Microalbumin (mg/l)	7,32	4,89	NS
Albumin (mg%)	4,16	2,36	NS
B-NAG/creatinin (u/mmol)	1,28	0,49	0,03
Microalbumin/creatinin (g/mmol)	1,06	0,4	NS

In most cases urinary concentrations of microalbumin, albumin and β-NAG were higher in JCA patients than those in controls, however all results showed high variability.

CONCLUSIONS. The study results revealed the presence of renal tubular damage in JCA patients without clinically recognized nephropathy. The assessment of β-NAG is simple and non invasive tool of diagnosing the earliest stages of nephropathy in JCA patients.

ADULT ONSET STILL'S DISEASE IN A 77 YEAR OLD MAN

R. Luukkainen[1], M. Salonoja[2], R. Nordberg[2], J. Hannukainen[3]

Departments of Rheumatology[1] and Geriatry[2], Satalinna Hospital Harjavalta, Department of Surgery[3], Satakunta Central Hospital, Pori, Finland

Adult onset Still's disease is a rare disease, which usually starts before the age of 35 years. Its most characteristic features are fever, joint pains and skin rash.

Case report: A 77 year old man was admitted to investigation in August 1999 because of fever up to 39.5° C that had lasted for 10 days and joint pains. In August 1980 he had had gastroenteritis caused by Yersinia enterocolitica III but no reactive arthritis. Since 1985 he has had once or twice a year high spiking fever (39-39.5° C) periods, joint pains and a shore throat lasting for two weeks but no rash. ESR has rised up to 100 mm/hour, CRP 120 mg/l, leucocytes 11000/ mm, but neutrophil count has been less than 80%. Bacterial blood cultures, rheumatoid factor (RF) and antinuclear antibodies (ANA) have been negative. Antiobiotics have had no effect on symptoms.

In August 1999 the patient's general condition was good. Synovitis was noticed in wrists and II-IV metatarsophalangeal joints of both feet. Chest X-ray showed pleuritis on the left side. ESR was 90 mm/hour, CRP 132 mg/l, blood leucocyte count 11100/mm^3, neutrophiles 76% and ANA, RF and bacterial blood culture were negative. The fever and other symptoms lasted altogether for two weeks. ESR and CRP became normal.

Adult onset Still's disease was diagnosed, although the patient fulfilled only 4 of the 5 required criteria by both Yamaguchi et al.(1992) and also Cush et al.(1986). The criteria are never absolute and in this case they are based on considerably younger patien materials. Prednisolone and sulphasalazine were started.

Conclusion: Adult onset Still's disease has to be considered in the differential diagnosis of fever even in geriatric patients.

THE EXOTIC INFECTION AS A DIFFERENTIAL DIAGNOSTIC PROBLEM OF J I A

D. Mozolová, E. Kováčová, J. Červenka, S. Caňová, J. Bírčák, J. Mrázová
1-st Department of Pediatrics of Medical Faculty of Comenius University, Department of Rickettsiology and Chlamydiology of Slovak Academy of Sciences

Conjunctivitis and fever was appeared in 8 1/2 year old girl on the 10-th day after her return from Dominican Republik. Three days later high fever till 39 C and the striking painful swelling of the left leg was appeared. She was admitted to our department. From beginning of her hospitalization the remittent febrile states lasted for following days. Exsudative arthritis on the right knee was appeared on the 3-rd day after her admittion. Conserning laboratory findings only high values of ESR, CRP and CIC were found. Remaining laboratory findings were negative. Owing to the atypical course of the disease the epidemiologicaldate were again confrontated. Patients mother remembered that in the time of being in Dominican Republik her girl was infested with lices through the contact with aborigine girl. A blood sample was taken for examination on rickettsiosis. Already the first titer of antibodies with ELISA testing and also by indirect immunofluorescency was positive. Longitudinal follow-up of the antibodies titres confirmed infection by Rickettsia conorii. This result positively excluded diagnosis of the juvenile idiopathic arthritis and confirmed the diagnosis of the reactive arthritis. The wide spectrum antibiotic therapy brought out no improvement. After the treatment with Doxycycline body temperature was finally normalised and joint findings were modified.

MRI IN DIAGNOSTICS OF CHANGES IN CERVICAL SPINE IN RHEUMATOID ARTHRITIS (RA) PATIENTS

Kwiatkowska B., Filipowicz-Sosnowska A., Poniatowska R., Krzemińska-Dąbrowska I.
The Institute of Rheumatology, Warsaw, Poland.

The aim of the study: The study was aimed as assessing the usefulness of MRI in diagnostics of cervical spine changes in rheumatoid arthritis patients as compared to conventional radiological studies. The MRI study was also correlated with neurological examination, complaints and disease activity.

Material: The study encompassed 30 patients (23 females and 7 males) with rheumatoid arthritis. Mean age was 54 ± 10,5 years, duration of the disease equaled on average to 14,3 ± 9,9 years. In 4 patients II stage (acc. to Steinbrocker) of radiological changes was observed, in 6 patients – III stage and in 20 patients stage IV. High disease activity (inflammation of > 6 joints, duration of morning stiffness > 1 h, BSR > 50 mm after 1 h, CRP > 20 mg/l) was found in 17 (56,7%) patients and moderate disease activity (inflammation of < 6 joints, morning stiffness < 1h, BSR < 50 mm after 1 h, CRP < 20 mg/l) in 13 patients (43,3%)

Method : The study assessed the complaints, neurological examination, radiological studies of cervical spine (AP and lateral projections), clinical disease activity and MRI study.

Results: In RA patients MRI study is more sensitive in assessing the changes in cervical spine than conventional radiological studies:
- herniation of cranial basis was found in radiological studies in 4 patients (13,3%) and by MRI in 11 patients (36,7%)
- MRI study allows to determine the presence and location of rheumatoid granulation, which is not possible by radiological studies
- MRI study showed in 2 (6,7%) patients lateral luxation and that was impossible with conventional radiological studies
- The MRI study also allowed to visualize changes in apical-occipital joints and apical-rotatory joints as well as erosive lesions in C1 and C2 vertebrae and narrowing of spinal canal not seen in conventional radiological studies. There were no correlations between the complaints, changes in neurological examination and changes seen in MRI study .In patients with high disease activity the following were more frequently found: apical-rotatory subluxations, presence of rheumatoid granulation, herniation of cranial basis, changes in apical-occipital joints and in lateral apical-rotatory joints and changes of C1 and C2 vertebrae. Narrowing of spinal canal and lateral luxation were found only in patients with high disease activity.

The studies performed have shown high usefulness of MRI studies in diagnostics of cervical spine changes in rheumatoid arthritis patients.

SURGICAL TREATMENT OF UPPER CERVICAL SPINE IN PATIENTS WITH RHEUMATOID ARTHRITIS, RISKY AND REWARDING.

KLEZL Z., CHARVAT F., VESELA M., FOUSEK J., PAVELKA K.
Department of Orthopedics and Traumatology, CMH Prague
Department of Radiology, CMH Prague
Institute of Rheumatology, Prague, Czech Republic.

Pathological changes on cervical spine in rheumatoid patients were well described by many authors. In the recent years more investigation has been focused on the timing and surgical technique in order to prevent or eliminate significant instability or compromise of spinal canal. Magnetic resonance imaging and elektrophysiological examination have proved to be important tools in decision making as well as multidisciplinary cooperation of numerous specialists.

We have reviewed 12 patients with rheumatoid arthritis (RA) who were operated on for upper cervical spine involvement (C0-C2) in 1996-1999. Indication criteria included increasing pain associated with axtlanto axial subluxation, atlanto-axial posterior subluxation with the retrodental interval 14 mm and smaller, cranial settling and lateral atlantoaxial subluxation greater than 2 mm. One must be aware of the fact, that radiological studies alone may not depict the extent of compression of the dural sac as they do not show the rheumatoid panus. As Dvorak has suggested, MRI should be performed in cases of suspected neurological compression.

Various surgical techniques and have been described to stabilize upper cervical spine and upper cervical spine to the occiput. Based on our previous experience, we have used 3 different instrumentations. The occipito cervical region was stabilized by the Ransford loop and sublaminar wires, the atlanto-axial instability was stabilized by two transarticular screws together with Gallie wiring and posterior fusion (according to Magerl) and posterior Brooks sublaminar wiring technique. Surgery is demanding, specially the drilling of canals for transarticular screws is associated with a high risk because of frequent variability of the position of vertebral arteries. Meticulous decortication with a high speed drill and use of autologous bone graft from the iliac bone is necessary to achieve satisfactory union rate in patients with marked osteoporosis, decreased healing potential and frequently other medical problems.

Close follow up of patients with RA is necessary in order to unveal onset of significant instability or incipient basilar invagination associated with cervical myelopathy. These cases can usually be treated from posterior approach only, avoiding the anterior, transoral aspproach with its specific complications and morbidity. Our results support our follow up protocol with imaging and elektrophysiological examination. Multidisciplinary cooperation of involved specialists leads to revealing of early neurological compromise and adequate surgical stabilization before the onset of disabling cervical myelopathy.

FAMOTIDINE IN THE TREATMENT OF GASTRODUODENAL ULCERS INDUCED BY NSAIDs

I. Rybár, J. Rovenský,

Research Institute of Rheumatic Diseases, Piešťany, Slovak Republic

A retrospective analysis of the healing of gastroduodenal peptic ulcers induced by non-steroidal antiinflammatory drugs (NSAID) by means of H2-antagonist famotidine 40mg o.d. in 22 patients with rheumatic diseases has been carried out. The NSAID treatment was not interrupted. There were 19 gastric ulcers and 9 duoenal ulcers in 22 patients. Healing rate after 4 weeks of the treatment was 63% (12/19) in gastric ulcers and 67% (6/9) in duodenal ulcers. Healing rate after 8 weeks of the treatment was 95% (18/19) in gastric ulcers and 100% (9/9) in duodenal ulcers. In subgroups of patients treated with the glucocorticosteroids and in patients with Helicobacter pylori infection, no statistically significant differences in the healing have benn recorded. Tolerance of famotidine in rheumatic patients was optimal.

CLINICAL EXPERIENCE IN THE APPLICATION OF KETONAL RETARD IN PATIENTS WITH SELECTED RHEUMATIC DISEASES

Raffayová, H., *Semetková, I., **Pjonteková, M.
Research Institute of Rheumatic Diseases, Nábrežie I. Krasku 4, Piešťany
*NZZ - the rheumatology out-patient department, Nitra
**NZZ - the rheumatology out-patient department, Kežmarok

Introduction and methods: The present study focuses on the effect of Ketonal R on pain and inflammatory activity in selected rheumatic diseases and is based on the results of a multicentre study of this preparation. Two hundred patients in total were included in the study and treated with a dose of 150 mg Ketonal R administered twice daily for a period of five months.
Results: Evaluations of the effect of Ketonal R on pain (VAS) showed marked reduction in pain after 7 days of Ketonal R treatment in 162 patients (88.0 percent) and further gradual reduction over 3 months of treatment. Its effect on inflammatory activity parameters in patients with RA (hand grip strength in 96.2 percent, the circumference of proximal interphalangeal joints in 81.5 percent) was also confirmed. With respect to acute phase reactants, the most favourable response to the therapy was found in erythrocyte sedimentation rate (ESR) which decreased in 43 patients (66.2 percent). Gastrointestinal manifestations were the most common side effects of the treatment and subsided in 9 percent of the patients after the dose had been reduced to 150mg/day or combined with H2 receptor blockers.
Conclusion: The result of the study of Ketonal R confirms its effectiveness especially in relieving pain as well as in reducing inflammatory activity in patients with inflammatory rheumatic diseases. Treatment with Ketonal R may be accompanied by dyspeptic disorders which are in most cases easily controllable by reduction of the dose of the drug, or by its combination with gastroprotective therapy. Other side effects were of minimal frequency, which also demonstrated a good tolerance of the drug.

THE APPEARANCE OF THE UPPER GASTROINTESTINAL TRACT (UGIT) AND HELICOBACTER PYLORI (Hp) INFECTION IN THE VASCULITIS COMPLICATED AND UNCOMPLICATED RHEUMATOID ARTHRITIS (RA) PATIENTS

A.Zubrzycka-Sienkiewicz,T.Wagner,*J Noworyta+, A.Filipowicz-Sosnowska
Department of Rheumatology,*Department of Pathology,+Unit of Bacteriology ,Institute of Rheumatology,Warsaw,Poland

Objective of the study was evaluation of UGIT in the 3 subsets of rheumatoid arthritis (RA) patients: with vasculitis (vas),with uncertain signs of vas and without vas.
Material and Methods : 90 RA in-patients /F-71,M-19,mean age 55,8±13,8y ,mean period of disease 9,2±8,7y/ consecutively admitted to hospital who fulfilled inclusion criteria(age-18-78y,taking one of NSAIDs:diclofenac ≥75mg/24h, piroxicam ≥10mg/24h,indomethacin ≥50mg/24h,naproxen ≥500mg/24h by at least 3 months no taking concomitantly more than 7,5mg prednisone daily,no treated by cytostatic drugs) were enrolled at the study.15 (16,6%)RA patients showed clinical features of vasculitis (VRA-I group), 22 (24,4%) had uncertain signs of vasculitis (II group),and 53 (60%) RA uncomplicated by vasculitis (III group) patients. All the patients regardless their GI complaints were undergone gastroduodenoscopy. The appearance of stomach and duodenum was assessed according to Lanza score(1981) .Helicobacter pylori (hp) infection has been confirmed by hist-path (stained by Giemsy method) and /or culture.
Results:Gastric ulcer(GU) has been detected in 8 (53,3%) i n vasRA-I group,and in 3 (13%) of group II and in 11 (21%) of III group,.Erosive gastritis(EG) occured in 5 (33%) of I group,3 (13%) of II group and in 16 (30%) of III group.Duodenal ulcer (DU) has been showed less frequently than GU and was observed only in 2 (13,3%) of I group and in 4 (7,5%) patients of III group.GU and/or DU and EG was observed in 14 (93,3%) of patients with RA complicated by vasculitis and in 6(26%) with uncertain signs of vas and in 28 (53%) of uncomplicated RA. III group.Hp infection has been detected significantly (p=0,003) more often in patients with EG and GU /DU in uncomplicated RA (group III) ,but no in vas RA (group I).
Conclusion: RA patients with clinically overt signs of vasculitis showed GU and EG significant more frequently p<0,01 than patients with uncomplicated RA or RA patients with only uncertain signs of vasculitis ,DU was observed in whole group less frequently than GU p<0,01.Hp infection is related with EG and GU/DU only in uncomplicated RA as it is in common population.

EFFICACY AND TOLERABILITY OF ARTHROTEC IN RHEUMATOID ARTHRITIS (RA) COMPLICATED BY GASTROPATHY OR PEPTIC ULCER

V.Nasonova, Yu.Mouraviev, AA.Grinko, A.Karataev, V.Yakushin, V.Sorokin.
Institute of Rheumatology of RAMS, Moscow

Study included 28 pts with reliable RA with complains compatible with gastropathy, 11 of them had ulcer syndrome, and 3 had ulcer cases in the family. Gastro-duodenoscopy was done before and 12 weeks after the treatment Arthrotec was prescribed by 3 tablets a day after meals.
Arthrotec decreased articiular pains (from 2.18 to 1.18 points), morning stiffness (from 178 to 54 min.), number of painful joints (from 8.4 to 3.2), number of inflamed joints (from 4.6 to 0.5). Positive dynamics of ESR (from 34.04 to 21.9 mm/hr) and hemoglobin (115.2-124.6 g/l) were also noted. The beginning of positive dynamics was noticed from the 2nd week of treatment.
According to clinical observation gastralgia on an empty stomach, after meals and in night time was only in separate pts, the same with other dyspeptic phenomena excluding heartburn. Endoscopic study in 12 weeks demonstrated reliable decreasing of morphological changes in cardiac area and stomach bottom and somewhat smaller decrease in the body of the stomach. Analogous changes occurred in mucous of duodenum. No ulcerous changes were observed during the treatment despite ulcerous history almost in half of pts. Side effects associated with prostaglandin's spastic effects were found in 7 pts but only in 2 cases in required to cancel Arthrotec.
Conclusion: 12-weeks multicentral study demonstrated that Arthrotec posses satisfactory antiinflammatory effect and favoured healing of erosive lesions of upper stomach areas mucous. Arthrotec can be recommended for RA pts treatment who has risk factors of developing of NSAID-gastropathies or its clinical-endoscopic manifestations.

COMBINATION THERAPY OF CYCLOSPORINE A WITH METHOTREXATE IN ACTIVE RHEUMATOID ARTHRITIS. OPENED THERAPEUTICAL TRIAL.

D.Tegzová, K.Pavelka, *K.Šírová,** V.Vlasáková
Institute of Rheumatology, Prague
**Out-patients Rheumatological Dept. , Ostrava*
***Dpt.of Medicine of the Hospital of České Budějovice*
Czech Republic

Objectives: The aim of study was to evaluate the effect and adverse events of combination therapy of cyclosporine A with methotrexate in active rheumatoid arthritis.
Methods: 37 patients with active rheumatoid arthritis were included into the study. All patients were treated for at least three month with methotrexate at minimal dose of 10 mg per week prior including into the study and effect of this therapy was proven insufficient. Than cyclosporine A was added to methotrexate at initial dose of 2,5mg/kg bw and this dose was gradually increased to 5mg/kg bw. Changes in ESR, CRP, joint indexes (number of swollen joints, number of tender joints) and algofunctional index (HAQ) were evaluated over six months of therapy. The adverse events were also monitored. X-ray progression will be also discussed.
Results: A significant decrease of all parameters was observed in the end of study compared with the values at the start of the trial. Adverse events during therapy occurred in 25 patients. There were chiefly hypertension, nephrotoxicity of cyclosporine A, gastrointestinal problems and infection. Because of this the therapy had to be suspended in 5 patients, in the remaining cases the complications were halted with appropriate treatment.
Discussion: Our data do show a very good effect of combination therapy of cyclosporine A with methotrexate . The adverse events occurring during the study ceased in most cases when appropriately treated and the therapy rarely had to be suspended.
Supported by Grant of IGA Ministry of Health Czech Republic NO 4886-3

TERMINATION OF DISEASE MODIFYING ANTIRHEUMATIC THERAPY IN RHEUMATOID ARTHRITIS

I. Ujfalussy, É. Koó, K.Imre, F.Gyulai, J.Ortutay,

Department D, National Institute of Rheumatology and Physiotherapy, Budapest, Hungary

Object: To compare the survival time and determine the causes of termination of the most frequently used disease modifying antirheumatic drugs in rheumatoid artrhitis.
Method: 122 patients' data -who received either methotrexate, sulfasalazine or i.m gold treatment - were reviewed according to standardised protocol. We have collected data on the patients' age at the beginning of disease, and DMARD treatment, duration of the treatment, and the cause of withdrawal. The statistical analysis was performed using a cumulative survival analysis of termination and a test of comparison between survival curves.
Results: 60 patients received i.m. gold, 43 MTX and 19 SSZ treatment. The longest median drug survival time was found among the aurothiomalate treated patients (59,1 month). There wasn't significant difference in the survival time between the gold, MTX and SSZ treated groups. Half of the patients received DMARD treatment for less than a year.
The most frequent termination due to side effects occurred in the i.m. aurothiomalate treated group. In the second half of the decade much more MTX and SSZ than gold treatment were indicated.
Conclusion: The less than 12 month duration on DMARD treatment is an insufficient treatment for RA. After Jan. 1. 1994 dramatically changed the sort of newly indicated DMARDs in Hungary.

Immunomodulation cycloferonum for treamnent patients with rheumatoid arthritis (visceral form)

Kuriata A.V., Geychenko V.P., Lycunets G.K.

Dnepropetrovsk State Medical Academy, Ukraine

Cycloferonum is an inductor with low-molecular weight of early α-, β-, γ-interferones, which are induced by immunocompetent cells (macrophages and T-, B-lymphocytes). This drug was included for therapy of 21 patients with rheumatoid arthritis (RA) middle activity and (or) autoimmune anemia, nephrithis, miocarditis, vasculitis. The glucocorticoides were used together with cycloferonum. The last one was prescribed 1,250 mg per course, intramuscular. The dose was 250 mg at 1, 2, 4, 6, 8 days. The criteria for prescribtion was a decrease of activity of T-supressors and disimmunoglobulinemia. The comparative group was presented by 15 patients with RA to whom immunomodulator was not used. The clinical efficacy was estimated by the appearance drug and infection complications. In a 3 weeks the positive effect was shown for 18 patients (85.7 % of the whole group), which used cycloferonum together with prednisolone (32.2 ± 2.2 mg/per day). In the comparative group the positive effect was shown for 10 patients (66.7 % of the whole group), the dose of prednisolone in this case was 46.2 ± 2.2 mg/per day. The use of cycloferonum did not show the accessory effect, meanwhile the comparative group had 2 cases of infectional complications (chronical nephrithis). So the use of cycloferonum gave the increase of therapy efficacy and decrease of both: pharmacological load and accessory effect.

THE TREATMENT OF RHEUMATOID ARTHRITIS (RA) AND ITS' COMPLICATIONS IN AGED PATIENTS.

Akimova T., Satybaldyev A., Ivanova M., Novosjolova T.,
Institute of rheumatology of RAMS. Moscow. Russia.

141 patients (pts) with RA (m/f-30/111) with the mean age 60.1 years (yrs) were followed up (mean follow up period -7.5 yrs). The acute onset of disease and generalized joint involvement had 90% of pts, early appearance of Rheumatoid factor had 80%, early destructive changes in joints 80%, rheumatoid nodules - 18% pts..
All of them had different degree of osteoporosis, in 19 pts it was very severe with spontaneous bone fracture (in 14) and vertebral deformity in 5 pts ("fish-like" and clinoid compression of vertebral bodies). Most of pts had such diseases as hypertention, atherosclerosis, cardiosclerosis, diabetis mellitus and other. All of pts recieved aminochinolin drugs and NSAID. Corticisteroids (Cs) received 54% of pts from 2months to 15 yrs (2 pts were treated with puls-therapy with solumedrole). Intraarticular injection of Cs obtained all pts (1-6 time in a year). Cytotoxics (C) recieved 38% of pts, sulfasalazine 10%, tauredone -6% pts. 21% of pts were treated only with aminochinolin drugs and NSAID.
Analysis showed that the mean dose of Cs in the pts with the bone fractures was 12.4 grammes (from 7.3 to 43.0) and in the pts with vertebral deformity 24.7 (from 16.4 to 43.8) grammes. Pts with systemic manifestations and pathology of vessels (Raynaud's syndrome), vasculitis received pentoxifylline, solcoseryl, curantyl. All the pts received the drugs that improved metabolic disorders in bones, such as sodium fluorid (coreberon, ossin), calcitonin, derivatives of vitamin D (vitamin D3). Miacalcic received 1/3 of pts mostly with severe osteoporosis.
Thus the treatment had favorable effect: in 90% decreased of disability, 6% of pts had remission during 1-7 and more yrs. In 8% of pts the clinical effect was satisfactory.
Conclusion.
The analysis of results showered that in aged RA pts were used mainly aminochinolin drugs and low doses of Cs . Cytostatics received 1/3 of aged RA patients, mostly with low doses of Cs. All of aged RA pts needs preventive therapy with drugs, that improve the metabolic bone changes.

THE TREATMENT OF ASEPTIC BONE NECROSIS (AN) IN AGED RHEUMATOID ARTHRITIS (RA) PATIENTS.

A.Satybaldyev, T.Akimova, M.Ivanova.
Institute of rheumatology of RAMS. Moscow. Russia.

Long-term follow up of 141 RA patients (pts) - m/f-30/111, mean age 60.1 years (yrs) with the onset of disease after 50 yrs (mean duration of follow up 7.5 yrs) revealed AN in 32 pts (m/f - 3/29, mean age at the onset of disease 57.6 yrs, mean duration of follow up 10.2 yrs)
All 32 pts had acute onset of disease, generalized joint involvement, rheumatoid nodules (RN) and other systemic lesions, early appearance of rheumatoid factor (RF), destructive changes in joints and resistance to NSAID.
Systemic manifestations had 21 (62%) of pts, RN - 10, vasculitis -12 (in 3 with trophic ulcers), lymphadenopathy - 3, polyneuropathy - 21, adhesive polyserositis - 5, amyloidosis -11, bone fractures in 5, vertebral deformity in 5. All pts were seropositive, 21 had III stage and 11 - IV stage according to x-ray examination. The localization of AN was as follow: hip -15,knee - 12,wrist - 3,shoulder - 1, elbow - 1.
In 10 pts AN was multiple, with localization in two and more joints: hip (7 pts) and knee (3 pts) joints, it appeared during 1 year. All of pts received aminochinolin drugs, with corticosteroids (Cs) - 10, Cs and cytostatics (C) -10, only C - 6, Cs and sulfasalasine - 2, Cs and tauredone - 2. All of pts received NSAID and Cs intraarticular (1 - 6 time in a year). The initial dose of Cs was no more than 15-20 mg of prednisolone pro die. During the course of treatment all of pts received sodium fluorid or calcitonin, vitamin D3 and retabolil. Besides they received pentoxifylline, solcoseryl, curantyl and local treatment with impulsive magnetic fields and laser-therapy. 5 pts were operated (4 – endoprosthesis of hip joint and 1 – arthroplasty of knee joint). After operation 2 pts walk without any support and 3 with crutches.
Conclusion.
AN appeared in 23% aged pts with RA. The most common localization of AN was hip and knee. The long-term treatment lead to clinical imrovement in all pts, they ability of joints was restored, the quality of life improved.
The preventive therapy in RA aged pts with AN with severe osteoporosis must be continued for a long time.