POSSIBLE INVOLVEMENT OF ADVANCED GLYCATION END PRODUCTS IN PERIODONTAL DISEASES

D. PIETROPAOLI, C. TATONE, A.M. D’ALESSANDRO and A. MONACO

Department of Health Sciences, University of L’Aquila, L’Aquila, Italy

Received February 3, 2010 – Accepted June 21, 2010

Periodontal diseases are considered as multifactorial conditions initiated by infection with pathogenic bacteria, promoted by inflammation and immune response against bacteria and modified by different environmental and genetic factors. Recently, interest in periodontal diseases has been increasing due to the awareness that the hyperinflammatory status associated with this disorder could impose a significant increase of reactive oxygen species (ROS) relevant to numerous systemic diseases driven by a pro-oxidant profile. A highly complex interplay occurs between oxidative stress and AGEs (Advanced Glycation End products), a group of heterogeneous compounds that form constantly under physiologic conditions, although their rate of formation is markedly increased in hyperglycemia and oxidizing conditions. Starting from the most relevant hypotheses on the pathogenesis of periodontal diseases, the present review outlines their relationship with oxidative stress and inflammation response in order to make a critical evaluation of the potential role of AGEs in periodontal deterioration. Although direct evidence for the presence of AGEs in the periodontal ligament is still lacking, valuable approaches based on the use of periodontal cells along with genetic and biochemical studies in animal models and chronic periodontal patients support a potential role for protein glycation in the aetiology and severity of this disease. Following a review of the current literature, the present study highlights the need for further investigation on the presence of AGEs in the periodontal ligament as a means for the comprehension of the pathogenic mechanisms underlying periodontal diseases in order to develop prevention and treatment modalities for this dysfunction.

HIV-RELATED ACUTE INFLAMMATORY LEUKOENCEPHALOPATHY OF UNDETERMINED ORIGIN: REVIEW OF THE LITERATURE

E. TAVAZZI, V. BARGIGGIA, A PICHIECCHIO1, S. DELBUE2, R. MASERATI3, S. BASTIANELLO1, P. FERRANTE2, L. MINOLI3, G. RICEVUTI4, M. CERONI and E. MARCHIONI

Unit of General Neurology, IRCCS National Neurological Institute "C. Mondino", Pavia; 1Neuroradiology Unit, IRCCS National Neurological Institute “C. Mondino”, Pavia; 2Department of Public Health – Microbiology – Virology, University of Milan; 3Department of Infectious Diseases, “Policlinico San Matteo” IRCCS Foundation, Pavia; 4University of Pavia, Department of Internal Medicine, Division of Geriatry, Santa Margherita Institute, Pavia, Italy

Received November 10, 2009 – Accepted May 6, 2010

HIV-related acute inflammatory leukoencephalopathy of undetermined origin (AIL) has been anecdotally described in literature as being responsible for cognitive and motor deficits. We carried out a review of all the cases of AIL published in literature. Articles were selected according to 2 criteria: acute onset of symptoms; undetermined aetiology and non-fulfilment of multiple sclerosis diagnostic criteria. They were then analyzed in terms of clinical, biological and instrumental features, therapy, diagnostic classification and prognosis. Although rare (21 patients out of about 4,000 publications), AIL is of particular interest, as the comprehension of its mechanisms could give some insight into the direct and immune-mediated actions of HIV within the brain. All the reported patients share several clinical, histopathological, radiological and CSF features, leading to hypothesize a similar aetiopathogenetic mechanism. Conversely, we observed a high heterogeneity of treatment and diagnostic classification, which could have conditioned the broad prognostic variability. The absence of a defined aetiology leads to consider these forms as a particular subgroup of “not determined leucoencephalopathies” (NDLE), with both MRI and histological pattern dominated by inflammation as distinctive feature.
ROLE OF ETANERCEPT IN THE TREATMENT OF TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME: PERSONAL EXPERIENCE AND REVIEW OF THE LITERATURE

L. CANTARINI, D. RIGANTE1, O.M. LUCHERINI2, R. CIMAZ3, F. LAGHI PASINI, C.T. BALDARI1, M. BENUCCI4, G. SIMONINI5, V. DI SABATINO, M.G. BRIZI and M. GALEAZZI

Interdepartmental Research Center of Systemic Autoimmune and Autoinflammatory Diseases, Policlinico Le Scotte, University of Siena, Siena; 1Department of Pediatric Sciences, Università Cattolica Sacro Cuore, Rome; 2Department of Evolutionary Biology, University of Siena, Siena; 3Ospedale Meyer-Rheumatology Unit, University of Florence, Florence; 4Rheumatology Unit ASL 10, Nuovo Ospedale S. Giovanni di Dio, Florence, Italy

Received December 22, 2009 – Accepted June 9, 2010

Tumor necrosis factor-α receptor (TNFR1)–associated periodic syndrome (TRAPS) is the most common autosomal-dominant autoinflammatory condition and is caused by mutations in the TNFRSF1A gene. TRAPS is characterized by recurrent attacks of fever typically lasting from 1 to 3 weeks; in addition to fever, common clinical features include mainly periorbital oedema, conjunctivitis, a migratory erythematous plaque simulating erysipela with underlying myalgia, and arthritis or arthralgia; serosal membrane inflammation is also possible. The identification of TNFRSF1A mutations as the genetic cause of TRAPS coincided with the wider use of biological agents in medicine and raised the possibility that blocking TNF could potentially represent the primary therapeutic goal in TRAPS, thus disclosing new treatment choices for this complex disease. In the past few years, isolated reports and case-series have been published suggesting that inhibition of TNF-α might represent a promising therapeutic approach in TRAPS. We present here our experience with etanercept in the treatment of patients affected with TRAPS, and we also add a review of the literature.

IL-31 A TH2 CYTOKINE INVOLVED IN IMMUNITY AND INFLAMMATION

M.L. CASTELLANI, P. FELACO1, R.J. GALZIO2, D. TRIPODI3, E. TONIATO, M.A. DE LUTIIS1, M. FULCHERI4, A. CARAFFA5, P. ANTINOLFI6, S. TETÈ5, M. FELACO1, F. CONTI6, F. PANDOLFI1, T.C. THEOHARIDES8 and Y.B. SHAIK-DASTHAGIRISAHEB9

Immunology Division, University of Chieti, Chieti, Italy; 1Department of Human Dynamics, University of Chieti, Italy; 2Neurosurgery Division, University of L’Aquila, Italy; 3School of Dentistry, University of Chieti, Italy; 4Department of Clinical Psychology, University of Chieti, Italy; 5Orthopaedics Division, University of Perugia, Perugia, Italy; 6Vasto Hospital, Chieti, Italy; 7Institute of Internal Medicine, Catholic University, Rome, Italy; 8Department of Pharmacology and Experimental Therapeutics, Biochemistry and Internal Medicine Tufts University School of Medicine, Tufts-New England Medical Center, Boston, MA, USA; 9Department of Medicine, Boston University School of Medicine, Boston, MA, USA

Received March 23, 2010 – Accepted September 13, 2010

Cytokines are immunal regulatory proteins, however they also play a relevant role in inflammatory diseases. IL-31 is a newly discovered cytokine expressed primarily in TH2 cells, introduced by activated CD4+ T cells. IL-31 is capable of inducing chemokines and other cytokines in several inflammatory diseases via its surface receptor. This cytokine is also produced by mast cells and mast cell line, suggesting a role in allergic diseases. In this editorial we revisit the biological role of IL-31 in immunity and inflammation.
DIVERGENT AND SYNERGISTIC REGULATION OF MATRIX METALLOPROTEASE PRODUCTION BY CYTOKINES IN COMBINATION WITH C-C CHEMOKINES

V.J. RICHARDSON

Division of BioMedical Sciences, Faculty of Medicine, Memorial University of Newfoundland, St John’ s, NL, Canada

Received November 11, 2009 – Accepted June 23, 2010

The chemotactic effects of chemokines on cells has long been known, but it is now clear that chemokines also have much broader activities and are also involved in a number of disease pathologies, such as rheumatoid arthritis, cancer metastasis and other inflammatory processes. This study investigates the effects of four C-C chemokines, CCL2, CCL3, CCL4 and CCL5 either alone or in the presence of two regulatory cytokines TNF-α and TGF-β and their effect on secretion of two matrix metalloproteases MMP, MMP-2 and MMP-9, and the expression of one membrane bound MMP, MMP-14, by a monocytic human cell line, MonoMac6. All four C-C chemokines were shown to be chemotactic, but only CCL2 and CCL4 had any significant stimulatory effect on MMP-9 and MMP-2, respectively. Both TNF-α and TGF-β were found to divergently enhance MMP-9 and MMP-2 secretion respectively, with stimulation indexes of two and five respectively. Simultaneous treatment with TNF-α and chemokine resulted in up to a fifteen-fold stimulation of MMP-9 secretion and treatment with TGF-β and chemokine resulted in up to a fifteen-fold stimulation of MMP-2 secretion, while TNF-α in combination with CCL4 stimulated MMP-14 expression five-fold. Chemokine receptor expression was also investigated using a calcium-sensitive dye and FACS analysis. CCL2, CCL3, and CCL5 all resulted in a detectable enhancement of cytoplasmic Ca\(^{2+}\) concentration. CCL4 was unable to activate Ca\(^{2+}\) mobilization, despite the presence of CCR5, the receptor for CCL4. There appeared to be no correlation between MMP production and chemotaxis. The strong synergy between chemokines and cytokines and the enhanced production of MMP may signify the differential regulatory mechanisms of the two cytokines and chemokines in disease pathology.

DIETARY SUPPLEMENTATION WITH FRUCTOOLIGOSACCHARIDES ATTENUATES AIRWAY INFLAMMATION RELATED TO HOUSE DUST MITE ALLERGEN IN MICE

A. YASUDA, K-I. INOUE\(^1\), C. SANBONGI, R. YANAGISAWA\(^2\), T. ICHINOSE\(^2\), T. YOSHIKAWA\(^4\) and H. TAKANO\(^2\)

Meiji Seika Kaisha, Ltd., Food and Health R&D Laboratories, Saitama; \(^1\)School of Pharmacy, Kitasato University, Tokyo; \(^2\)Environmental Health Sciences Division, National Institute for Environmental Studies, Ibaraki; \(^3\)Department of Health Science, Oita University of Nursing and Health Science, Oita; \(^4\)Department of Gastroenterology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Received December 28, 2009 – July 12, 2010

Fructooligosaccharides (FOS) are prebiotic supplements that can enhance immunological responses in the host to activate mucosal immunity, probably through regulation of gastrointestinal microflora. An area that has not been investigated, however, is the therapeutic potential of prebiotics on allergic airway diseases. The purpose of this study is to evaluate the effects of dietary supplementation with FOS on a murine model of airway inflammation induced by the house dust mite allergen Dermatophagoides farinae (Der f). Male C3H/HeN mice were intratracheally administered with Der f and were fed a diet containing 0% or 2.5% FOS ad libitum. Supplementation with FOS alleviated mite allergen-related airway inflammation characterized by eosinophilic inflammation and goblet cell hyperplasia, which was evidenced by cytological and histological examinations. In addition, the FOS-supplemented diet reduced the serum allergen-specific IgG\(_1\) level as compared with a control diet in the presence of the mite allergen. Moreover, FOS tended to suppress the expression of IL-5 and eotaxin in the lungs, which is enhanced by mite allergen. These results suggest that dietary supplementation with FOS can prevent/improve airway inflammation induced by the mite allergen. This effect can be at least partially associated with the inhibition of allergen-specific Ig production and probably with that of IL-5 and eotaxin expression.
BENZENE METABOLITES INHIBIT THE RELEASE OF PROINFLAMMATORY MEDIATORS AND CYTOKINES FROM HUMAN BASOPHILS

I. BORRELLI, S. LOFFREDO, R.I. STAIANO, A. FRATTINI, A. BERGAMASCHI, G. MARONE and M. TRIGGIANI

Institute of Occupational Health, Catholic University of the Sacred Heart, Rome; 1Division of Clinical Immunology and Allergy, Center for Basic and Clinical Immunology Research (CISI), University of Naples “Federico II”, Naples, Italy

Received August 6, 2009 – Accepted May 14, 2010

Benzene and its metabolites have been involved in the pathogenesis of chronic lung inflammation and allergic disorders such as bronchial asthma. However, the effects of these xenobiotics on human basophils, key cells in the development of respiratory allergy, have not been investigated. We examined the effects of hydroquinone (HQ) and benzoquinone (BQ), two important chemicals implicated in benzene toxicity, on the release of preformed (histamine) and de novo synthesized mediators (cysteinyl leukotriene $\text{C}_4$, $\text{LTC}_4$, and IL-4) from human basophils. Preincubation of basophils purified from normal donors with HQ (3-100 μM) inhibited up to 30% histamine release induced by anti-IgE and up to 55% of that induced by the $\text{Ca}^{2+}$ ionophore A23187. HQ had no effect on histamine release induced by formyl-methionyl-leucyl-phenylalanine (f-Met-Leu-Phe). Preincubation of basophils with BQ (3-100 μM) resulted in the concentration-dependent inhibition of histamine release (up to 70%) induced by anti-IgE, A23187 and f-Met-Leu-Phe. HQ completely suppressed the de novo synthesis of $\text{LTC}_4$ from basophils challenged with anti-IgE or f-Met-Leu-Phe and the production of IL-4 in cells stimulated with anti-IgE. These results indicate that two major benzene metabolites, HQ and BQ, inhibit the release of proinflammatory mediators and Th2-promoting cytokines from basophils activated by different stimuli. These results suggest that benzene metabolites interfere with multiple intracellular signals involved in the activation of human basophils.

T CELL ACTIVATION STATE IN THE INDUCED SPUTUM OF ASTHMATICS TREATED WITH BUDESONIDE

A. VATRELLA, F. PERN, G. PELAIA, R. PARRELLA, R. MASELLI, S.A. MARSICO and C. CALABRESE

Department of Clinical and Experimental Medicine, Division of Respiratory Disease, University “Federico II” of Naples; 1Department of Experimental and Clinical Medicine, Division of Respiratory Disease, University “Magna Graecia” of Catanzaro; 2Third Division, Cotugno Hospital, Naples; 4Department of Cardiothoracic and Respiratory Sciences, Division of Respiratory Disease, Second University of Naples, Italy

Received December 4, 2009 – Accepted June 3, 2010

Bronchial hyperresponsiveness and airway infiltration with eosinophils and T lymphocytes are key features of asthma. In particular, CD4$^+$ T cells are currently believed to play a pivotal role as initiators and coordinators of the asthmatic inflammatory response and, therefore, they represent a crucial target of corticosteroid treatment. The aim of the present investigation is thus to evaluate, in patients with mild asthma, the effects of inhaled corticosteroid therapy on the following parameters: (i) functional state of CD4$^+$ T cells; (ii) airway eosinophilia; (iii) bronchial hyperresponsiveness to methacholine. The study was completed by twenty asthmatic, atopic subjects, subdivided into two groups of ten and treated for 12 weeks with either inhaled budesonide (200 μg twice daily) or terbutaline alone (500 μg twice daily), respectively. Expression of CD4$^+$ T cell activation markers was measured in induced sputum at baseline and after 1, 4, 8 and 12 weeks of treatment by flow cytometry, which showed a down-regulation of HLA-DR and CD25 surface proteins in the budesonide group, compared with the control group; these differences resulted as being statistically significant through weeks 4-12. Budesonide also induced a quick, sharp reduction in the percentage of eosinophils detectable in induced sputum, as well as a more gradual progressive improvement in airway hyperresponsiveness to methacholine. Therefore, in addition to assessing various indices of bronchial inflammation, flow cytometry can be reliably applied to induced sputum in order to monitor, even in mildly symptomatic patients, the effects of anti-asthma treatments on T cell activation.
NA⁺/H⁺ EXCHANGER 1- AND AQUAPORIN-1-DEPENDENT HYPEROSMOLARITY CHANGES DECREASE NITRIC OXIDE PRODUCTION AND INDUCE VCAM-1 EXPRESSION IN ENDOTHELIAL CELLS EXPOSED TO HIGH GLUCOSE

R. MADONNA¹, E. MONTEBELLO¹, G. LAZZERINI², M. ZURRO¹ and R. DE CATERINA¹²

¹Cardiology and Center of Excellence on Aging, “G. d’Annunzio” University, Chieti; ²CNR Institute of Clinical Physiology, Pisa, Italy

Received May 11, 2009 – Accepted November 3, 2009

Since diabetic hyperglycaemia causes hyperosmolarity, we investigated the contribution of hyperosmolarity in the proinflammatory endothelial effects of hyperglycemia, and sought to unravel the mechanisms involved. Human aortic endothelial cells (HAEC) were incubated for short-term (1-3 days) or long-term (1-2 weeks) exposures to 5.5 mmol/L glucose (normoglycemia, basal), high glucose (25 and 45 mmol/L, HG), or a hyperosmolar control (mannitol 25 and 45 mmol/L, HM), in the presence or absence of the aquaporin-1 (AQP1) inhibitor dimethylsulfoxide (DMSO), the Na⁺/H⁺ exchanger 1 (NHE-1) inhibitor cariporide (CA), the protein kinase C (PKC) inhibitor calphostin C or the PKCβ isoform inhibitor LY379196 (LY). Both short- and long-term exposures to HG and HM decreased the expression of the active, phosphorylated form of endothelial nitric oxide synthase (Ser1146-eNOS) and, in parallel, increased vascular cell adhesion molecule (VCAM)-1 protein at immunoblotting. After 24 h incubation with HG/HM, we observed a significant similar and concentration-dependent enhancement of AQP1 expression. DMSO and CA inhibited hyperosmolarity-induced VCAM-1 expressions, while increasing nitrite levels and Ser1146-eNOS expression. Gene silencing by small interfering RNA reduced the expression of AQP1 and suppressed HG- and HM-stimulated VCAM-1 expression. Calphostin C and LY blunted hyperosmolarity-induced VCAM-1 expression, while increasing the expression of Ser1146-eNOS and nitrite production. Thus HG decreases eNOS activation and induces total VCAM-1 expression in HAEC through a hyperosmolar mechanism. These effects are mediated by activation of the water channels AQP1 and NHE-1, and a PKCβ-mediated intracellular signaling pathway. Targeting osmosignaling pathways may represent a novel strategy to reduce vascular effects of hyperglycemia.
THE ROLE OF ETANERCEPT ON THE EXPRESSION OF MARKERS OF T HELPER 17 CELLS AND THEIR PRECURSORS IN SKIN LESIONS OF PATIENTS WITH PSORIASIS VULGARIS

E. ANTIGA1,2, W. VOLPI1, C. CHIARINI1, E. CARDILICCHIA3, L. FILI3, C. MANUELLI1,3, P. PARRONCHI3, P. FABBRI1 and M. CAPRONI1

1Department of Dermatological Sciences, University of Florence, Florence; 2Department of Clinical Physiopathology, University of Florence, Florence; 3Center for Research, Transfer and High Education (DENOTHe), Department of Internal Medicine, University of Florence, Florence, Italy

Received January 27, 2010 – Accepted June 15, 2010

Very recently, it has been demonstrated that CD161, retinoic acid–related orphan receptor γt (RORγt) and CC-chemokin receptor 6 (CCR6) can be considered good surface markers to detect T helper 17 cells and their precursors, T cell populations that are considered to play an important role in the pathogenesis of psoriasis. In the present study, we evaluate the clinical involvement by calculating the PASI score and the number of CD4+, CD161+, RORγt+ and CCR6+ cells before and after a 12-week course with etanercept or acitretin in patients with moderate-to-severe, plaque-type psoriasis vulgaris. Ten patients were given etanercept 50 mg twice weekly and 10 patients acitretin 0.4 mg/kg per day, both for 12 weeks. At the baseline and at the end of the treatment PASI was calculated, and skin biopsies were taken to evaluate the expression of CD4, CD161, RORγt and CCR6 by immunohistochemistry. As controls, 10 patients with atopic dermatitis (AD) were included in the study. After 12 weeks, PASI was significantly lower than at the baseline for both groups. However, etanercept-treated patients showed lower PASI than acitretin-treated ones. While CD4+ cell numbers were similar in both diseases, all the other markers, that are considered more specific for Th17 cells and their precursors, were more expressed in psoriasis than in AD. Furthermore, only etanercept, but not acitretin, was able to significantly reduce CD161+, RORγt+ and CCR6+ cells in skin lesions of patients with psoriasis. Our study provides further evidence of the role of the Th17 pathway in the pathogenesis of psoriasis. Furthermore, our findings suggest that etanercept is able to downregulate the expression of the recently recognized markers of Th17 cells and their precursors CD161, RORγt and CCR6, while acitretin is not. This activity on the Th17 lineage may contribute to the efficacy of etanercept in the treatment of psoriasis.

IDENTIFICATION OF IP-10 AND IL-5 AS PROTEINS DIFFERENTIALLY EXPRESSED IN HUMAN COMPLICATED AND UNCOMPLICATED CAROTID ATHEROSCLEROTIC PLAQUES

E. PROFUMO, B. BUTTARI, M.E. TOSTI1, C. ALESSANDRI2, G. VALESINI2, L. MARCUCCIO3, C. TESORI1, R. CAPOANO3, B. SALVATI3 and R. RIGANÒ

Department of Infectious, Parasitic and Immune-mediated Diseases, Istituto Superiore di Sanità, Rome; 1National Centre of Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità, Rome; 2Division of Rheumatology, Department of Clinical Medicine and Therapy, University of Rome Sapienza, Policlinico Umberto I, Rome; 3Department of Surgical Sciences, University of Rome Sapienza, Policlinico Umberto I, Rome, Italy

Received April, 19. 2010 – Accepted June 17, 2010

Inflammation plays a crucial role in the development and progression of atherosclerotic plaques. The aim of this study is to compare culture supernatants from uncomplicated and complicated carotid atherosclerotic plaques by a multiplex approach, to assess the molecular mediators associated with a complicated plaque phenotype. Atherosclerotic plaques were obtained from 17 patients undergoing carotid endarterectomy. Supernatants from plaque cultures were evaluated by Bio-Plex cytokine assay to determine 27 pro- and anti-inflammatory cytokines, chemokines and growth factors. Complicated plaques secreted higher levels of IP-10 (p = 0.027) and lower levels of IL-5 (p = 0.045) than did uncomplicated ones. Distinctive secretory patterns of cytokines, chemokines and growth factors were present in the two types of plaque. Our study identifies IP-10 and IL-5 as proteins differentiating complicated and uncomplicated plaques from human carotid arteries and provides new insights into the interplay of molecular mediators with atherosclerotic plaque progression.
CAN CYCLOSPORINE-A ASSOCIATED TO METHOTREXATE MAINTAIN REMISSION INDUCED BY ANTI-TNF AGENTS IN RHEUMATOID ARTHRITIS PATIENTS?  
(CYNAR PILOT STUDY)

A. MIGLIORE, E. BIZZI, U. MASSAFRA, F. VACCA, L.S. MARTIN MARTIN¹, C. FERLITO², E. POESTÀ², M. GRANATA³ and B. LAGANÀ²

Operative Unit of Rheumatology, S.Pietro FBF Hospital, Rome; ¹Department of Internal Medicine, Regina Apostolorum Hospital, Albano Laziale, Rome; ²UOS for Autoimmune Diseases, “Sapienza” University, Second Medical School of Rome; ³UOC of Rheumatology, San Filippo Neri Hospital, Rome, Italy

Received March 17, 2010 – Accepted July 13, 2010

Biological therapies, such as etanercept, adalimumab and infliximab, have demonstrated good efficacy in inducing rheumatoid arthritis to low disease activity levels. Nevertheless, their cost, as well as the related risk of side effects, especially in long-term therapies, are still high. Furthermore, there is a good deal of evidence proving loss of efficacy of such therapies in the long term, often necessitating the shift from one specific anti-TNF biological treatment to another. There are also other open debates on the amount of time a patient should undergo an anti-TNF therapy, on the possibility of inducing a complete remission in early arthritis and, once remission or low disease activity is obtained, on the possibility of interrupting the anti-TNF-based therapy. In this study we investigated whether A-Cyclosporin and Methotrexate association may be effective in maintaining low disease activity obtained by anti-TNF therapies. Twenty-three rheumatoid arthritis-affected patients, whose diagnosis was made according to ACR criteria, with a disease duration of less than 3 years, and DAS28<3.2 that reached a level of low disease activity within 6-8 months from beginning anti-TNF and Methotrexate therapy, were enrolled in the study. After the suspension of anti-TNF therapy, patients were started on A-Cyclosporine (2-3 mg/kg/day) and Methotrexate (15mg/week) therapy. DAS28, Pain VAS, Erythrosedimentation Rate (ESR), and C Reactive Protein (CRP) were all tested at time 0 and at 6 months, as well as liver and kidney profiles, after the interruption of the anti-TNF therapy and the beginning of A-Cyclosporine and Methotrexate therapy. Side effects were also recorded. Of 23 patients undergoing the A-Cyclosporin and Methotrexate therapy for maintaining low disease activity in rheumatoid arthritis obtained by 6-8 months of anti-TNF therapy, 21 completed the study with a 6 month follow-up. Thirteen patients maintained clinical parameters within low disease activity values, while 8 patients showed an increase in DAS28 and other parameters. Only two patients showed an increase in blood pressure that was diagnosed after two months from the beginning of the A-Cyclosporin and Methotrexate therapy. The reduction in the dosage of A-Cyclosporin from 3mg/kg/day to 2mg/kg/day caused a slow normalization of blood pressure values. Our data seem to suggest that more than half of the patients undergoing A-Cyclosporin and Methotrexate therapy seemed to maintain low disease activity parameters of rheumatoid arthritis, obtained after 6-8 months of anti-TNF therapy. Further studies on larger populations are necessary in order to confirm such results and identify predictor factors for different responses.
A STUDY OF ADENOSINE-DEAMINASE GENETIC POLYMORPHISM IN RHEUMATOID ARTHRITIS

G.D. SEBASTIANI, N. BOTTINI1, E. GRECO1, P. SACCUCCI1, G. CANU1, P. LUCARELLI1, F. GLORIA-BOTTINI2 and L. FONTANA1

St. Camillo Hospital, Rheumatology Unit, Rome; 1Department of Internal Medicine, University of Rome Tor Vergata, School of Medicine, Rome; 2Department of Biopathology and Imaging Diagnostics, University of Rome Tor Vergata, School of Medicine, Rome; 3Institute of Molecular Biology and Pathology, National Research Council, Rome, Italy

Received September 29, 2009 – Accepted July 27, 2010

Recent investigations suggest that Adenosine Deaminase (ADA) could play a role in susceptibility to rheumatoid arthritis (RA). The purpose of our study is to investigate the possible role of genetic variability of ADA in the susceptibility to RA. We studied three intragenic ADA polymorphisms, ADA1, ADA2 and ADA6, in a sample of 91 subjects with RA and in 246 healthy subjects from the same Caucasian population and compared genotype and pairwise haplotype distributions between cases and controls. No statistically significant differences between RA and controls are observed for ADA genotypes. A borderline difference for ADA1-ADA2 haplotype distribution is observed due to a decreased proportion of ADA1*2/ADA2*2 haplotype in RA compared to controls. Our data indicate a borderline effect of ADA gene polymorphism on susceptibility to RA that need to be confirmed in other clinical settings.

TREATMENT OF PSORIASIS WITH DIFFERENT DOSAGE REGIMENS OF ETANERCEPT: PRELIMINARY RESULTS FROM THE TaRANTA PLASTIC STUDY GROUP


2nd Dermatology Clinic, MIDIM Department, University of Bari; 1Unit of Dermatology, Ospedale Miulli, Acquaviva delle Fonti (BA); 2Unit of Dermatology, Ospedale Perrino, Brindisi; 3Unit of Dermatology, Ospedale SS Annunziata, Taranto; 4Unit of Dermatology, Ospedale Vito Fazzi, Lecce; 5Unit of Dermatology, Ospedale Fatebenefratelli, Benevento, Italy

Received March 25, 2010 – Accepted August 6, 2010

This pilot open-label study is aimed to assess clinical response in psoriasis patients receiving diverse dose regimens of etanercept, consisting of the same global cumulative dose of etanercept administered over different treatment periods. Eligible patients were assigned sequentially in a 1:1 ratio to receive: etanercept 50 mg once weekly (QW) or 50 mg twice weekly (BIW) for 12 weeks. The final analysis included a total of 72 patients. At week 12 the Psoriasis Area and Severity Index (PASI) and Skindex-29 scores notably improved in both treatment arms, without significant differences between the two groups. The rate of patients attaining a PASI improvement ≥ 50% (PASI 50) at week 12 was 92% in the high-dose group. In these patients, etanercept dosage was decreased to 50 mg QW from week 13, with persistence of the PASI 50 response at week 24 in all cases. Thereafter, treatment was discontinued up to week 36 and almost 30% of patients experienced a gradual relapse of their psoriasis within this period. In the low-dose group, the PASI 50 response was observed in 75% of patients. These responders continued to be treated with etanercept 50 mg QW up to week 36 with persistence of the PASI 50 in 100% of cases at week 24 and 93% at week 36. In the low-dose regimen, 8 patients who did not respond at week 12 underwent dose escalation to 50 mg BIW for a further 12 weeks. At week 24, six of these patients gained the PASI 50 response, 4 of whom maintained the response up to week 36, after treatment discontinuation from week 24. Our results confirm that etanercept is very effective and well-tolerated in psoriasis and that the drug dosages and treatment duration may be modulated and adapted to clinical needs in a flexible way.
LIPOPOLYSACCHARIDE FROM *PORPHYROMONAS GINGIVALIS* STIMULATES RAT MAST CELLS TO CYSTEINYL LEUKOTRIENE GENERATION AND UPREGULATES TOLL-LIKE RECEPTOR -2 AND -4 EXPRESSION

Ł. KONOPKA, M. WIERZBICKI and E. BRZEZIŃSKA-BŁASZCZYK

Department of Experimental Immunology, Medical University of Łódź, Łódź, Poland

Received April 13, 2010 – Accepted September 6, 2010

Mast cells are found in all tissues of the oral cavity and it is suggested that they take part in the development of oral inflammation. As *Porphyromonas gingivalis* is widely recognized as a major pathogen in the development and progression of gingivitis and periodontitis, the aim of our study is to determine the effect of *P. gingivalis* lipopolysaccharide (LPS) on mast cell degranulation, cysteinyl leukotriene (cysLT) generation, and migration, as well as Toll-like receptor (TLR)-2 and -4 expression. Experiments were carried out *in vitro* on rat peritoneal mast cells. LPS-induced mast cell histamine release was estimated by a spectrofluorometric method and cysLT generation by ELISA test. Mast cell migration in response to this antigen was examined according to Boyden’s modified method and TLR expression was determined by flow cytometry. We found that *P. gingivalis* LPS did not induce mast cell degranulation and histamine release. However, activation of mast cells with this bacterial antigen resulted in generation and release of significant amounts of cysLTs. We also documented that LPS from *P. gingivalis* did not stimulate mast cell migration, even in the presence of laminin, whereas it strongly upregulated TLR2 and TLR4 expression on mast cells. Observations that *P. gingivalis* LPS activates mast cells to generate and release proinflammatory mediators such as cysLTs and modulates TLR2 and TLR4 expression indicates that these cells might be involved in the emergency of inflammatory processes evolved in response to *P. gingivalis* infection.

BENEFICIAL EFFECTS OF CHLORELLA-11 PEPTIDE ON BLOCKING LPS-INDUCED MACROPHAGE ACTIVATION AND ALLEVIATING THERMAL INJURY-INDUCED INFLAMMATION IN RATS

J.Y. CHERNG, C.C. LIU¹, C.R. SHEN², H.H. LIN³ and M.F. SHIH³

Department of Chemistry & Biochemistry, National Chung Cheng University, Chia-Yi, Taiwan; ¹Department of Cosmetic Science, Chia-Nan University of Pharmacy and Science; ²Department of Medical Biotechnology and Lab Sciences, Chang Gung University, Tao-Yuan, Taiwan; ³Department of Pharmacy, Chia-Nan University of Pharmacy & Science, Tainan, Taiwan

Received April 29, 2010 – Accepted September 2, 2010

*Chlorella* possesses various remarkable biological activities. One component, Val-Glu-Cys-Tyr-Gly-Pro-Asn-Arg-Pro-Gln-Phe (*Chlorella*-11 peptide) was found to be able to suppress LPS-induced NO production and inflammation. However, the molecular mechanism behind these findings and the consistency between *in vitro* and *in vivo* data have not been investigated. LPS-activated RAW 264.7 macrophages were used to study *in vitro* molecular anti-inflammatory effects of *Chlorella*-11 peptide. After activation, NO production and the expression of iNOS and NF-κB proteins as well as iNOS mRNA were measured using Griess colorimetric assay, Western blotting and RT-PCR, respectively. Alterations in PGE2 and TNF-α contents were also monitored by ELISA. For *in vivo* studies, thermal injury Wistar rats were used and inflammatory indications e.g. serum malondialdehyde (MDA), TNF-α levels and skin erythema were evaluated 48 h after injury implementation. *In vitro* results showed that *Chlorella*-11 peptide produced a dose- and time-dependent inhibition on NO production. The effective inhibition could remain for at least 6 h after LPS activation. It was also found that the expression of LPS-induced iNOS mRNA, iNOS and NF-κB proteins were diminished by the peptide treatment. Concurrently, the levels on TNF-α and PGE2 contents were also monitored by ELISA. For *in vivo* studies, thermal injury Wistar rats were used and inflammatory indications e.g. serum malondialdehyde (MDA), TNF-α levels and skin erythema were evaluated 48 h after injury implementation. *In vitro* results showed that *Chlorella*-11 peptide produced a dose- and time-dependent inhibition on NO production. The effective inhibition could remain for at least 6 h after LPS activation. It was also found that the expression of LPS-induced iNOS mRNA, iNOS and NF-κB proteins were diminished by the peptide treatment. Concurrently, the levels on TNF-α and PGE2 production after LPS activation were also inhibited. These findings are in agreement with the *in vivo* data that animal serum MDA and TNF-α levels and skin erythema in rats were considerably reduced compared to the control group (saline-treated). The significance of this study sheds light on the effectiveness of *Chlorella*-11 peptide in preventing inflammation progression *in vitro* and *in vivo* and its potential for clinical applications.
MICROARRAY ANALYSIS OF NF-κB SIGNALING PATHWAYS IN PBMC OF MICE INFECTED BY TRICHLINELLA SPIRALIS

I. SYMEONIDOU, S. PAPPA1, A. KOURELIS2, A. ANOGEIANAKI3, I. FRYDAS, E. KARAGOUNI4 and M. HATZISTILIANOU1

Laboratory of Parasitology and Parasitic Diseases, School of Veterinary Medicine, Aristotle University of Thessaloniki, Thessaloniki; 12nd Department of Paediatrics, School of Medicine, Aristotle University of Thessaloniki; 2Department of Genetics, Development and Molecular Biology, Biology School, Aristotle University of Thessaloniki, Thessaloniki; 3Physiology Department, School of Medicine, Aristotle University of Thessaloniki; 5Laboratory of Cellular Immunology, Institute Pasteur Hellenique, Athens, Greece

Received May 15, 2010 – Accepted July 15, 2010

The NF-κB pathway gene expression profiles were compared between 10, 20 and 39 days after Trichinella spiralis experimental infection in BALB/c mice. Out of 128 genes, 19 (14.8%) genes were present in non-infected and post-infected mice. The expression of 7 (36.8%) genes was downregulated 10 and 20 days post-infection while 3 (15.8%) genes were upregulated 39 days post-infection. The present study lists the candidate genes of the NF-κB signaling pathway that were commonly and differentially expressed between the specific points of T. spiralis infection, thus suggesting that these genes need to be further investigated to reveal the mechanism of the T. spiralis modulation of the NF-κB signaling pathways.

IN VITRO ACTIVITY OF CEFDITOREN VERSUS OTHER ANTIBIOTICS AGAINST S. PNEUMONIAE CLINICAL STRAINS ISOLATED IN ITALY

G. TEMPERA, P.M. FURNERI, C. FERRANTI, C. GENOVESE, S. RIPA1, S. UNGHERI2 and G. NICOLETTI

Department of Microbiological and Gynaecological Sciences, University of Catania; 1Department of Molecular, Cellular and animal Biology, University of Camerino; 2Institute of Microbiology, University of Milano, Italy

Received May 13, 2010 – Accepted June 2, 2010

Over the last twenty years there has been an alarming increase in isolation of Streptococcus pneumoniae strains with a reduced susceptibility not only to penicillin, but also to other betalactams and macrolides. This phenomenon justifies the great interest in new antibiotics. Cefditoren, a new aminothiazolyl oral cephalosporin, recently commercialized in Italy, is characterized by an extended activity against penicillin-resistant S. pneumoniae. The aim of this study is to evaluate the incidence of the resistance/susceptibility to various antibiotics in 1000 strains of S. pneumoniae (678 SPSS, 219 SPPI and 103 SPPR), clinically isolated during 2009. The data obtained by our in vitro study show that cefditoren is the most active agent against S. pneumoniae. In fact, the MIC90 values of 0.5 µg/ml obtained could be particularly significant in terms of therapeutic predictivity.
IN VIVO CHARACTERIZATION OF ZIRCONIA TOUGHENED ALUMINA MATERIAL:
A COMPARATIVE ANIMAL STUDY

G. MACCAURO, A. CITTA DINI\textsuperscript{1}, G. MAGNANI\textsuperscript{2}, S. SANGIORGI\textsuperscript{2}, F. MURATORI, P.F. MANicone\textsuperscript{3}, P. ROSSI IOMMETTI\textsuperscript{3}, D. MAROTTA, A. CHIERICHINI\textsuperscript{4}, L. RAFFAELLI\textsuperscript{3} and A. SGAMBATO\textsuperscript{1}

Department of Orthopaedics and Traumatology, Catholic University, Rome; \textsuperscript{1}Institute of General Pathology, Catholic University, Rome; \textsuperscript{2}ENEA, Faenza Research Center, Faenza; \textsuperscript{3}Institute of Clinical Dentistry, Catholic University; \textsuperscript{4}Institute of Anesthesiology, Catholic University, Rome, Italy

Received March 3, 2010 – Accepted June 28, 2010

The development of a new chromia-doped Zirconia Toughened Alumina (ZTA) material was previously reported as displaying mechanical properties suitable for implants with load bearing applications, such as orthopaedic and dental implants. This type of biomaterial is expected to be in contact with living tissues for a long period of time and its long-term toxicity must be carefully evaluated. In this study the suitability of this ZTA material as a candidate biomaterial for orthopaedic implants and dental devices was further investigated in vivo in comparison to alumina and zirconia, which are currently used in orthopaedic and dental surgery. Cylinders of the materials were implanted in vivo in white rabbits, and local and systemic tissue reactions were analyzed at different time intervals after surgery. Radiologic examinations displayed the absence of radiolucence around cylinders and no signs of implant loosening up to twelve months. No tumours developed in the animals either locally (at the site of implantation), or systemically in the peripheral organs. The results obtained suggest that this new ZTA material does not display any long term pathogenic effect in vivo. These findings extend our previous observations on the biocompatibility and the absence of any long-term carcinogenic effect in vitro of this material which displays interesting properties for biomedical applications. In conclusion, we report the in vivo characterization of a new chromia-doped ZTA material and confirm its suitability as a candidate biomaterial for orthopaedic implants and dental devices since it does not give any local nor systemic toxicity even after a long period of time after implantation.
THE EFFECTS OF ALCOHOLISM PHARMACOTHERAPY ON IMMUNE RESPONSES IN ALCOHOL-DEPENDENT PATIENTS

S. FRANCHI, P. SACERDOTE, S. MORETTI, G. GERRA¹, V. LECCESE², M.V. TALLONE³, A.E. PANERAI and L. SOMAINI²

Department of Pharmacology, University of Milano, Milano, Italy; ¹United Nations Office on Drugs and Crime, Global Challenges Section, Division for Operations, Vienna, Austria; ²Addiction Treatment Centre, Health Local Unit, ASL BI Biella, Italy; ³Department of Clinical Laboratory, Health Local Unit, ASL BI, Biella, Italy

Received February 24, 2010 – Accepted April 30, 2010

Chronic alcohol use has profound modulatory effects on the immune system. Both the innate and the acquired immunity are compromised. The use of pharmacotherapy is increasingly applied to enhance the percentage of success in maintaining alcoholic patients in remission. Disulfiram, naltrexone and gamma hydroxybutiric acid are the drugs used for this purpose in Italian Addiction Services. In this study we analyze the effect of pharmacotherapy of alcohol dependence on immune responses in alcoholics. Six groups were studied. Group A included 10 patients who were still using alcohol. Group B consisted of 10 patients abstinent from alcohol in treatment only with group therapy. Groups C, D and E were composed of 10 patients each, treated for at least 6 months with oral doses of gamma hydroxybutiric acid, naltrexone or disulfiram respectively. Ten age- and sex-matched healthy volunteers who never misused alcohol were included as a control group. Lymphoproliferation and peripheral mononuclear cell production of the Th1 cytokines IL-2 and IFN-γ, the Th2 cytokine IL-4, and of the pro-inflammatory cytokines IL-1 and TNF-α were evaluated in all the patients and controls. The level of activity of the hypothalamus pituitary adrenal axis was assessed. Both ACTH and cortisol levels in plasma were elevated in alcoholic patients with no treatment. In this group a significant alteration of cytokine production was observed. TNF and IFN-γ were lower than controls, while the Th2 cytokine IL-4 was increased. These altered levels state for a Th1/Th2 unbalance characterized by decreased Th1 response in the presence of Th2 predominance. In patients undergoing pharmacological treatment, none of the immune parameters were different from those observed in healthy controls, independently of the type of drug administered. These data indicate that pharmacotherapy more than group therapy treatment is able to ameliorate the immune system functioning in alcoholic patients.

INTERKERATIN PEPTIDE-PROTEIN INTERACTIONS THAT PROMOTE HPV16 E7 GENE EXPRESSION

A. LUCCHESE, R. SERPICO, A. GUIDA, V. CRINCOLI¹, C. SCULLY² and D. KANDUC³

Department of Odontostomatology, Orthodontics and Surgical Disciplines, University of Naples (SUN), Naples, Italy; ¹Department of Odontostomatology and Surgery, University of Bari, Bari, Italy; ²UCL-Eastman Dental Institute, London, England; ³Department of Biochemistry and Molecular Biology, University of Bari, Bari, Italy

Received January 6, 2010 – Accepted June 17, 2010

Human papillomavirus (HPV) 16 E7 gene product encodes the major transforming activity of the virus so as to induce neoplastic transformation. Continued expression of HPV16 E7 protein is required for both the establishment and maintenance of the transformed cellular phenotype. Therefore, understanding of the molecular and biochemical factors leading to the expression of E7 protein is important in relation to HPV-associated diseases. Previously, we identified a rare codon usage and a specific interaction between cytokeratin (CK) 7 and HPV16 E7 mRNA as factors modulating HPV16 E7 expression. In the present study we report that CK19, a biochemical marker of squamous oral and cervical cancer carcinogenesis, promotes the expression of HPV16 E7 oncoprotein by binding to the CK7⁹₂-⁹₇SEQIKA peptide. These findings shed light on the dynamic functionality of the intermediate filament cytoskeleton, open new perspectives for investigating the role of CKs in controlling HPV16 E7 expression, and suggest new therapeutic avenues for HPV-associated carcinomas.
LONG-TERM SAFETY AND EFFICACY OF TOPICAL CYCLOSPORINE IN 156 CHILDREN WITH VERNAL KERATOCONJUNCTIVITIS

N. PUCCI, R. CAPUTO1, F. MORI, C. DE LIBERO1, L. DI GRANDE, C. MASSAI, R. BERNARDINI and E. NOVEMBRE

Allergy and Clinical Immunology Unit, and 1Clinical Ophthalmology Unit, Anna Meyer Children’s Hospital, Department of Pediatrics, University of Florence, Italy

Received February 14, 2010 – Accepted July 2, 2010

Vernal keratoconjunctivitis (VKC) is a chronic and potentially sight-threatening disease. Topical corticosteroids (Cs) seem to be the only effective treatment for this condition, although severe side effects may occur owing to their prolonged use. More recently, cyclosporine (Cyc) eye drops have been reported as a valid alternative, but so far such treatment has only been successfully experimented for a short time and in small numbers of patients. The aim of our study is to evaluate the long term safety and efficacy of topical cyclosporine eye drops in children suffering from VKC. Over a period of 7 years we followed a large group of children suffering from severe VKC. They were selected to start cyclosporine eye drop treatment, because of the prompt relapse of their disease as soon as they stopped topical corticosteroids administration. All patients were followed-up in an ambulatory care assessment. A total of 156 children with VKC were treated with topical cyclosporine eye drops over a period ranging from two to seven years [mean time 3.8±1.09 years] during the seasonal relapse [range 9-66 months; mean time 24.7±10.4 months]. Two formulations, at 1% and 2% (82% and 18% respectively) concentrations, of cyclosporine eye drops were made. The dosage administered was one drop in each eye from two to four times a day, depending on the severity of the disease and the season. The ocular objective scores were determined and compared every year, at the beginning and at the end of each treatment period. Blood samples were collected once a year in order to check both kidney and liver functions, as well as cyclosporine serum levels. We enrolled 156 patients (mean age 8.31±2.79 years; 116 males and 40 females) who were followed-up over a period of 7 years [156 (100%) children during the first and the second year; 138 (88.5%) patients until the third year; 90 (57.7%) until the fourth year; 32 (20.5%) until the fifth year; 10 (6.4%) until the sixth year and 2 (1.3%) until the seventh year]. The ocular objective scores significantly improved (p<.001) over the years when comparing them at the beginning and the end of each seasonal treatment period, except for the last year. Over the treatment period, non-significant changes were recorded in terms of kidney and liver enzymatic activities and also in terms of cyclosporine serum levels. Cyclosporine eye drops, either at 1% or 2% concentrations, resulted safe and effective for long-term treatment of VKC in 156 children. The lack of significance of the score results during the seventh year can be explained by the small number of subjects treated for such a long period. A systematic ocular examination and both liver and kidney functional investigations allowed us to exclude the possibility of local or systemic side effects due to cyclosporine. If either transient or long-lasting, the occurrence of burning was referred by some of the patients treated, but none of them required to discontinue the drug. In conclusion, this is the first study showing that topical cyclosporine is easily handled even by children, with safe and effective results even when it is used over a long period of time. Our findings, though encouraging, need to be confirmed by further studies.
ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND INTELLECTUAL DISABILITY: A STUDY OF ASSOCIATION WITH BRAIN-DERIVED NEUROTROPHIC FACTOR GENE POLYMORPHISMS

A. AURELI, T. DEL BEATO, P. SEBASTIANI, A. MARIMPIETRI, C. V. MELILLO, E. SECHI and S. DI LORETO

Institute for Organ Transplantation and Immunocytology (ITOI) – CNR, L’Aquila; 1Childhood and Adolescence Neuropsychiatric Clinic; University of L’Aquila, ASL n. 4, L’Aquila, Italy

Received January 10, 2010 – Accepted July 5, 2010

Symptoms of attention-deficit hyperactivity disorder (ADHD) have been found in several studies of children with intellectual disabilities (ID) but the two diseases are not always associated. Several lines of evidence implicate the involvement of brain-derived neurotrophic factor (BDNF) in ADHD, and it may also be relevant in ID due to its known involvement in the development of the central nervous system (CNS) and in learning/memory functions. We genotyped paediatric patients with ADHD and ID for the Val66Met and 270 C/T polymorphisms in BDNF. Diagnosis of ADHD and ID was confirmed by the clinicians in accordance with DSM-IV criteria. The G/A genotype of the Val66Met SNP was associated with both ADHD and ID, and the G allele was significantly associated with ADHD. The C/C genotype of the C270T SNP was significantly overrepresented in both ADHD and ID groups compared with the controls. Data suggest that both BDNF polymorphisms could play a role in the etiology of ADHD. In addition, we present the first results suggesting that these BDNF SNPs are significantly associated with ID.

ALLERGIC AND NON-ALLERGIC DRUG HYPERSENSITIVITY REACTIONS IN CHILDREN


Department of Allergology, Policlinico “A. Gemelli”, Catholic University of the Sacred Heart, Rome, Italy

Received September 30, 2009 – Accepted July 26, 2010

Adverse drug reactions (ADR) are an important medical problem. The aim of this study is to investigate the clinical characteristics of children with ADR and to assess the tolerability of alternative drugs in children (under 16 yrs of age) with a history of ADR. We studied 278 children (132 males and 146 females). Patients were studied by recording personal history and performing in vivo skin testing, in vitro laboratory tests and challenge tests. Patients who had experienced mild adverse reactions underwent challenge tests without any premedication; patients with a clinical history of moderate reactions, received a premedication with sodium cromolyn 30 min before the oral challenge; patients with a clinical history of severe reactions or undergoing parenteral challenges, were given an antihistamine 30 minutes before. A total of 660 adverse events were reported with 126 different drugs involved. Antimicrobial agents were the most involved drugs (51.7%). Non-steroidal anti-inflammatory drugs were involved in 22.7% of episodes. The most reported symptoms were cutaneous. Allergy testing was negative in 272 patients. A diagnosis of drug allergy was reported for 6 patients. A total of 669 challenge tests were performed. 639 were negative at first attempt while 22 were positive. Eight were repeated using a different premedication and resulted negative. Hypersensitivity drug reactions in children are mainly non-allergic. A premedication with sodium cromolyn or with oral H1-antihistamines may be useful in preventing ADR.
Systemic sclerosis (SSc) is characterized by excessive fibrosis throughout the body. There are two major subsets of SSc, diffuse cutaneous Systemic sclerosis (dSSc) and limited cutaneous Systemic sclerosis (lSSc). Fibroblasts play a key role in SSc. The expression and function of the urokinase (uPA)-mediated plasminogen activation (PA) system, a well-characterized system of serine-proteases involved in several pathological processes, has been investigated in SSc fibroblasts. The expression of the components of the PA system, including uPA, its type-1 and type-2 inhibitors (PAI-1 and PAI-2) and its receptor (uPAR), was examined by Western blot in fibroblasts from patients affected by limited and diffuse forms of SSc. uPA and PAI-1 secretion increased only in fibroblasts from lSSc lesions compared to normal fibroblasts. PAI-2 levels were decreased in fibroblasts from both SSc forms. Interestingly, fibroblasts from areas not adjacent to the lesions (not-affected) of the diffuse form showed reduced levels of PAI-1 and increased uPAR expression. Adhesion experiments showed reduced adherence to VN of fibroblasts from ISSc lesions and from non-affected areas of the diffuse form, as compared to normal controls. These results suggest a role for uPA and PAI-1 in the ISSc form, likely related to the activation of latent forms of cytokines and to the accumulation of ECM components, whereas a role for uPAR can be hypothesized in the evolvement of the diffuse form, based on its up-regulation in the non-affected areas.
Haptoglobin (Hpt) is an acute phase protein characterized by three major phenotypes (Hpt 1-1, Hpt 2-1 and Hpt 2-2). The Hpt 2-2 phenotype is associated with increased prevalence of various systemic diseases, including autoimmune disorders. Moreover, the Hpt 2-2 phenotype induces a shift from Th1 to Th2 response and increases fibrotic processes. On this basis, we performed serum proteomic analysis of patients with Systemic Sclerosis (SSc), a connective tissue disorder associated with Th2-type immune response and characterized by interstitial and perivascular fibrosis due to different factors (including genetic, environmental, immunological and microchimeric factors). Serum of 23 SSc outpatients (4 males, 19 females, mean age 54±5.3 years) diagnosed according to the American Rheumatism Association (ARA) criteria, were considered for the proteomic analysis and compared to serum of 21 control subjects. Serum depleted of HAP was analyzed by 2-DE, and Hpt chain spots were identified by WB. The expression frequency of each Hpt α chain in SSc patients and controls was compared and quantitative analysis of spot expression (% Vol) was performed. Above all, our study amplifies the limited data in the literature on proteomic analysis in SSc, also confirming previous data that revealed a significant increase of haptoglobin type 2–2 and a concomitant decrease of the 1–1 phenotype in SSc patients. Moreover, our results demonstrate that c spots are more prevalent in SSc patients than in controls (91.3% vs 55.5%, p<0.05), while the expression frequency of a and b spots does not change. In patients Hpt 2-1 or Hpt 1-1 e spot is less abundant. According to our results, the c and e spots can be considered markers for SSc and thus be of use for the early diagnosis of connective tissue disorders and in establishing appropriate treatment.
HOMOCYSTEINE, VITAMIN B$_{12}$ AND FOLIC ACID LEVELS IN PSORIATIC PATIENTS AND CORRELATION WITH DISEASE SEVERITY

V. BRAZZELLI, V. GRASSO, L. FORNARA, E. MOGGIO, G. GAMBA$^1$, S. VILLANI$^2$ and G. BORRONI

Department of Human and Hereditary Pathology, Institute of Dermatology, $^1$Department of Internal Medicine, $^2$Department of Health Sciences Section of Medical Statistics and Epidemiology, University of Pavia and Foundation IRCCS Policlinico San Matteo, Pavia, Italy

Received January 13, 2010 – Accepted July 23, 2010

Hyperhomocysteinaemia represents an independent risk factor for atherosclerotic cardiovascular disease, stroke, peripheral arterial occlusive disease and venous thrombosis. Psoriasis is a chronic inflammatory skin disease associated with increased atherothrombosis and cardiovascular risk profile. The aim of this study is to investigate homocysteine, folic acid and vitamin B12 levels in a cohort of psoriatic patients and its relationship with the severity of the disease. A retrospective observational study in 98 patients with chronic plaque psoriasis and 98 healthy controls was performed. Total plasma homocysteine level, folic acid, vitamin B$_{12}$ and PASI index were assessed in every patient. Patients with psoriasis had plasma homocysteine levels higher than controls (57% of cases and 25% of controls; $p<0.0001$). Folic acid and vitamin B$_{12}$ plasma levels were lower in psoriatic patients than in controls ($p = $ NS), lower levels of vitamin B$_{12}$ were found in patients with hyperhomocysteinaemia compared to patients with a normal value of homocysteine ($p = 0.0009$). The severity of psoriasis assessed according to PASI (19.51±16.26) did not directly correlate either with higher levels of homocysteine or with vitamin B$_{12}$ and folic acid plasma levels. In conclusion, a significantly higher prevalence of hyperhomocysteinaemia was found in psoriatic patients compared to healthy controls. A significant correlation between hyperhomocysteinaemia and lower vitamin B$_{12}$ levels, but not folic acid, was evidenced. On the contrary, our data do not correlate the high level of homocysteine with higher PASI scores or psoriasis type, suggesting that homocysteine level can be considered an independent risk factor in psoriatic patients.
APELIN PLASMA LEVELS PREDICT ARRHYTHMIA RECURRENCE IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION

C. FALCONE1,2,4, M.P. BUZZI1,2, A. D’ANGELO3, S. SCHIRINZI1,2, R. FALCONE1, R. RORDORF3, A. C. CAPETTINI1, M. LANDOLINA3, C. STORTI2 and G. PELISSERO4

1Interdepartmental Center for Research in Molecular Medicine (CIRMC), University of Pavia, Pavia; 2Department of Cardiology, Istituto di Cura Città di Pavia University Hospital, Pavia; 3Department of Cardiology, Fondazione IRCCS San Matteo Hospital, Pavia; 4IRCCS San Donato Hospital, Milano

Received March 1, 2010 – Accepted August 5, 2010

Low levels of the regulatory peptide apelin have been reported in patients with lone atrial fibrillation (AF). We evaluate the potential utility of assessing apelin plasma levels as a predictor of AF recurrence in individuals presenting for electrical cardioversion. Plasma levels of apelin, brain natriuretic peptide (BNP) and high-sensitivity C-reactive protein were measured in 93 patients, with persistent AF before successful external electrical cardioversion.Significantly lower apelin plasma levels were found in patients with AF recurrence as respect to population with persistence of sinus rhythm during a six months follow-up. The hazard increased with duration of AF, left atrial dimension, BNP concentrations. Subjects with apelin levels below the median had a hazard ratio of 3.1 of arrhythmia recurrence with respect to those with high apelin levels (p< 0.05). A significant difference in BNP levels was found between patients with and without AF recurrence during the follow-up. After adjusting for potential confounders, both BNP and apelin retained their statistical significance as independent predictors of arrhythmia recurrence. Patients with both low apelin and elevated BNP had a worse prognosis compared with those with either low apelin or elevated BNP alone. Low plasma apelin levels before external electrical cardioversion are an independent prognostic factor for arrhythmia recurrence in patients with AF treated with antiarrhythmic drugs. Apelin may be of particular value for the identification of high-risk patients in addition to BNP.
PHARMACOLOGICAL FUNCTIONAL MRI ASSESSMENT OF THE EFFECT OF IBUPROFEN-ARGININE IN PAINFUL CONDITIONS

S. DELLI PIZZI1, D. MANTINI1,2,3, A. FERRETTI1,2, M. CAULO1,2, I. SALERIO4, G.L. ROMANI1,2, C. DEL GRATTA1,2 and A. TARTARO1,2

1Department of Neuroscience and Imaging, “G. d’Annunzio” University, Chieti; 2Institute for Advanced Biomedical Technologies, “G. d’Annunzio” University Foundation, Chieti; 3Laboratory for Neuro-psychophysiology, K.U. Leuven Medical School, Leuven, Belgium; 4Innovation and Medical Sciences, Zambon SpA, Bresso, Milano, Italy

Received April 12, 2010 – Accepted September 6, 2010

Pharmacological functional magnetic resonance imaging (phMRI) is a valuable tool for the investigation of pharmacological effects of a drug on pain processing. We hypothesized that the ibuprofen-arginine combination, in line with its characteristic analgesic properties, may influence the phMRI response at the central level, as compared to placebo. Ten healthy subjects underwent a double-blind, placebo-controlled, randomized, cross-over phFMRI study with somatosensory painful stimulation of the right median nerve. We measured the blood oxygen level dependent (BOLD) signal variations induced in conditions of pain after oral administration of either ibuprofen-arginine or placebo formulations. Independent component analysis (ICA) was used for the analysis of the fMRI data, without assuming a specific hemodynamic response function (HRF), which may be altered by drug administration. Median nerve electrical painful stimulation mainly activated the primary contralateral and the secondary somatosensory cortices, the insula, the supplementary motor area, and the middle frontal gyrus. Placebo and ibuprofen-arginine administration induced activation bilaterally in the premotor cortex, and an overall reduction in the other pain-related areas, which was more prominent in the left hemisphere. A task-related increase of BOLD signal between drug and placebo was observed bilaterally in the primary somatosensory area and the middle frontal gyrus without any changes in subjective pain scores. Overall, our findings show that ibuprofen-arginine, in line with the characteristic analgesic properties of ibuprofen, influences the BOLD response in specific pain-related brain areas with respect to placebo, with a vasoactive effect possibly due to arginine.
THE CLINICAL EFFICACY OF A SUBLINGUAL MONOMERIC ALLERGOID AT DIFFERENT MAINTENANCE DOSES: A RANDOMIZED CONTROLLED TRIAL

M. MAROGNA, F. COLOMBO, C. CERRA, M. BRUNO, A. MASSOLO, G.W. CANONICA, P. FALAGIANI and G. PASSALACQUA

Pneumology Unit, Cuasso al Monte, Macchi Hospital Foundation, Varese, Italy; 1Scientific Department, Lofarma S.p.A., Milan, Italy; 2Dept. of Ecosystem and Public Health, Faculty of Veterinary Medicine, University of Calgary, Calgary, Alberta, Canada; 3Allergy and Respiratory Diseases, University of Genoa, Italy

Received April 8, 2010 – Accepted May 19, 2010

Sublingual immunotherapy is widely recognized as a viable treatment for allergic rhinitis and asthma, but the optimal dosage is still under debate, especially with modified allergens. We assessed the clinical effects of a monomeric allergoid across 3 different maintenance doses in mite-monosensitized patients with rhinitis and intermittent asthma. Eighty-nine patients allergic to HDM were randomized to 3 maintenance doses of monomeric allergoid (Lais®, Lofarma) or medications only. All the patients recorded their symptoms and rescue drug consumption in a diary card from November to February. Additionally, nasal eosinophil count, spirometry and methacholine bronchial challenge were performed at the beginning of the study and after 3 years. The symptom scores showed a clear improvement in all the three active arms versus baseline and versus the controls, irrespective of the dose. Likewise, a similar improvement versus baseline was seen for nasal inflammation and bronchial hyperreactivity. The SLIT with monomeric allergoids produces clinically significant results across a wide range of doses. The absence of significant side effects, even at high doses, is probably due to their low level of allergenicity.

LARGE GRANULAR LYMPHOCYTE LEUKEMIA WITH PURE RED CELL APLASIA ASSOCIATED WITH AUTOIMMUNE POLYENDOCRINOPATHY-CANDIDIASIS-ECTODERMAL DYSTrophy: AN UNFORTUITOUS ASSOCIATION?

B. HERVIER, M. RIMBERT, H. MAISONNEUVE and MA. HAMIDOU

Department of Internal Medicine, C.H.U. de Nantes Hôtel-Dieu, Nantes; Laboratory of Immunology, C.H.U. de Nantes Hôtel-Dieu, Nantes; 2Onco-hématology Department, CHD La Roche Sur Yon, France

Received March 10, 2009 – Accepted June 18, 2010

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a recessively inherited monogenic disease caused by a mutation in the autoimmune regulator (AIRE) gene. AIRE plays a major role in central (thymic) immune tolerance. In the absence of AIRE, autoimmunity develops that is especially targeted at endocrine tissues. T-cell large granular lymphocyte (T-LGL) leukemia is a monoclonal lymphoproliferative disease characterized by persistent and indolent lymphocytosis. Autoimmune manifestations, such as rheumatoid arthritis or autoimmune cytopenia, are also common. We report the case of a patient with APECED, who presented with pure red cell aplasia associated with T-LGL leukemia. The association of T-LGL leukemia and APECED is very rare and may not be fortuitous. The immunological mechanisms of this association are discussed.
A LONG-LASTING RESPONSE TO SORAFENIB TREATMENT IN AN ADVANCED HEPATOCELLULAR CARCINOMA PATIENT


Department of Endocrinology and Clinical Oncology, Referential Rare Tumors Center, University Federico II, Naples; RADIOLOGY DIVISION, University Federico II, Naples, Italy

Received March 5, 2010 – Accepted April 30, 2010

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide. No effective systemic treatment has been established, except for sorafenib chemotherapy. In fact, sorafenib has proved to provide a statistically significant survival extension of about two months in two phase III trials in the North America-Europe area and in the Asia-Pacific area, which respectively reported a median survival after treatment of 10.7 and 6.5 months, respectively. We report the case of an HCC patient, who received a four-month therapy with sorafenib with a clinical, biochemical and radiographic response, but had to interrupt treatment because of a myocardial infarction. Surprisingly, despite no antitumor treatment having been administered for about a year, the patient has shown no tumor progression and is currently on a close follow-up. Should other similar cases be presented, a subset of patients with long-lasting response to sorafenib might be identified.

JC VIRAL REACTIVATION IN A PEDIATRIC PATIENT WITH CROHN’S DISEASE


Department of Public Health Sciences, “Sapienza” University, Rome; Department of Pediatrics, “Sapienza” University, Rome; National Institute for Infectious Diseases “Lazzaro Spallanzani”, Rome, Italy

Received February 24, 2010 – Accepted May 25, 2010

This is a report concerning human polyomavirus JC (JCV) reactivation in a pediatric patient with Crohn’s disease (CD) during the treatment with 5-aminosalicylic acid (5-ASA), a non-steroidal anti-inflammatory drug (NSAID). We examined 9 bioptic samples from three different bowel districts (ileum, cecum, rectum) of this child. These samples were analyzed by Quantitative PCR (Q-PCR) to investigate the presence of JCV DNA. JCV DNA was detected in one rectum biopsy taken two months after 5-ASA treatment. Although our result must be validated in a larger group of subjects and with a longer follow-up period, it underlines the importance of JCV monitoring in CD patients.
SUDDEN PROGRESSION FROM IMPAIRED GLUCOSE TOLERANCE TO TYPE 2 DIABETES AFTER DISCONTINUATION OF ADMINISTRATION OF ANTI-TUMOR NECROSIS FACTOR-ALPHA ANTIBODY INFlixIMAB

F. URSINI, E. SUCCURRO, A. GREMBIALE, S. RUDI, R.D. GREMBIALE and F. ARTURI

Division of Internal Medicine, University of Catanzaro “Magna Graecia”, Catanzaro, Italy

Received December 16, 2009 – Accepted July 5, 2010

We present the case of a 45-year-old man with psoriasis and psoriatic arthritis and concomitant impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). In this patient, refractory to DMARD’s, infliximab was started to control the arthritis. After achieving clinical remission of the disease, infliximab was discontinued and a 75 g- oral glucose tolerance test (OGTT) was performed. After the test, we observed a conversion from IFG/IGT glucose tolerance status to type 2 diabetes. No diet, lifestyle or therapy modifications were made during the observation period. Autoimmune diabetes was ruled out by serum antibodies determination and body weight remained constant, sustaining a protective role of infliximab in the worsening of glucose tolerance.

ETANERCEPT THERAPY IN PATIENTS WITH PSORIASIS AND CONCOMITANT HCV INFECTION

M.C. GARAVAGLIA and G. ALTOMARE

Department of Dermatology, University of Milan, Istituto Ortopedico Galeazzi IRCCS, Milan, Italy

Received February 3, 2010 – Accepted July 22, 2010

Treatment of patients with psoriasis and/or psoriatic arthritis and concomitant hepatitis C infection remains difficult. Except for cyclosporine, other drugs have proved unacceptable because of hepatotoxicity in patients with HCV. With the advent of anti-TNF-alpha drugs, including etanercept, new therapeutic options have become available. Our study population was five patients with psoriasis and/or psoriatic arthritis and concomitant chronic HCV infection undergoing etanercept therapy. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and viral load were used as markers for liver damage and disease progression, respectively. The Psoriasis Area Severity Index (PASI) was used as a reference parameter for evaluating the therapeutic efficacy of etanercept therapy in improving the clinical skin picture. AST, ALT, viral load and PASI were monitored at 3-month intervals starting from the beginning of therapy up to two years after initiation of etanercept therapy. In four out of five patients, liver enzyme levels and viral load remained substantially unchanged during the course of therapy. In the one remaining patient, viral load and liver enzyme levels increased during etanercept therapy, and then decreased following the initiation of Peg-IFN/ribavirin in combination with anti-TNF-alpha therapy. PASI scores decreased in all five patients. Our data suggest that etanercept therapy is safe and provides an efficacious therapeutic alternative in patients with psoriasis and concomitant HCV infection.