EFFORTS TO COUNTERACT LOCALLY THE EFFECTS OF SYSTEMIC IMMUNOSUPPRESSION: A REVIEW ON THE USE OF IMIQUIMOD, A TOPICAL IMMUNOSTIMULATOR IN ORGAN TRANSPLANT RECIPIENTS

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The potent systemic immunosuppression therapy necessary to sustain a life-saving solid organ transplant is associated with an increased incidence of various infections including human papillomavirus infection and skin cancers in organ transplant recipients. Imiquimod, a topical agent that functions through local induction of a specific anti-viral or anti-tumor immune response, appears to be a promising therapeutic option that could potentially counteract in situ the effects of systemic immunosupression in this vulnerable group. Up-to-date studies using this local immune-response modifier in transplanted patients have yielded reassuring and encouraging results regarding its safety and efficacy in this population. However, in order to establish the use of imiquimod as a standard treatment option for organ transplant recipients, additional research and clinical trials are required.

HELICOBACTER PYLORI THERAPY IN CHILDREN: OVERVIEW AND CHALLENGES

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Helicobacter pylori is one of the most common infections found in humans. It was first identified in 1982 and by 1989 had been associated with gastric inflammation and ulcers in adults and children. During the 1990’s evidence emerged of its etiologic role in stomach cancers in adults. That the infection is common and may have serious consequences, has led to an avalanche of research during the last twenty years. During this time, there have been many studies on children which have sought an effective and safe treatment to eradicate the infection, but as yet, no therapy regimen has been found which is always effective and safe. This article provides information, from a pediatric point of view, on the major developments in the therapeutics and therapy of H. pylori infection. It examines first-line treatment regimens, evaluates the efficacy of the main drugs used in the management of (primary) H. pylori infection in children, assesses the potential for the use of probiotics and sequential therapy, examines therapeutic options after failure of initial treatment, and discusses factors affecting eradication rate, including antibiotic resistance, adherence to therapy, and bacterial factors.
Cytokines may influence brain activities especially during stressful conditions, and elevated levels of IL-6 and C-reactive protein have been pointed out in subjects with Major Depression. If pro-inflammatory cytokines play a causative role in major depressive disorders, one would expect that antidepressants may down-regulate these cytokines or interfere with their actions, leading to improvement of depressive symptoms. Accumulating evidence has been published that antidepressants modulate cytokine production and this is particularly true for Tricyclics and Selective serotonin reuptake inhibitors (SSRIs), but the influence of newer antidepressants acting on both serotonin (5-HT) and norepinephrine (NE) such as venlafaxine, duloxetine and mirtazapine on cytokine levels has not been extensively studied. However, both pre-clinical and clinical studies examined in this review have demonstrated that newer serotonin-noradrenalin antidepressants can inhibit the production and/or release of pro-inflammatory cytokines and stimulate the production of anti-inflammatory cytokines, suggesting that reductions in inflammation might contribute to treatment response. Moreover, the results of the present review support the notion that the serotonin-noradrenalin antidepressants venlafaxine and mirtazapine may influence cytokine secretion in patients affected by MD, restoring the equilibrium between their physiological and pathological levels and leading to recovery. To date, no studies have evaluated the effect of duloxetine, the newest serotonin-noradrenalin antidepressant, on cytokine levels and therefore this should be evaluated in future studies.
Tumour necrosis factor (TNF) is primarily secreted by monocytes/macrophages and activated T lymphocytes in response to fungal infections. TNF acts through TNF receptor 1 (TNFR1) triggering a pro-inflammatory response, and therefore plays a pivotal role in immune regulation and host immune responses. We hypothesized that single nucleotide polymorphisms (SNPs) in TNFR1 gene may influence the innate immune response against Aspergillus. Three SNPs were genotyped in 275 individuals (144 immunocompromised haematological patients with high-risk of developing IPA and 131 healthy controls): TNFR1\_383(A/C) \( (rs2234649) \) and TNFR1\_609(G/T) \( (rs4149570) \) in the 5' UTR region, and TNFR1\_36(A/G) SNP \( (rs767455) \) in the first exon of the gene. Of the 144 haematological patients, 77 patients developed Invasive Pulmonary Aspergillosis (IPA) infection and the remaining 67 patients were not infected. TNFR1\_36(A/G) and TNFR1\_609(G/T) were associated with IPA susceptibility \( (p=0.033 \) and \( p=0.018 \), respectively). A role of TNFR1 genetic variants in the susceptibility of patients to develop IPA was also supported by the significantly lower TNFR1 mRNA expression level in IPA than in IPA-resistant patients and the strong correlation between the TNFR1\_609 genetic variant and the expression levels of TNFR1. There was also a tendency for a higher frequency of galactomannan (GM) positivity in patients with TNFR1\_609(G/G) genotype than in patients with TNFR1\_609(G/T) \( (p=0.0909) \) or TNFR1\_609(T/T) \( (p=0.0913) \) genotype. Predictive sequence analysis of the effects of TNFR1\_609 promoter polymorphism revealed that this SNP might play a critical role in modifying the affinity of ICSBP/IRF-8, a transcription factor that is involved in the TNFR1-mediated activation of NFκB signalling pathway. Taken together, these data suggest that TNFR1 polymorphisms influence the risk of IPA disease and might be useful for risk stratification strategies. These findings need to be confirmed in validation studies with larger samples of haematological patients.
ROLE OF EFFECTOR CELLS (CCR7^−CD27^+) AND EFFECTOR-MEMORY CELLS (CCR7^−CD27^+) IN DRUG-INDUCED MACULOPAPULAR EXANTHEMA


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Maculopapular exanthema (MPE) induced by drugs is a T-cell mediated reaction and effector cells may play an important role in its development. We assessed the effector and cutaneous homing phenotype in peripheral blood cells from allergic patients after drug stimulation. This study included 10 patients and 10 controls. The effector phenotype (CCR7^−CD27^+^−^), chemokine receptors (CCR4 and CCR10), and activation (CD25^low^) and regulatory markers (CD25^high^) were measured by flow cytometry in both peripheral blood mononuclear cells (PBMCs) and CD4-T-lymphocytes. Proliferation was determined by 5-(−)-carboxyfluorescein diacetate succinimidyl ester (CFSE) assay and the migratory capacity by a chemotaxis assay using CCL17 and CCL27. Compared to controls, CCR7^−CD27^− cells were increased in patients without (p=0.003) and with drug stimulation (p<0.001) and had significantly higher proliferation (p=0.010). CCR10 expression was increased in patients after drug stimulation in total and memory CD27^− T-cells. Lymphocyte migration with CCL27 was higher in patients with drug stimulation (p=0.048), with a decrease in CCR7^−CD27^− (p<0.0001) and an increase in CCR7^−CD27^+ (p=0.017). In patients, CD4-T-lymphocytes were significantly activated after drug stimulation (p<0.001). In conclusion, we show that effector memory CD4^+ T-cells (CCR7^−CD27^+) respond specifically to the drug responsible for MPE and confirm previous data about the involvement of CCR10 in cell trafficking to the skin.
DECREASED INTERSTITIAL FOXP3+ LYMPHOCYTES IN USUAL INTERSTITIAL PNEUMONIA WITH DISCREPANCY OF CXCL12/CXCR4 AXIS

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Regulatory T cells (Treg) play a critical role in immune homeostasis and expansion of Treg is controlled by chemokine receptors. The chemokine CXCL12 and its G-protein-coupled receptor (CXCR4) are involved in the development of idiopathic pulmonary fibrosis (IPF), but the association of Treg with the CXCL12/CXCR4 axis has not been documented. The aim of this study is to determine the distribution and extent of CXCL12/CXCR4 expression in idiopathic type of pulmonary fibrosis, and the relation of Treg expansion in the interstitium of pulmonary fibrosis patients to CXCL12/CXCR4 expression. CXCL12 expression was examined by immunostaining and ELISA in tissue specimens from patients with usual interstitial pneumonia (UIP, n=15), patients with fibrotic non-specific interstitial pneumonia (f-NSIP, n=4), and controls (n=6). CXCR4 expression was examined by in situ hybridization and immunoblotting. Expression of CD45, CD3, CD20, transcription factor forkhead box P3 (FOXP3), and CD25 was assessed by immunostaining. Fibrosis was evaluated by determining the established fibrosis (EF) score. The CXCL12/CXCR4 axis was upregulated in UIP and f-NSIP, and CXCL12 derived from lung tissue attracted CXCR4+ cells, CXCR4+ cells showed a CD3+ cell distribution pattern. The interstitial FOXP3+/CD3+ and CD25+/CD3+ cell ratios were lower in UIP than f-NSIP, but the CXCR4+/CD3+ cell ratio was not different. The FOXP3+/CD3+ cell ratio and EF score were inversely correlated. These findings suggest that the CXCL12/CXCR4 axis contributes to inflammation in UIP and f-NSIP by promoting the accumulation CXCR4+ lymphocytes, and a decrease of Treg is correlated with the severity of fibrosis in UIP.
Myoga (Zingiber Myoga Roscoe) is a perennial plant with a pungent smell from its flower buds. It is native to East Asia and has been reported to cause allergic contact dermatitis. The purpose of this study is to assess the allergenicity of myoga related to its major chemical components, α-pinene, β-pinene, limonene, limonene oxide and β-phellandrene, which are supposed to be the causative agents of contact dermatitis among myoga cultivators. We performed a toxicity study of the volatile constituents of myoga using the local lymph node assay (LLNA), in which limonene, limonene oxide and β-phellandrene had positive responses and the EC3 was 35.8%, 8.22%, and 0.54%, respectively. EC3 for both α-pinene and β-pinene was over 100%. Both chemicals failed to induce positive responses in the LLNA. While the maximization rating of limonene, limonene oxide and phellandrene were evaluated as moderate, extreme, and extreme respectively, α-pinene and β-pinene were evaluated as weak in the previously reported GPMT. The usage of LLNA was also confirmed by comparing with previously reported GPMT results to detect the allergenicity of myoga constituents. The actual risk of humans developing an allergy to myoga constituents depends on many factors. The concentration of the compounds, the frequency and duration of exposure and the condition of the skin are supposed to be important factors.
EFFECTS OF BUDERSONIDE ON P38 MAPK ACTIVATION, APOPTOSIS AND IL-8 SECRETION, INDUCED BY TNF-α AND HAEMOPHILUS INFLUENZAE IN HUMAN BRONCHIAL EPITHELIAL CELLS


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Non-typeable Haemophilus influenzae (NTHi) is one of the most frequently involved pathogens in bacterial exacerbations of chronic obstructive pulmonary disease (COPD). In the airways, the main tissue target of NTHi is bronchial epithelium, where this pathogen can further amplify the inflammatory and structural changes induced by proinflammatory cytokines such as tumour necrosis factor-α (TNF-α). Therefore, the aim of this study is to investigate, in primary cultures of human bronchial epithelial cells, the effects of NTHi on signal transduction pathways, apoptotic events and chemokine production activated by TNF-α. Moreover, we also evaluated the effects exerted on such cellular and molecular phenomena by a corticosteroid drug. p38 mitogen-activated protein kinase (MAPK) phosphorylation was analyzed by Western blotting, using an anti-phospho-p38 MAPK monoclonal antibody. Apoptosis was assayed by active caspase-3 expression. Interleukin-8 (IL-8/CXCL8) was detected in cell-free culture supernatants by ELISA. TNF-α induced a significant increase in p38 MAPK phosphorylation. NTHi was able to potentiate the stimulatory actions of TNF-α on caspase-3 expression and, to a lesser extent, on IL-8 secretion. These effects were significantly \( P < 0.01 \) inhibited by a pharmacological pre-treatment with budesonide. These results suggest that TNF-α is able to stimulate, via activation of p38 MAPK signalling pathway, IL-8 release and airway epithelial cell apoptosis; the latter effect can be markedly potentiated by NTHi. Furthermore, budesonide can be very effective in preventing, through inhibition of p38 MAPK phosphorylation, both structural and proinflammatory changes elicited in bronchial epithelium by TNF-α and NTHi.
EFFECTS OF PHOSPHATIDYLCHOLINE AND SODIUM DEOXYCHOLATE ON HUMAN PRIMARY ADIPOCYTES AND FRESH HUMAN ADIPOSE TISSUE


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Recent studies introduced the novel concept of chemical lipolysis where phosphatidylcholine (PC), an active component of commercial preparations, plays a pivotal role. Other studies suggested that sodium deoxycholate (DOC), an excipient contained in medical preparations, could be the real active component performing an adipocytolytic action. We investigated the effects of PC and DOC on human primary adipocyte cultures and on human fresh adipose tissue. Human adipocytes isolated by Rodbell’s method, were cultured onto type I collagen-coated glass coverslips, placed into 24-well tissue culture plates. Cells were incubated with or without DOC (5-7-9%), PC (5%) or DOC/PC mixture and observed under phase contrast microscope. After incubation, cells were stained with Oil Red-O and with acridine orange/ethidium bromide to observe necrotic cells with phase contrast microscope and fluorescent microscope, respectively. Histological specimens from adipose tissue biopsies were observed with phase contrast microscopy and with scanning electron microscopy. To investigate the lipid pattern variability in the different experimental conditions, culture medium obtained from the different treatments was subjected to lipid extraction and subsequently to thin layer chromatography (TLC). Microscopic observation of adipocytes showed that DOC treatment led to a detrimental morphological effect in a dose-dependent manner. PC treatment did not significantly affect adipocyte viability. On the contrary, results from experiments aimed to analyze the effects of PC/DOC combined treatment suggested a PC protective role against the DOC harmful effects on adipocytes. Results indicated that clinical effects, observed in local treatment with pharmaceutical preparation, could be due only to DOC, a detergent inducing nonspecific lysis of cell membranes following adipocyte necrosis. On the other hand, PC could likely be incorporated in the lipid bilayer, thus strongly reducing the disruptive DOC effects.

DIVERGENT EFFECTS OF INFLIXIMAB AND ANAKINRA THERAPIES ON MACROPHAGE PHENOTYPE FROM PATIENTS WITH REFRACTORY RHEUMATOID ARTHRITIS

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Previously, we documented the co-expression of the inducible nitric oxide synthase (NOS2) and protein kinase C-eta (PKC-η) in peripheral blood-derived macrophages (PBDM) from moderate to severe rheumatoid arthritis (RA) patients with elevated plasma nitric oxide levels but not from those with non-inflammatory osteoarthritis (OA) or normal plasma NO levels. The presence of PKC-η was found to be required before macrophages could acquire the NOS2-positive phenotype and make copious levels of NO. In the current study, we report the divergent effects of two biological-based RA therapies which target TNFα function (infliximab) or IL1 response (anakinra) on the development of the NOS2-positive macrophage phenotype. Both infliximab and anakinra were effective in improving disease symptoms. However, treatment with anakinra, but not infliximab led to a complete suppression of NOS2 expression in PBDM and consequently, a more pronounced reduction in plasma NO levels. Data also revealed a requirement of both TNF-α and IL-1 in the development of the NOS2-positive macrophage phenotype. Finally, the data have shed light on the molecular mechanisms by which NO production may be regulated during disease progression to severe RA, and thus, offer a novel insight into the identification of future therapeutic targets for the treatment of inflammatory diseases.
To assess the long-term efficacy and safety profile and the patient-reported outcomes (PRO) in patients with moderate-to-severe plaque-type psoriasis receiving continuous etanercept treatment. An open-label study was conducted to evaluate etanercept as long-term treatment for moderate-to-severe plaque psoriasis. Continuous therapy was administered at a dose of 50 mg subcutaneously twice weekly for 12 weeks followed by a continuous treatment with 50 mg subcutaneously once weekly or 25 mg twice weekly throughout a 96-week study. The primary measure of efficacy was the proportion of patients with PASI 75 at week 24, 48 and 96. Patient-reported outcomes (PRO) were also assessed during the study, at week 24, 48 and 96, including the Dermatology Life Quality Index (DLQI) and the Psoriasis Disability Index (PDI). At baseline, mean PASI score, DLQI and PDI for patients eligible to initiate treatment with etanercept showed significant disease severity, quality-of-life impairment and psoriasis-related disability. At week 96, patients showed statistically significant and meaningful improvements. The continuous etanercept regimen provided a consistent improvement in both clinical disease parameters and PRO measures.
The aim of the study is to examine the tissue expression and localization of the somatostatin receptors (SSTRs) in prostate cancer (PCa) with neuroendocrine (NE) differentiation. The five SSTR subtypes (SSTR1 to 5) were evaluated immunohistochemically in the secretory cells of normal-looking epithelium (Nep), high-grade prostatic intraepithelial neoplasia (HGPIN) and PCa in 20 radical prostatectomies (RPs) with Gleason score 3+3=6 acinar PCa; 20 RPs with GS 4+4=8 and 4+5=9 PCa; and 20 RPs with PCa with NE differentiation. The basal cells were evaluated in Nep and HGPIN. In all groups the stromal smooth muscle and endothelial cells were also analyzed. Concerning the secretory cells, (i) the greatest mean proportions of cells with strong cytoplasmic staining in PCa were seen for SSTR2, mainly in the group of RP with NE differentiation, and for SSTR4 in all three groups; (ii) Membrane staining was seen for SSTR3 and SSTR4; the mean percentages of positive cells, higher in SSTR3 than in SSTR4, decreased from Nep to HGPIN and PCa in all three RP groups; in the latter two, the mean percentages were similar; and (iii) Nuclear staining was seen with SSTR4 and SSTR5; for SSTR4, the mean percentages in the PCa of the three groups were higher than in HGPIN and Nep, the highest proportion being with PCa with NE differentiation. Concerning the basal cells, in Nep the mean proportions of cells with strong staining intensity were greater for SSTR1 and SSTR3 than for the other subtypes, the lowest being with SSTR2; in HGPIN the highest mean propositions of positive cells was with SSTR3, the proportions in the three RP groups being similar. Concerning the stromal smooth muscle and endothelial cells, the highest mean values being in SSTR1 and the lowest in SSTR5; for the former subtype the highest proportion of endothelial cells with strong intensity was seen in the RP NE group. In conclusion, this immunohistochemical study expands our knowledge on the expression and localization of five SSTRs in the various tissue components in the prostate with PCa with NE differentiation, compared with conventional PCa. Typing somatostatin receptor expression in NE tumours could be of relevance to target somatostatin analogue-based diagnostic approach and treatment.
SUPPLEMENTATION WITH ESSENTIAL AMINO ACIDS IN MIDDLE AGE MAINTAINS THE HEALTH OF RAT KIDNEY

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Chronic kidney diseases are a social and economic problem, and diet has long been recognized as a fundamental modulator of kidney health in human and experimental models. Age-dependent alterations in mitochondrial function play a crucial role in the development of diseases of aging, and mitochondrial disorders have been observed in experimental models of kidney failure. Recently, the beneficial dietary effect of a specific mixture of essential amino acids (EAA) has been studied in elderly subjects, but no data were collected from the kidney. The aim of this study was to assess whether daily supplementation of the diet with EAA at the beginning of senescence could preserve renal health. We used middle-aged (18-month-old) male Wistar rats fed a standard diet and water ad libitum (M-aged group) or a diet with added EAA (1.5 g/kg per day) dissolved in drinking water for 3 months (M-aged+EAA group). Young (2-month-old) rats fed a standard diet for 3 months were used as controls. Mitochondrial morphology and markers for collagen, cyt-c-oxidase, HSP60, GRP75, eNOS, iNOS, Bax, Bcl2 and VEGF were analyzed in glomeruli and tubules. EAA supplementation limited fibrosis and increased the capillary tuft area in the glomeruli of M-aged rats. VEGF and eNOS were enhanced in glomeruli and the peritubular space with the EAA-supplemented diet. Mitochondrial cyt-c oxidase, Bcl2, and chaperones increased in the distal tubules of the EAA group to levels similar to those observed in the young group. Mitochondrial area and density after EAA intake did not differ from young groups. The results suggest that prolonged EAA intake could represent a strategy for maintaining the healthy status of the kidney in M-aged animals.

APOPTOSIS AND AUTOIMMUNITY INDUCED BY CLODRONATE IN SYSTEMIC LUPUS ERYTHEMATOSUS MONONUCLEAR CIRCULATING CELLS

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The aim of this study is to evaluate the effect of clodronate on apoptosis of human systemic lupus erythematosus circulating mononuclear cells and to analyze possible correlations with changes in autoantibody production in vitro. Lympho-monocytes from 20 SLE patients were isolated and incubated with or without addition of 1 µM clodronate for 72 hours. Apoptosis and release of genomic material was assessed by immunofluorescent detection of cleaved caspase-3 and by Cell-Death-Detection ELISAPLUS kit (Roche). Anti-Nucleosome IgG and anti-dsDNA IgM and IgG autoantibody levels were determined in supernatants by commercially available ELISA kits. Clodronate induced apoptosis in monocytes as confirmed by cleaved caspase-3 immunostaining and by quantification of cleaved nucleosome in the supernatants (treated 0.22±0.05 O.D. vs untreated 0.09±0.04 O.D.; P<0.001). This finding was coupled with a significant increasing in supernatants of IgG anti-Nucleosome (treated 6.5±1.1 vs untreated 5.5±0.6 IU/mL; p=0.001) and IgM (treated 5.0±1.8 vs 2.8±1.5 IU/mL; p=0.02) anti-dsDNA autoantibody levels. Our findings stressed the pro-apoptotic activity of clodronate, as well as its potential autoimmunity induction in SLE mononuclear circulating cells. Clinical studies could clarify the role of bisphosphonates on autoantibody production and worsening of disease activity.
The aim of this study is to evaluate the sensitivity, specificity and safety of challenge tests and their usefulness in the diagnosis of latex allergy. Forty adult subjects (F/M = 34/6, aged 18-66 yrs) with a history of adverse reactions after latex exposure and positive prick test and/or specific IgE to latex were enrolled. They were compared with 20 control subjects. They underwent provocative (cutaneous, mucous-oral, sublingual, conjunctival, nasal, bronchial, vaginal) tests. Symptoms and drug scores were recorded for each patient during challenges. All patients reacted to at least one of the following: cutaneous, nasal and conjunctival tests. No systemic reactions requiring epinephrine occurred. Of the challenges, the vaginal test resulted as the safest, but it had low sensitivity and many limits related to the procedure. According to our data, bronchial and nasal tests had the highest sensitivity (76% and 82% respectively), and were more precise than other tests in determining latex exposure and symptoms, but the bronchial test also presented the highest rate of risk. Mucous and cutaneous tests resulted as the most reliable. For all the tests, specificity and positive predictive value were 100%. All control subjects resulted negative to all challenges. There were no statistically significant changes in skin and serologic tests between the first and second visits. Correlations between MIS and skin tests and between MIS and serum tests were not found. Challenges can be considered safe diagnostic procedures. Tests that most faithfully reproduce natural exposure, on the basis of a patient’s history, are preferable.

SUBLINGUAL ALLERGOID IMMUNOTHERAPY: A NEW 4-DAY INDUCTION PHASE IN PATIENTS ALLERGIC TO HOUSE DUST MITES

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Sublingual immunotherapy with monomeric allergoid (allergoid SLIT), given according to the standard scheme, has proved effective and safe in many clinical trials. However, its build-up phase requires a long time ranging from 16 days to 14 weeks. This study therefore investigated whether, with a four-day up-dosing, the same benefit could be achieved in a shorter time. Thirty rhinitic and/or asthmatic patients (16 M and 14 F, mean age 36±8.2 years) allergic to house dust mites (HDM) with or without other sensitizations were randomized to allergoid SLIT or standard drug therapy. The build-up phase lasted four days. The first day the patients took a 300 AU tablet, the second day two 300 AU tablets, the third day three 300 AU tablets and the fourth day four 300 AU tablets. The total amount taken during the up-dosing was 3000 AU. Patients were then treated for 12 months at the dosage of 2000 AU/week (total amount of allergen: 104,000 AU/year). The symptom score and drug consumption were recorded from November to February on monthly diary cards. At baseline and after 12 months a Visual Analogue Scale (VAS) was used to rate the patients’ well-being. Skin prick test reactivity was evaluated before and after the 12-month treatment in both groups using 10 mg/mL histamine as reference. VAS scores rose significantly (about 45%) in both groups in comparison to baseline (p=0.001). In addition, there was a significantly greater reduction of the global symptoms score (about 52%) - but not in drug consumption - in the SLIT group in comparison to controls (p=0.0004). The SLIT group showed a highly significant reduction (about 39%) in skin prick test reactivity (p=0.000003) while the control group remained unchanged (p=0.5226). No severe adverse events were observed. Even with this short four-day up-dosing, the allergoid SLIT proves to be safe. In addition, it is already effective in patients allergic to HDM after 12 months, and significantly reduces allergen-specific skin reactivity.
EXAMINATION OF PERIODONTAL PATHOGENS IN STENOTIC VALVE SPECIMENS AND IN WHOLE BLOOD SAMPLES IN PATIENTS AFFECTED BY AORTIC VALVE STENOSIS AND CHRONIC PERIODONTITIS

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Periodontitis may be a risk factor for atherosclerosis and coronary heart disease. The influence of periodontal pathogens in cardiovascular diseases needs further investigation. Therefore, the aims of this clinical study are: to test the presence of periodontal bacteria DNA in aortic valves and to assess the concomitant presence of the same periodontal bacteria DNA in whole blood samples in patients affected by aortic valve stenosis and chronic periodontitis. Nineteen consecutive patients (12 males and 7 females, age: 49-85 years) were enrolled in this study after having been subjected to a complete periodontal evaluation to confirm the diagnosis of chronic periodontitis. All patients were scheduled for aortic valve replacement surgery. After clinical and microbial periodontal examination, the aortic valve tissue specimens were obtained by excision during valve replacement surgery and the patients were subjected to the whole blood sampling before the surgery. The polymerase chain reaction technology was used to detect the putative periodontal pathogens Tannerella forsythia, Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Fusobacterium nucleatum, Campylobacter rectus, Eikenella corrodens and Treponema denticola. Neither the 19 aortic valve specimens nor the blood samples were positive for the genoma of the selected periodontal pathogens. The selected periodontal pathogens did not colonize the aortic valve of patients affected by stenosis and bacterial genoma was not present in whole blood samples. A high blood pressure at the aortic valve may prevent the adhesion and proliferation of bacterial colonies.

EFFECTIVENESS OF A PROPOLIS AND ZINC SOLUTION IN PREVENTING ACUTE OTITIS MEDIA IN CHILDREN WITH A HISTORY OF RECURRENT ACUTE OTITIS MEDIA

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Recurrent acute otitis media (rAOM) is frequently encountered in infants and children and the lack of any definitive treatment has led parents and physicians to try complementary and alternative therapies. We evaluated the efficacy of a propolis and zinc suspension in preventing AOM in 122 children aged 1-5 years with a documented history of rAOM, who were prospectively, blindly, randomized 1:1 to receive the suspension plus elimination of environmental risk factors or elimination of environmental risk factors only. AOM- and respiratory-related morbidity were assessed at study entry and every four weeks. In the 3-month treatment period AOM was diagnosed in 31 (50.8%) children given the propolis and zinc suspension and in 43 (70.5%) controls (p=0.04). The mean number of episodes of AOM per child/month was 0.23 ± 0.26 in the propolis and zinc group and 0.34 ± 0.29 in controls (reduction 32.0%, p=0.03). The administration of a propolis and zinc suspension to children with a history of rAOM can significantly reduce the risk of new AOM episodes and AOM-related antibiotic courses, with no problem of safety or tolerability, and with a very good degree of parental satisfaction. No effect can be expected on respiratory infections other than AOM.
LACTOFERRIN EFFICACY VERSUS FERROUS SULFATE IN CURING IRON DISORDERS IN PREGNANT AND NON-PREGNANT WOMEN

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Iron homeostasis in pregnancy compensates for increased iron requirements and in women of child-bearing age for iron loss in menses. Oral administration of ferrous sulfate, prescribed to cure iron deficiency (ID) and ID anemia (IDA), often fails to increase hematological parameters and causes adverse effects. Recently, we demonstrated safety and efficacy of bovine lactoferrin (bLf) in pregnant women suffering from ID/IDA. Two clinical trials were conducted on pregnant and non-pregnant women of child-bearing age suffering from ID/IDA. In both trials, women received oral administration of bLf 100 mg/twice/day (Arm A), or ferrous sulfate 520 mg/day (Arm B). Hematological parameters, serum IL-6 and prohepcidin were assayed before and after therapy. Unlike ferrous sulfate, bLf increased hematological parameters ($P<0.0001$). In pregnant women, bLf decreased serum IL-6 ($P<0.0001$), and increased prohepcidin ($P=0.0007$). In non-pregnant women bLf did not change the low IL-6 levels while it increased prohepcidin ($P<0.0001$). Ferrous sulfate increased IL-6 ($P<0.0001$) and decreased prohepcidin ($P=0.093$). bLf established iron homeostasis by modulating serum IL-6 and prohepcidin synthesis, whereas ferrous sulfate increased IL-6 and failed to increase hematological parameters and prohepcidin. bLf is a more effective and safer alternative than ferrous sulfate for treating ID and IDA.

IBUPROFEN AND LIPOIC ACID DIAMIDE AS CO-DRUG WITH NEUROPROTECTIVE ACTIVITY: PHARMACOLOGICAL PROPERTIES AND EFFECTS IN β-AMYLOID (1-40) INFUSED ALZHEIMER’S DISEASE RAT MODEL

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Both oxidative stress and inflammation are elevated in brains of Alzheimer’s disease patients, but their pathogenic significance still remains unclear. Current evidence support the hypothesis that non-steroidal anti-inflammatory drugs (NSAIDs) and antioxidant therapy might protect against the development of Alzheimer’s disease, and ibuprofen has the strongest epidemiological support. In the present work our attention was focused on (R)-α-lipoic acid considered as a potential neuroprotective agent in Alzheimer’s disease therapy. In particular, we investigated a new co-drug (1) obtained by joining (R)-α-lipoic acid and ibuprofen via a diamide bond, for evaluating its potential to antagonize the deleterious structural and cognitive effects of β-amyloid (1-40) in an infused Alzheimer’s disease rat model. Our results indicated that infusion of β-amyloid (1-40) impairs memory performance through a progressive cognitive deterioration; however, ibuprofen and co-drug 1 seemed to protect against behavioural detriment induced by simultaneous administration of β-amyloid (1-40) protein. The obtained data were supported by the histochemical findings of the present study; β-amyloid protein was less expressed in 1-treated than in ibuprofen and (R)-α-lipoic acid alone-treated cerebral cortex. Taken together, the present findings suggest that co-drug 1 treatment may protect against the cognitive dysfunction induced by intracerebroventricular infusion of β-amyloid (1-40) in rats. Thus, co-drug 1 could prove useful as a tool for controlling Alzheimer’s disease-induced cerebral amyloid deposits and behavioural deterioration.
ANTIPROLIFERATIVE, PROTECTIVE AND ANTIOXIDANT EFFECTS OF ARTICHOKE, DANDELION, TURMERIC AND ROSEMARY EXTRACTS AND THEIR FORMULATION

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Artichoke, dandelion, turmeric extracts and rosemary essential oil are commonly used as ingredients in many herbal preparations to treat hepatic and gallbladder disorders. In the present work we compare the activity of each single extract with a commercial mixture for antiproliferative, antiradical and protective effects against induced oxidant stress effect. In ABTS and DPPH tests, turmeric extract is the most active, followed by artichoke and dandelion. All samples exhibited antiproliferative activity in a dose-dependent manner against HepG2 cells. In the same cell lines, the protective effect of pre-treatment with the extracts were detected by evaluating the prostaglandin E2 release, a marker of oxidative stress induced by hydrogen peroxide. The treatments with the extracts were efficient in reducing the release of PGE2 induced by oxidative stimulus. The positive results of the cell viability test, together with the protective and antiradical activity confirm the rationale for the use of these ingredients in commercial formulations as a health aid tool in modern phytotherapy.

INHIBITORY ACTIVITY OF CRANBERRY EXTRACT ON THE BACTERIAL ADHESIVENESS IN THE URINE OF WOMEN: AN EX-VIVO STUDY

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Strains of uropathogenic E. coli are responsible for approximately 90% of community-acquired, uncomplicated cystitis, and fimbriae represent the adhesive factors enabling E. coli to be anchored to uroepithelial cells in the first step of the infectious process. Recently, a few studies have shown that a correlation between the consumption of cranberry (Vaccinium macrocarpon) and prevention of UTI is related to the ability of proanthocyanidins to reduce the bacterial adhesion to uroepithelial cells. In this study we evaluate the inhibitory activity of urine of healthy women treated with tablets containing cranberry extract on the adhesiveness of E. coli to uroepithelial human cells. Two groups of 12 female volunteers each, aged between 18 and 65 years, were enrolled, one group with negative history and one group with positive history of recurrent cystitis. Subjects were treated with the active product or placebo in a random, cross-over, double-blinded sequence for one week in each of the two treatment sequences. Urine samples were collected at the beginning and the end of each study period. Tests of bacterial adhesiveness were performed with two strains of E. coli (ATCC 25922 and ATCC 35218) on HT1376 human bladder carcinoma cells. Significant reductions of bacterial adhesiveness were observed in women who received cranberry extract (-50.9%; p<0.0001), regardless of their medical history and the treatment period in the cross-over sequence. No changes were observed with placebo (-0.29%; n.s.). This ex-vivo study showed that the assumption of cranberry extract in suitable amounts can have an anti-adhesive activity on uropathogenic E. coli.
CLINICAL EXPERIENCE WITH SPIRAMYCIN IN BISPHOSPHONATE-ASSOCIATED
OSTEONECROSIS OF THE JAW

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Bisphosphonate-related osteonecrosis of the jaw (BRONJ) consists of an exposure of the jaw bone
that persists for over 8 weeks in patients with positive history for bisphosphonates. Symptomatology is
characterized by dull and ceaseless pain, and in advanced stages, the exposure of necrotic bone is evident,
which is frequently associated with purulent secretions and faetor oris. Despite many different studies
on BRONJ, there are no general guidelines to treat this disease. In this work, the authors present their
experience in BRONJ conservative therapy with spiramycin by comparing the results achieved with
amoxicillin and clavulanic acid. From January 1, 2008 to June 30, 2008, our department received 25 patients
who were affected by osteonecrosis secondary to bisphosphonates. Thirteen had taken bisphosphonates
for osteoporosis and 12 for malignancies. We divided the 25 patients into two groups: those who had not
received any treatment and those who had received treatment. The first group of 13 patients had been
treated only with spiramycin (S). The results from this group were only evaluated to test the efficacy of
spiramycin and were not considered in the study. The second group of 12 patients had not undergone any
previous treatment. This group was further divided in two groups of 6 patients each; one group was treated
with spiramycin and the other with amoxicillin and clavulanic acid (ACA). The following criteria were
used to evaluate the results of the study: pain, sensibility deficits, purulent secretion and bone exposure. All
group results were evaluated according to the criteria chosen, and positive results were achieved in both
groups S and ACA, such as reduction or disappearance of pain, sensibility deficits and purulent secretion
and healing of bone exposition, although spiramycin showed itself to be more effective than the combination
of amoxicillin and clavulanic acid. Spiramycin is a macrolide antibiotic with a wide spectrum of activity
against Streptococci, Pneumococci, Diplococci, Gonococci and Staphylococci, which are typical in BRONJ.
No resistance was indicated. Administration of the antibiotics can be intravenous, intramuscular, rectal or
oral, which remains the most frequently used since spiramycin elimination also occurs with saliva and the
antibiotic reaches high concentrations in the oral cavity where BRONJ is situated. Good compliance to the
spiramycin regimen was observed in all three groups, with a general improvement in all of the parameters
considered. In only two cases did patients have to undergo surgical curettage. The results showed that
spiramycin can be a first choice drug in the treatment of BRONJ, and it should be strongly considered for
patients where previous antibiotic therapy did not prove to be effective.
FUNCTIONAL INFRARED IMAGING OF PAROXYSMAL ISCHEMIC EVENTS IN PATIENTS WITH RAYNAUD’S PHENOMENON

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The use of thermal infrared (IR) imaging together with the study of the thermal recovery from a controlled cold challenge has been proposed in the diagnosis and follow-up of therapeutic response of Raynaud’s Phenomenon (RP) and Systemic Sclerosis (SSc). The controlled cold challenge test usually performed during IR investigations may induce a RP in patients with the latter condition. In our Institution we routinely perform capillaroscopy and thermal IR to follow-up SSc patients. In this paper, we describe the thermal recovery patterns shown by two SSc patients (a 40 year-old male with diffuse variant of SSc and a 71 year-old female with a limited variant of SSc) who presented ischemic and paroxysmal RP attack while recovering from the routine controlled cold challenge test. During RP attack, the cutaneous temperature of some fingers continued to decrease for some minutes even after the cessation of the cold stress. To the best of our knowledge, to date, no literature report has documented the thermal behaviour of SSc patients’ fingers which occasionally present ischemic and paroxysmal response. Triggering of ischemic RP attack appears to not rely only on morphological and structural finger impairment, but also upon other aspects, like the emotional attitude of the subject and the possible discomfort experienced with the proceeding of the functional cold stress test.

SUCCESSFUL TREATMENT OF SCHNITZLER’S SYNDROME WITH ANAKINRA AFTER FAILURE OF RITUXIMAB TRIAL

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We report a 50-year-old man who presented with a 5-year history of an intermittent widespread pruritic urticarioid rash and fever, fatigue, arthralgia and a monoclonal immunoglobulin-M paraprotein. The patient was initially treated with antihistamines and corticosteroids without the disappearance of symptoms. A skin biopsy from the urticarial rash on the thorax was performed, revealing dermal mononuclear and polymorphonuclear cell infiltrate and normal epidermis. A diagnosis of Schnitzler’s syndrome (SS), a rare disorder in which the simultaneous occurrence of monoclonal gammopathy and chronic urticaria is usually observed, was made. After an unsuccessful trial with rituximab at a dosage of 375 mg/sqm weekly for 4 consecutive weeks, the patient was treated with anakinra, an inhibitor of interleukin-1α that is thought to be involved in the pathogenesis of the disease, at a dose of 100 mg daily given subcutaneously. He showed a prompt response to the drug and he is still well and symptom-free after 12 months of follow-up. On the basis of both this experience and the review of the literature we conclude that anakinra may be a promising option for the treatment of SS. However, these results need to be confirmed on a larger number of patients.
Polysensitization is a feature of allergic rhinitis (AR) that significantly impairs the quality of life (QoL) of AR patients. Allergen-specific immunotherapy is the only causal therapy for AR. However, the polysensitization phenomenon may represent a crucial obstacle as far as it concerns the choice of the allergen extract which should be used for immunotherapy. Therefore, a real-life based multi-centre study, named POLISMAIL, has been designed which aims at evaluating the behaviour of some allergists managing polysensitized AR patients. The effect of two-year SLIT treatment in those patients was also evaluated. A single allergen extract was used for two-thirds of patients, whereas a mix of two allergens was chosen for the remaining patients. The severity grade of AR and the type of diagnosis were significantly improved by 2-year SLIT. In addition, SLIT significantly improved QoL. Both outcomes confirm that SLIT with one or two allergen extracts achieves a significant improvement in polysensitized patients. In conclusion, the POLISMAIL study demonstrates that polysensitization should not represent a counter-indication for prescribing immunotherapy. The choice to limit SLIT to 1-2 allergen extracts was sufficient and effective in improving symptoms and QoL.

AUTOLOGOUS SERUM SKIN TEST REACTIVITY AND BASOPHIL HISTAMINE RELEASE TEST IN PATIENTS WITH NASAL POLYPOSIS: PRELIMINARY RESULTS

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An eosinophilic inflammatory process is generally observed in patients suffering from nasal polyposis (NP), however its onset has not yet been defined. It has been suggested that immune activation of inflammatory cells may be the cause. The aim of this study is to verify whether autoantibodies and/or histamine-releasing factors are present in the serum of patients suffering from NP. In fact, we assume that autoantibodies and/or histamine-releasing factors, as already demonstrated in chronic idiopathic urticaria and asthma, may be involved in the pathogenesis of NP. In this case-control analytical study 40 patients with NP and 27 control subjects underwent the in vivo autologous serum skin test (ASST). The sera from 6 patients suffering from NP and 9 control group subjects, who had all been previously studied and randomly selected, underwent basophil histamine release assay from normal donor as a pilot study. The ASST showed positive results in 55% of patients suffering from NP versus 8% of the control group (p=.00006), the basophil histamine release test (BHRT) turned out positive in all patients tested and in 11% of the control group. We found a weak positive correlation between the percentage of histamine release and the wheal diameter. ASST reactivity is very frequent in patients suffering from NP, thus suggesting the presence of histamine-releasing factors in the blood stream. The BHRT was positive in the serum of all patients, thus suggesting the presence of anti-FceRI, anti-IgE autoantibodies and/or other histamine-releasing factors, the presence of which can play a role in triggering and maintaining the eosinophilic inflammatory process in NP.
SAFETY AND EFFICACY OF CALCIUM FOLINATE IN PSORIASIS:
AN OBSERVATIONAL STUDY

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An association between psoriasis and cardiovascular diseases has been reported, and treatment of this condition is often considered difficult because the conventional systemic therapies often show several side effects. To assess the efficacy and tolerability of a new drug, folinate calcium, to treat psoriasis, a total of 58 patients affected by active psoriasis were enrolled in a variable period study. These patients had clinically stable, plaque psoriasis involving ≥ 6% body surface area. Thirty of these patients were treated with folinate calcium therapy, 15 mg orally once daily, for a variable period based on each patient’s clinical response. The comparison was made with 28 psoriatic patients treated with conventional systemic therapies (cyclosporine, acitretin, etanercept, efalizumab, infliximab, adalimumab). A clinical improvement was observed in both group, but in the first one we did not observe any side effects, whereas some important side effects were observed in the second. These preliminary results support the effectiveness and tolerability of folinate calcium treatment in psoriasis.

THE PARALLEL EVOLUTION OF IMMUNOLOGY AND PHARMACOLOGY

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Immunology is the systematic evaluation of the means through which human beings protect themselves and respond to the attack of internal and external agents, and Edward Jenner (1749-1823) and Louis Pasteur (1822-1895) are considered pioneers of this field. Jenner observed the protective effect of cowpox against smallpox and inoculated the cowpox in human beings to protect them from the often lethal smallpox. Pasteur developed in his laboratory a vaccine against rabies and elaborated methods for attenuating the virulence of pathogenic microorganisms while maintaining their immunogenicity. Pharmacology is the area of medical science dealing with drugs and their uses, and it was during the nineteenth century that it assumed its status of scientific specialty, mainly in German-speaking Europe, through the establishment of pharmacological institutes and dedicated laboratories. The discovery and the synthesis of drugs and the systematic evaluation of their activity have constituted through time a scientific field in which immunology and pharmacology have met and given origin to notable progress in the history of science. The development of chemotherapy, as well as of organ and tissue transplantation, in the twentieth century has been decisively promoted by both immunology and pharmacology. In the last three decades the relationship between these two scientific branches has become increasingly closer in basic research, clinical science, medical education and also editorial scientific activity, as documented by the Journal hosting this paper.
COMBINATION THERAPY OF LAMIVUDINE AND INTERFERON-ALPHA IN PEDIATRIC PATIENTS WITH CHRONIC HEPATITIS B IN BANGLADESH: A SAFE AND EFFECTIVE THERAPEUTIC APPROACH FOR PEDIATRIC CHB PATIENTS IN DEVELOPING COUNTRIES

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Hepatitis B virus (HBV) is mainly transmitted during birth or perinatal period, however, treatment is not usually recommended for pediatric patients with chronic hepatitis B (CHB). Twelve pediatric patients with CHB in Bangladesh were treated with both lamivudine and interferon. Lamivudine was given at a dose of 3 mg/kg, daily for 12 months. Two months after commencement of lamivudine therapy, all patients were given interferon-α (3 million IU/square meter of body surface area) three times weekly, subcutaneously for 10 months. Combination therapy was safe for all pediatric CHB patients. The levels of serum HBV DNA became undetectable (<500 copies/ml) in 8 patients and reduced in 4 patients after the end of therapy. Anti-HBe was detected in 10 of 12 patients at this time point. The levels of serum alanine aminotransferase (ALT) were significantly reduced in these patients (p<0.05) due to therapy. Neither flare of HBV DNA nor elevation of serum ALT were detected during follow-up. In conclusion, combination therapy with lamivudine and interferon-α represents a new and novel therapeutic option for treatment of pediatric CHB patients.

CD4+ AND CD4- CD1D-RESTRICTED NATURAL KILLER T CELLS IN PERINATALLY HIV-1 INFECTED CHILDREN RECEIVING HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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We conducted a cross-sectional study on 43 Italian perinatally human immunodeficiency virus-type 1 (HIV-1) infected children receiving highly active antiretroviral therapy (HAART) and 26 age-matched healthy controls to explore CD1d-restricted NKT subsets. CD4+ CD1d-restricted natural killer (NKT) cell depletion was evidenced in 26 HIV-1 infected children with active viral replication despite HAART. Conversely, no alteration was evidenced in 17 children with undetectable viral load, suggesting full recovery in both CD4+ and CD4- CD1d-restricted NKT cell subsets. The loss of CD4+ NKT cells in unresponsive children may have clinical consequences, including autoimmune disorders or cancer development. Future therapeutic perspectives are suggested.
ECZEMA AND FOOD ALLERGY IN AN ITALIAN PEDIATRIC COHORT: NO ASSOCIATION WITH TLR-2 AND TLR-4 POLYMORPHISMS

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Recent studies have indicated that Toll-like receptor polymorphisms or their impaired signalling, specifically TLR-2 and TLR-4, were correlated with a higher risk for allergy. The purpose of this study is to evaluate the associations of TLR-2 and TLR-4 single nucleotide polymorphisms (SNP) and atopic traits in a cohort of 159 Italian allergic children (102 affected by eczema and 57 by IgE-mediated food allergy) and 147 healthy controls recruited in Rome, Italy. DNA was isolated from the peripheral blood and TLR-2 R753Q/TLR-4 D299G polymorphisms were determined by TaqMan MGB probes using Real-Time PCR technique. In the control group, the TLR-2 polymorphism R753Q had a prevalence of 2.5% while the frequency of the TLR-4 D299G was 12%. None of the 159 allergic patients showed the R753Q SNP. By contrast, 7/57 patients with food allergy (12%) and 6/102 subjects with eczema (6%) carried the TLR-4 mutation. In our cohort, no evidence of correlation between TLR-2 or TLR-4 polymorphism and eczema and food allergy incidence and/or severity was found. Further studies are needed to clarify the possible role of TLR-2 and TLR-4 polymorphism in allergic disease, in Italian children.

THE ROLE OF ANTI–CYCLIC CITRULLINATED PEPTIDE ANTIBODY IN PERIODONTAL DISEASE

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The anti–Cyclic Citrullinated Peptide Antibodies (anti-CCP) are produced locally in the inflamed synovium of Rheumatoid arthritis (RA) patients, suggesting that citrullinated proteins are located in the inflamed synovium. In scientific literature were find periodontal bacterial DNA in serum and synovial fluid of RA with PD patients. RA and adult periodontitis share common pathogenetic mechanisms and immunologic and pathological findings RA. One oral pathogen strongly implicated in the pathogenesis of periodontal disease (PD), Porphyromonas gingivalis, possesses a unique microbial enzyme, peptidylarginine deiminase (PAD), the human equivalent of which has been identified as a susceptibility factor for RA. Under this point of view, we speculate about the presence of anti-CCP antibodies in sera of PD with RA patients. We conducted this study to evaluate and compare the diagnostic and predictive utility of anti-CCP antibodies in patients with PD and patients with PD and RA. Anti-CCP antibody was not found in 21 sera (U/ml<10), included RA controls, while only 1 patient with chronic PD and probing depth of 7,1 mm was identified positive for anti-CCP (22.2 U/ml). Our data do not support a role for anti-CCP in diagnoses of periodontal disease.