NEURO-IMMUNO-ENDOCRINE PROCESSES IN VITILIGO PATHOGENESIS

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Vitiligo is a cutaneous disorder of depigmentation, clinically characterized by well-demarcated, white macules of varying size and distribution. It can affect up to 2% of the population, especially younger ages. In spite of recent findings implicating genetic, immune and oxidative stress factors, the exact pathogenesis of vitiligo remains obscure. Here, we briefly discuss the prevailing theories, and offer new suggestions that could explain in part the damage of melanocyte in the vitiliginous lesions. Our emerging hypothesis is that neuropeptides released from peripheral nerve endings could synergize with new cytokines to adversely affect melanocyte function and viability. These may include corticotropin-releasing hormone (CRH) and neurotensin (NT), as well as interleukin 33 (IL-33) and thymic stromal lymphopoietin (TSLP). Such interactions could serve the basis for further research, possibly leading to new treatments.
On a planetary scale, Metabolic Syndrome (MetS) is the third cause of inability after malnutrition and nicotinism, even higher than water shortage and sedentariness. In the USA, the prevalence is estimated at over 25% of the population; in Italy, it involves approximately 25% of men and even 27% of women. These are very high figures, corresponding to approximately 14 million affected individuals. The prevalence is alarming and must not be underestimated, particularly in the dental field, where more than one patient out of four sitting in a dentist’s chair is affected. The etiology of periodontal disease has not yet been clarified, and recently the idea to consider it as a multifactor pathology has been developed. Cofactors such as the formation of free radicals of oxygen (ROS), oxidative stress, lipid peroxidation, and formation of glycation end-products (AGEs) probably play an important role in the onset of periodontal disease. The AGEs are compounds physiologically produced by the cells. However, they accumulate and cause pro-inflammatory conditions, when the cellular clearance fails, or in hyperglycemic and oxidative states. All these conditions can be clinically summarized as Metabolic Syndrome. The purpose of this literature review is to establish a relationship between two pathologies with very high prevalence: Metabolic Syndrome and Periodontal Disorder. The literature seems to have clarified that MetS involves a pro-oxidation status, which induces AGE formation. AGEs play a very important role in the course and severity of periodontal diseases.
WHY GLUCOCORTICOSTEROIDS SHOULD REMAIN IN THE LIST OF PROHIBITED SUBSTANCES: A SPORTS MEDICINE VIEWPOINT

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In addition to their therapeutic applications, glucocorticosteroids have been widely used and abused in the belief that these substances may enhance athletic performance. Analysis of athlete urine samples by antidoping laboratories around the world support this conclusion. It is commonly accepted in medical practice to use local glucocorticosteroid injections in the treatment of non-infectious local musculotendinous inflammatory conditions conveying symptom relief and often a speedier return to sporting activity. This practice is not to be considered illicit, but sports physicians must accept that such an intervention is not in itself an immediate cure and that an athlete will still require a period of recuperation before continuing sporting activity. How long such a period of recuperation should last is a matter of conjecture and there is little concrete data to support what is, or what is not, an acceptable period of inactivity. In the interest of athlete safety, we would propose to maintain systemic glucocorticosteroids on the World Anti-Doping Agency’s (WADA) list of prohibited substances, both in and out-of-competition as well as a mandatory period of 48 hours of rest from play after receiving a local glucocorticosteroid injection.
STATINS AND CARDIOVASCULAR RISK IN RHEUMATIC DISEASES

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Chronic inflammatory rheumatic diseases are associated with an increased risk of cardiovascular (CV) atherosclerotic events. The inflammatory state, which is the hallmark of chronic rheumatic diseases, is the important driving force for accelerated atherogenesis. Since the control of traditional risk factors alone is insufficient in reducing the risk, much attention has been directed towards the potential use of statins. Statins, a family of drugs that suppress cholesterol biosynthesis by inhibiting the hydroxymethyl glutaryl coenzyme A reductase, have been shown to significantly reduce CV-related morbidity and mortality. In addition to lower lipid levels, several non-lipid lowering pleiotropic effects, including anti-inflammatory and immunomodulatory activities, make statins potential therapeutic agents in chronic rheumatic diseases. However, lipid metabolism in chronic rheumatic diseases is complex, since inflammatory states can induce alterations in lipid levels and function, so that cholesterol target levels from general guidelines may not be adequate in chronic inflammatory rheumatic diseases. Larger trials are needed to refine the precise benefits and health-utility associated with this therapy.
IL-37 (IL-1F7) THE NEWEST ANTI-INFLAMMATORY CYTOKINE WHICH SUPPRESSES IMMUNE RESPONSES AND INFLAMMATION


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Cytokines such as interleukins, chemokines and interferons are immunomodulating and inflammatory agents, characterized by considerable redundancy, in that many cytokines appear to share similar functions. Virtually all nucleated cells, but especially epithelial cells and macrophages, are potent producers of cytokines. The objective of this study is to review the detailed mechanism of action and the biological profiles of IL-37, the newest anti-inflammatory cytokine. This review focuses on IL-37, a key cytokine in regulating inflammatory responses, mainly by inhibiting the expression, production and function of proinflammatory cytokines: IL-1 family pro-inflammatory effects are markedly suppressed by IL-37.
**IN VITRO AND IN VIVO THERAPEUTICS OF β-THUJAPLICIN ON LPS-INDUCED INFLAMMATION IN MACROPHAGES AND SEPTIC SHOCK IN MICE**

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β-thujaplicin, an active constituent from *Chamaecyparis obtusa*, has been shown to have acaricidal and antimicrobial effects. Very few studies have focused on the potential of the anti-inflammatory effect of β-thujaplicin. Moreover, its capability of inhibiting inflammatory mediators e.g. TNF-α gene transcription, nitric oxide (NO) and prostaglandin E2, remains unknown. Besides those molecular mechanisms behind the anti-inflammatory effect of β-thujaplicin, solid proof of its effectiveness in vivo has not yet been studied. In our study, in vitro effects of β-thujaplicin were verified on RAW 264.7 macrophages which were stimulated by LPS. Indomethacin was used as a positive control. The inducible NO production after stimulation was measured by Griess reagent. PGE2, IL-6 and TNF-α were measured by ELISA methods. Protein expressions of iNOS, COX2, and NF-κB were evaluated by Western blotting. Septic ICR mice were administered 20 mg/kg of LPS and then the mortality rate was monitored. Within the concentration range which was devoid of cytotoxicity, β-thujaplicin exhibited a clear dose-dependent inhibition on LPS-induced NO production. Furthermore, β-thujaplicin inhibited LPS-induced PGE2, IL-6, and TNF-α production as well as iNOS, COX2, and NF-κB protein expression more substantially potent than indomethacin. In agreement with the in vitro study, β-thujaplicin was shown to be effective in vivo for inhibiting LPS-induced NO and TNF-α production and a significant decrease in mortality rate of mice suffering from septic shock was observed. This study demonstrates the potential of β-thujaplicin in treatment of inflammation and sepsis. These effects occur through an efficient blockage of TNF-α and iNOS production. β-thujaplicin efficacy is comparable to that of indomethacin thus it can be a substitution but bear less depletion of PGE2, making this compound very promising in clinical applications.
APP/PS1 TRANSGENIC MICE TREATED WITH ALUMINUM: AN UPDATE OF ALZHEIMER’S DISEASE MODEL

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There is still no animal model available that can mimic all the cognitive, behavioral, biochemical, and histopathological abnormalities observed in patients with Alzheimer's disease (AD). We undertook to consider the interaction between genetic factors, including amyloid precursor protein (APP) and presenilin-1 (PS1), and environmental factors, such as Aluminum (Al) in determining susceptibility outcomes when studying the pathogenesis of AD. In this article, we provide an AD model in APP/PS1 transgenic mice triggered by Al. The animal model was established via intracerebral ventricular microinjection of aluminum chloride once a day for 5 days in APP/PS1 transgenic mice. Twenty wild type (WT) mice and 20 APP/PS1 transgenic (TG) mice were separately divided into 2 groups (control and Al group), and a stainless steel injector with stopper was used for microinjection into the left-lateral cerebral ventricle of each mouse. The Morris water maze task was used to evaluate behavioral function of learning and memory ability on the 20th day after the last injection. This AD model's brain was analyzed by: (1) amyloid β immunohistochemical staining; (2) Tunnel staining; (3) apoptotic rates; (4) caspase-3 gene expression. Here, decrease of cognitive ability and neural cells loss were shown in APP/PS1 transgenic mice exposed to Al, which were more extensive than those in APP/PS1 TG alone and WT mice exposed to Al alone. These findings indicate that there is a close relationship between over-expression of APP and PS1 genes and Al overload. It is also suggested that APP/PS1 TG mice exposed to Al have potential value for improving AD models.
GITR-EXPRESSING REGULATORY T-CELL SUBSETS ARE INCREASED IN TUMOR-POSITIVE LYMPH NODES FROM ADVANCED BREAST CANCER PATIENTS AS COMPARED TO TUMOR-NEGATIVE LYMPH NODES

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Lymph node (LN) infiltration by neoplastic process involves important changes in lymph node immune microenvironment. In particular, regulatory T cells (Treg) seem to have a key role in altering the immunoediting function of the immune system which leads to the elusion of the tumor from immune surveillance. In this study, we evaluate the expression of T-cell markers in CD4+ and CD8+ subsets from tumor-positive and tumor-negative lymph nodes from the same, advanced stage breast cancer patient. The study was carried out on 3 patients and similar results were obtained. Flow cytometric analysis of CD8+ cells demonstrated a significant difference in the expression of CD25, CD45RA, CD45RO, and GITRL (Glucocorticoid-Induced TNF receptor-Related ligand). Flowcytometric analysis of CD4+ cells demonstrated a significant difference in the expression of GITR (Glucocorticoid-Induced TNF receptor-Related), CD25, FoxP3 (Forkhead box P3), CD28, and CD45RA. Multiple staining allowed the identification of two Treg subpopulations, CD4+CD25^{high}GITR^{+}CD127^{low} and CD4+CD25^{low}GITR^{+}CD127^{+} cells, proving that both are increased in the positive nodes in comparison with the negative nodes from the same patient. We identified for the first time the CD4+CD25^{low}GITR^{+}CD127^{+} Treg subpopulation in cancer, and the 2.6 fold increase in positive LN suggests that this Treg subpopulation could be a key player in metastasis. We also found GITRL expression in the CD8 lymphocytes, which may also contribute to the changes of metastatic lymph node microenvironment. These findings make both GITR and GITRL good possible co-candidates for future therapeutical intervention against metastasis and perhaps also as disease evolution biomarkers.
IS THERE A ROLE FOR PROSTATE TUMOUR OVEREXPRESSED-1 IN THE DIAGNOSIS OF HGPIN AND OF PROSTATIC ADENOCARCINOMA? A COMPARISON WITH α-METHYLACYL CoA RACEMASE

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Prostate Tumour Overexpressed-1 (PTOV1) was recently identified as a novel gene and protein during a differential display screening for genes overexpressed in prostate cancer (PCa). α-Methyl-CoA racemase (AMACR) mRNA was identified as being overexpressed in PCa. PTOV1 and racemase were immunohistochemically evaluated in PCa, high-grade prostatic intraepithelial neoplasia (HGPIN), atrophy and normal-looking epithelium (NEp) in 20 radical prostatectomies (RPs) with pT2a Gleason score 6 prostate cancer with the aim of analyzing the differences in marker expression between PTOV1 and AMACR. The level of expression of PTOV1 and AMACR increased from NEp and atrophy through HGPIN, away from and adjacent to prostate cancer, to PCa. With the ROC curve analysis the overall accuracy in distinguishing PCa vs HGPIN away from and adjacent to cancer was higher for AMACR than for PTOV1. In conclusion, AMACR can be considered a more accurate marker than PTOV1 in the identification of HGPIN and of PCa. However, PTOV1 may aid in the diagnosis of PCa, at least to supplement AMACR as another positive marker of carcinoma and to potentially increase diagnostic accuracy.
ENDOTHELIAL PROGENITOR CELL-DERIVED MICROVESICLES IMPROVE NEOVASCULARIZATION IN A MURINE MODEL OF HINDLIMB ISCHEMIA

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Paracrine mediators released from endothelial progenitor cells (EPCs) have been implicated in neoangiogenesis following ischemia. Recently, we demonstrated that microvesicles (MVs) derived from EPCs are able to activate an angiogenic program in quiescent endothelial cells by a horizontal transfer of RNA. In this study we aim to investigate whether EPC-derived MVs are able to induce neoangiogenesis and to enhance recovery in a murine model of hindlimb ischemia. Hindlimb ischemia was induced in severe combined immunodeficient (SCID) mice by ligation and resection of the left femoral artery and mice were treated with EPC-derived MVs (MVs), RNase-inactivated MVs (RnaseMVs), fibroblast-derived MVs or vehicle alone as control (CTL). Since MVs contained the angiogenic miR-126 and miR-296, we evaluated whether microRNAs may account for the angiogenic activities by treating mice with MVs obtained from DICER-knock-down EPC (DICER-MVs). The limb perfusion evaluated by laser doppler analysis demonstrated that MVs significantly enhanced perfusion in respect to CTL (0.50±0.08 vs 0.39±0.03, \(p < 0.05\)). After 7 days, immunohistochemical analyses on the gastrocnemius muscle of the ischemic hindlimb showed that MVs but not fibroblast-MVs significantly increased the capillary density in respect to CTL (MVs vs CTL: 24.7±10.3 vs 13.5±6, \(p < 0.0001\)) and (fibroblast-MVs vs CTL: 10.2±3.4 vs 13.5±6, ns). RNaseMVs and DICER-MVs significantly reduced the effect of MVs (RNaseMVs vs CTL: 15.7±4.1 vs 13.5±6, ns) (MVs vs DICER-MVs 24.7±10.3 vs 18.1±5.8, \(p < 0.05\)), suggesting a role of RNAs shuttled by MVs. Morphometric analysis confirmed that MVs enhanced limb perfusion and reduced injury. The results of the present study indicate that treatment with EPC-derived MVs improves neovascularization and favors regeneration in severe hindlimb ischemia induced in SCID mice. This suggests a possible use of EPCs-derived MVs for treatment of peripheral arterial disease.
IMPACT OF DIFFERENT CONCENTRATIONS OF HUMAN RECOMBINANT GROWTH HORMONE ON T LYMPHOCYTES

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The aim of the present study is to evaluate the effects induced by increasing concentrations of human recombinant growth hormone on T lymphocytes. Ten healthy volunteers and twelve subjects with symptomatic allergies were enrolled in the study. Peripheral blood mononuclear cells and purified T lymphocytes were cultured in the presence of graded concentrations of growth hormone. Following appropriate in vitro stimulations, the proportion of apoptotic T cells, the percentage of activated T lymphocyte subpopulations, the phytohemagglutinin responsiveness and the Th2 response were assessed by flow cytometry analysis. Moreover, in order to evaluate the phosphoinositol-3-kinase signaling pathway involvement, cells were also analyzed after treatment with LY294002. The treatment with different concentrations of growth hormone did not influence the activation pattern of un-stimulated T lymphocytes. On the contrary, growth hormone was able to modify the CD38/HLA-DR co-expression of T cells activated with phytohemagglutinin. A different response was observed when samples obtained from healthy donors and from subjects with symptomatic allergies were analysed. Moreover, growth hormone treatment was able to increase the Th2 response in the samples obtained from healthy donors only. The results of the present study strongly support the hypothesis that growth hormone administration may play an important role in conditions of impaired/activated immune systems. The observation that growth hormone administration at high doses may reverse its effects and that it may promote a Th2-oriented response have significant clinical implications when considering the use of this hormone for artificially enhancing the physical performances of healthy athletes.
INCREASED PERCENTAGES OF TUMOR NECROSIS FACTOR-α+/INTERFERON-T+LYMPHOCYTES AND CALPROTECTIN+/TUMOR NECROSIS FACTOR-Α+ MONOCYTES IN PATIENTS WITH ACUTE KAWASAKI DISEASE

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In vivo exposure to microorganisms resident in the oral cavity is considered as a possible cause of Kawasaki disease (KD), and some epitopes derived from streptococci display homology with Factor H of Complement. Additionally, calprotectin, a major calcium binding protein released by neutrophils and activated monocytes, could be directly involved in endothelial damage occurring in KD. The aim of our study is to evaluate the percentages of IFN-γ+ and/or TNF-α+ lymphocytes and double positive calprotectin/TNF-α+ monocytes (CD14+) after in vitro stimulation with streptococcal- and/or Factor H-derived peptides, in patients with acute KD. Peripheral Blood Mononuclear Cells (PBMCs) obtained from KD patients and febrile controls were stimulated in vitro with peptides. After culture, cells were collected, stained with fluorochrome-labelled monoclonal antibodies against CD3, CD14, calprotectin, IFN-γ and TNF-α, and cytofluorimetric analyses were performed. Our results showed increased percentages of TNF-α+/IFN-γ+ lymphocytes in KD patients in respect to controls when PBMCs were stimulated with streptococcal or Factor H-derived epitopes. In addition, also calprotectin+/TNF-α+ monocytes from KD patients were activated after PBMC in vitro stimulation. These findings lead us to speculate that some peptides, derived from oral streptococci and cross-reactive with the human Factor H of Complement, could induce lymphocyte and monocyte activation potentially involved in the pathogenesis of KD. Our results should be confirmed by further studies enrolling more patients and controls than those analyzed in our study.
EXPRESSION OF GELATINASES (MMP-2, MMP-9) AND CYCLOOXYGENASES (COX-1, COX-2) IN SOME BENIGN SALIVARY GLAND TUMORS

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Salivary gland tumors, most of which are rare benign tumors, represent a histologically heterogenous group with the greatest diversity of morphological and cellular features. The aim of this study is to analyse the expression and possible interactions between gelatinases (MMP-2, MMP-9) and cyclooxygenases (COX-1, COX-2) in some benign salivary gland tumors. We investigated the expression of gelatinases and cyclooxygenases in control salivary gland, Pleomorphic adenoma and Warthin’s tumor through immunohistochemistry and Reverse Transcription – Polymerase Chain Reaction (PCR). We identified the expression of both classes of enzyme in normal samples and in the two types of pathological samples without any quantitative differences. From the present data no significant differences emerge in the expression of these enzymes among the different pathologies examined. Nevertheless, due to the small number of samples included in this study, general statements regarding correlation between the degree of severity of the tumoral pathology and the quantitative expression of these potential tumoral markers can not be made.
NEUROTROPHINS, THEIR RECEPTORS AND KI-67 IN HUMAN GH-SECRETING PITUITARY ADENOMAS: AN IMMUNOHISTOCHEMICAL ANALYSIS

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Pituitary adenomas are a diverse group of tumors arising from the pituitary gland. Typically, they are small, slow-growing, hormonally inactive lesions that come to light as incidental findings on radiologic or postmortem examinations, although some small, slow-growing lesions with excessive hormonal activity may manifest with a clinical syndrome. The family of neurotrophins plays a key role in the development and maintenance of the pituitary endocrine cell function and in the regulation of hypothalamo–pituitary–adrenocortical axis activity. The objective of our experimental study is to investigate the localization of the neurotrophins, their relative receptors and to detect the expression level of Ki-67 to determine whether all these factors participate in the transformation and development of human pituitary adenomas. A very strong expression of Neurotrophin-3 (NT-3) and its receptor TrKC was observed in the extracellular matrix (ECM) and vessel endothelium, together with a clear/marked presence of Brain-derived neurotrophic factor (BDNF), and its receptor TrKB, thus confirming their direct involvement in the progression of pituitary adenomas. On the contrary, NGF (Nerve growth factor) and its receptor TrKA and p75NTR were weakly expressed in the epithelial gland cells and the ECM.
COMPARISON OF IMMUNO-PHENOTYPES OF STEM CELLS FROM HUMAN DENTAL PULP AND PERIODONTAL LIGAMENT

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It has been established that human dental pulp and periodontal ligament contain a population of mesenchymal stem cells (MSCs). However, the phenotypic analysis in terms of putative stem cell markers expressed by these stem cell populations is incomplete. It is relevant to understand whether stem cells derived from closely related tissues are programmed differently. The aim of the present study is to analyze whether these stem cells depict distinct characteristics by gaining insight into differences in their immunophenotype. Dental pulp and periodontal ligament tissue samples were obtained from extracted impacted wisdom teeth. Cell cultures were analyzed for surface and intracellular markers by indirect immunofluorescence. Detailed immunophenotype analysis was carried out by flow cytometry using relevant markers. The present study data shows dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs) expressed embryonic stem (ES) cell markers Oct-4, Nanog and mesodermal marker Vimentin by indirect immunofluorescence. PDLSCs, however, had a weak expression of Nanog. Immunophenotyping revealed strong expression of MSC markers (CD73, CD90) in DPSCs and PDLSCs. Differences were observed in expression of stemness-related markers. DPSCs displayed increased percentages of SSEA4, CD13 and CD166 and decreased CD9 expression compared to PDLSCs. Both stem cells express common MSC markers, different levels of expression suggests there might be more than one stem cell population existing within these tissues which differ in their embryonic status, and DPSCs are a more primitive stem cell population in comparison to PDLSCs.
ABERRANT β-CATENIN AND LEF1 EXPRESSION MAY PREDICT THE CLINICAL OUTCOME FOR PATIENTS WITH OROPHARYNGEAL CANCER


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β-catenin, normally expressed on the epithelial cell surface, plays a crucial role in cadherin-mediated cell adhesion. Recent evidence suggests that β-catenin is also involved in other functions such as intracellular signaling via the Wnt pathway by creating a nuclear complex with members of the Lymphoid-Enhancer-Factor/T-Cell-Factor (LEF/TCF) family of transcription factors, and gene regulation that it is implicated in the development of several tumors. Little information is available on β-catenin expression and its main partner in the Wnt signaling pathway, LEF1, in oropharyngeal squamous cell carcinomas (OP-SCCs). The aim of this study is to investigate the expression of β-catenin and LEF1 expression in human primary OP-SCCs and to evaluate their clinical and prognostic significance. OP-SCCs and normal peritumoral areas were analyzed by immunohistochemistry, Western-blot and RT-PCR. β-catenin was overexpressed in tumors in comparison to normal peritumoral areas and displayed predominantly intracellular (cytosolic/nuclear) localization in 62% of the tumors. Immunoreactivity was correlated with clinicopathological parameters and long-term follow-up, and a significant association was found between protein expression and development of local recurrences (P =0.03). The OP-SCCs with poor clinical outcome, which displayed intracellular β-catenin expression, were also strongly positive for LEF1, with their co-expression statistically significant (P = 0.040). All (100%) advanced (stages 3+4) SCCs, 66.7% of the SCCs with positive lymph nodes and 80% of the SCCs that developed local recurrences were LEF1 positive. Cox regression analysis confirmed a poorer overall survival in cases with high expression of β-catenin and LEF1. Our results suggest that assessing intracellular β-catenin and LEF1 expression might help in patient risk stratification and outcome prediction, and serve as novel therapeutic targets in advanced OP-SCC.
ALTERED IMMUNE RESPONSES DURING SEPTICAEMIA IN PATIENTS SUFFERING FROM HAEMATOLOGICAL MALIGNANCIES

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Septicaemia is a frequent complication in patients with haematological malignancies. In this study we analysed markers of inflammation/immune activation (C-reactive protein, interleukin-6, neopterin), tryptophan metabolites and mannose binding lectin (MBL) levels consecutively in 36 septic patients with haematological malignancies (HM) and “non-haematological” diseases [intensive care unit (ICU) patients]. During septicaemia different chronological sequences for inflammation markers CRP, IL-6 and neopterin were seen in HM and ICU patients. Septic ICU-patients presented with significantly increased tryptophan degradation and higher neopterin and CRP levels at baseline, while MBL levels were lower in this group compared to subjects with HM. Concentrations of inflammation markers were linked to each other and associated with enhanced tryptophan degradation. Patients who died during follow-up of 28 days tended to have lower baseline MBL concentrations than survivors. Septic patients with HM showed an impaired pro-inflammatory immune response compared to patients with non-haematological diseases.
PROSTAGLANDIN E\textsubscript{2} TO DIAGNOSE BETWEEN REVERSIBLE AND IRREVERSIBLE PULPITIS

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The aim of this work is to verify a correlation between the grade of inflammation and the concentration of PGE\textsubscript{2} in human dental pulp. A total of 25 human dental pulps were examined by histological analysis and radioimmunologic dosage of PGE\textsubscript{2}. The pulps used in this experiment were from healthy and symptomatic teeth; the first ones were collected from teeth destined to be extracted for orthodontic reasons. An increase was observed of PGE\textsubscript{2} in reversible pulpitis compared with healthy pulps and with the irreversible pulpitis and the clear decrease of these when NSAIDs are taken. This study demonstrates that PGE\textsubscript{2} level is correlated to histological analysis thus allowing to distinguish symptomatic teeth in reversible and irreversible pulpitis.
The first two authors contributed equally to this study

One of the key challenges in reconstructive bone surgery is to provide living constructs that possess the ability to integrate in the surrounding host tissue. Bone graft substitutes and biomaterials have already been widely used to heal critical-size bone defects due to trauma, tumor resection and tissue degeneration. In the present study, gelatin-based cryogels have been seeded with human SAOS-2 osteoblasts followed by the in vitro culture of the cells. In order to overcome the drawbacks associated with static culture systems, including limited diffusion and inhomogeneous cell-matrix distribution, the present work describes the application of a bioreactor to physically enhance the cell culture in vitro using an electromagnetic stimulus. The results indicate that the physical stimulation of cell-seeded gelatin-based cryogels upregulates the bone matrix production. We anticipate that the scaffolds developed consisting of human bone proteins and cells could be applied for clinical purposes related to bone repair.
Exhaled nitric oxide (FeNO) has been associated with bronchial eosinophilia and with airway hyperresponsiveness (AHR) in mild stable asthma. We previously demonstrated in a large project that allergen exposure is able to raise FeNO and to worsen AHR to bradykinin. We postulated that allergen-induced increase in FeNO could be related to heightened mucosal eosinophils and AHR to bradykinin in atopic asthma. We performed a new immunohistochemical analysis on bronchial biopsy specimens, previously obtained from the same large project, in order to assess the number of mucosal eosinophils (EG-2+ cell) and other inflammatory cells at 48 hours after diluent and allergen exposures. Inflammatory cell counts were related to FeNO and AHR to BK (expressed as logPD _20_ bradykinin). In 10 atopic mild asthmatics, we found that the numbers of EG-2+ and CD4+ cells in bronchial submucosa were significantly increased after allergen compared to the respective counts after diluent (p < 0.01). EG-2+ cells in the bronchial submucosa were negatively correlated with logPD _20_ bradykinin only after allergen challenge (rho = -0.709, p = 0.027). We also found a positive strong correlation between EG-2+ cells and FeNO values in atopic asthmatics at 48 hours after both diluent (rho = 0.746, p = 0.017) and allergen (rho = 0.644, p = 0.049) challenge. FeNO values negatively correlated with responsiveness to bradykinin only after allergen challenge (rho = -0.675, p = 0.039). This study indicates that after allergen exposure heightened level of exhaled NO may reflect augmented airway eosinophilic inflammation and airway responsiveness to bradykinin indicating loss of asthma control.
IMMUNOHISTOCHEMICAL PROFILE OF NEUROTROPHINS AND MIB-1 IN JUGULOTYMPANIC PARAGANGLIOMAS: PROGNOSTIC VALUE AND REVIEW OF THE LITERATURE

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Jugulo-tympanic paragangliomas are the most common primary neoplasm of the middle ear, but little is still known about the histological features differentiating the benign and malignant forms. We investigated, with an immunohistochemical procedure, the expression of neurotrophins with their receptors, in fifteen samples of paragangliomas, and MIB-1 in order to consider them as prognostic factors of malignancy. We observed a general positivity for NGF – TrKA – NT4 – TrKC in the cytoplasm, and a strong expression for BDNF in the extracellular space. MIB-1 was moderate in the nucleus of neoplastic cells, weak in the cytoplasm and totally absent in the extracellular space. The comparison between the clinical recurrences and the rate of cytoplasmatic neurotrophins showed strong immunoreactivity in recurrent patients. It should be emphasized that 2 of the 3 recurrences had a wider distribution of the neutrophins, leading to hypothesize the involvement of these substances in the cell proliferation of glomus tumors. Malignant forms of these rare glomus tumors cannot be clearly identified using MIB-1 as a prognostic marker, although we can affirm that neurotrophins and their receptors can be considered as a panel of potential diagnostic markers to monitor the development of such malignancies. Although the small number of patients does not allow definitive conclusions to be made, our findings showed a possible trend towards significance which requires a more powerful study to evaluate this further.
MEDICAL MANAGEMENT AND SUBLINGUAL IMMUNOTHERAPY PRACTICES IN PATIENTS WITH HOUSE DUST MITE-INDUCED RESPIRATORY ALLERGY: A RETROSPECTIVE, OBSERVATIONAL STUDY

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The primary objective of this study is to retrospectively describe the treatment regimens (initiation, maintenance, dosage and duration) in sublingual immunotherapy (SLIT) with house dust mite (HDM) extracts in routine practice in France. The secondary objectives include a description of the respiratory allergies that led to treatment and an evaluation of the treatment’s efficacy and safety, patient satisfaction and compliance (as assessed by the physician) and patient management practices. Randomly-selected allergy specialists each included ten patients over the age of five with a respiratory allergy and proven sensitization to HDM (positive skin test and/or specific IgE >0.7 kUI) and in whom SLIT had been initiated in 2002 or 2005. The participants were monitored for at least two years. A total of 139 physicians participated in the study and contributed data from 1,289 patients (57% of whom were under the age of 18). More than 70% of the patients suffered from moderate-to-severe allergic rhinitis and 50% also suffered from asthma. More than 60% of the patients were polysensitized. A shift to shorter SLIT protocols was observed over time. Longer protocols tended to be used in children. Compliance was deemed good or very good in 84% of the patients. Treatment was deemed effective or very effective in 82% of the patients. Symptoms of rhinitis and/or asthma improved in 66% and 63% of the patients respectively, with a concomitant reduction in symptomatic medication intake. The majority of the patients were satisfied with their treatment, which was well tolerated. The results of this large, retrospective, observational study confirm the efficacy and tolerability of HDM SLIT in routine French practice in a “real-world” setting.
The aim of rhinosinusitis treatment is to restore sinusal eutrophism and to normalize ventilation and mucociliary transport. Frequently the improvement of sinusal physiological conditions is associated with a reduction of infections and pulmonary symptoms. The treatment of these diseases often requires the combination of medical and surgical strategies. In particular, the aim of the medical therapy is multiple: to treat the infection (with antibiotics), to reduce the mucosal swelling (with corticosteroids) and to improve mucus drainage (with mucolytics or muco-regulators). The use of atomized nasal douche, as a washing of the nasal fossas, is chosen because of its local action minimizing systemic adverse effects. The surgical treatment is secondary to medical failure, and it is focused on clearing the sinusal ostia in the sphenoethmoidal recess and the osteomeatal complex. In case of recurrent sinonasal diseases the importance of the surgical operation is represented by the fact that the medical treatment better reaches the target in the sinusal space. This study is focused on the primary medical treatment of acute recurrent rhinosinusitis. The patients who immediately needed surgical treatment were excluded from the study (because of the presence of an anatomical obstruction of the osteomeatal complex and/or the sphenoethmoidal recess, hence non-susceptible to improvement by medical therapy alone), and these patients were immediately addressed to undergo a CT scan examination in order to be involved in a future surgical programme. The medical treatment for those forms which do not require antibiotics (i.e. when infections are not involved), is based on the use of topical corticosteroids. While there are controversies on the real efficacy of adding mucolytic agents to the steroids, they are commonly prescribed in clinical practice, with the rationale of reducing viscosity and improving clearance of mucus in order to help the restoration of the physiological sinus conditions. The primary aim of the medical treatment is to reduce the number of acute episodes and thus to increase the time between the exacerbations, allowing a good quality of life without necessitating surgical procedure.
NEUROPROTECTIVE AND ANTI-INFLAMMATORY ACTIVITIES OF ATORVASTATIN IN A RAT CHRONIC CONSTRUCTION INJURY MODEL

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Atorvastatin is an HMG-CoA reductase inhibitor used to treat hypercholesterolemic conditions associated with hypertension. This study aims to investigate the anti-inflammatory and neuroprotective effects of atorvastatin on peripheral neuropathic pain. Peripheral neuropathic pain was induced by chronic constriction injury (CCI) in Sprague-Dawley rats. Rats were divided into 3 groups including sham-operated, CCI, and atorvastatin-treated. Atorvastatin (10 mg/kg) or phosphate-buffered saline was orally administered for 2 weeks. All animals were assessed by neurobehavioral tests before surgery and at days 3, 7, 14 after surgery. Inflammatory and neuroprotective factors were evaluated by Western blot analysis. eNOS, COX2 and iNOS in the sciatic nerve were also studied using immunohistochemistry. Atorvastatin attenuated CCI-induced nociceptive sensitization and thermal hyperalgesia in a time-dependent manner. Atorvastatin improved CCI-induced neurobehavioral/inflammatory activity by inhibition of TGF-β, pIkB/IkB, NFκB, COX2, iNOS, EP1 and EP4 in the sciatic nerve. Atorvastatin was also found to increase neuroprotection factors pAkt/Akt, eNOS and VEGF. Taken together, these data indicate that atorvastatin could protect the sciatic nerve against CCI-induced neuroinflammation and nociception.
A COMPARATIVE STUDY OF LORATADINE SYRUP AND CYPROHEPTADINE HCL SOLUTION FOR TREATING PERENNIAL ALLERGIC RHINITIS IN TAIWANESE CHILDREN AGED 2-12 YEARS

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We assessed the efficacy of loratadine syrup compared with cyproheptadine HCl solution for treating children aged from 2 to 12 years with perennial allergic rhinitis (PAR) in Taiwan. Sixty children with mite-induced PAR were enrolled and randomly placed into two treatment groups: loratadine syrup or cyproheptadine HCl solution. Treatment efficacy and symptom changes from baseline to post-treatment were evaluated by total symptom scores and visual analogue scales (VAS) during a 2-week period. There were no differences in age, gender, height, or weight between the two groups. After 2 weeks of treatment, there was a significantly greater reduction in symptom scores in the loratadine group than in the cyproheptadine group ($p<0.001$). Clinical and subjective VAS showed significant differences in percentage changes from baseline between the loratadine and cyproheptadine groups at all time points (all $p<0.001$, in favor of loratadine). Clinical VAS change at week 1: 95.1 vs 11.3; subjective VAS change at week 1: 88.6 vs 13.6; clinical VAS change at week 2: 125.5 vs 18.3; subjective VAS change at week 2: 101.4 vs 7.1. Thus, loratadine was superior to cyproheptadine for alleviating both nasal and non-nasal symptoms of perennial allergic rhinitis in Taiwanese children aged 2-12 years.
AvidinOX® FOR TISSUE TARGETED DELIVERY OF BIOTINYLATED CELLS

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AvidinOX®, a product containing aldehyde groups, generated by ligand-assisted sugar oxidation of avidin by sodium periodate, maintains the capacity to bind biotin with very high affinity and exhibits the property to chemically link cellular and tissue proteins through Schiff’s base formation thus residing in tissues for weeks. In recent studies, we have shown that AvidinOX exhibits much higher persistency in the skeletal muscle than native avidin. The aim of the present study is to evaluate whether AvidinOX-biotin interaction might be exploited to target biotinylated cells to an AvidinOX pre-treated muscle. To accomplish this we performed the following experiments: 1) The proliferation and differentiation properties of biotinylated C2C12 myoblasts were tested in vitro upon linkage to AvidinOX; 2) Bone marrow-derived cells (BMDC) were isolated from GFP positive transgenic mice [strain C57 BL/6-tg (UBC-GFP)] and after biotinylation (bBMDC) were intravenously administered to naïve and MAVA⁺ (Mouse anti Avidin Antibody) C57/B6 mice previously injected with AvidinOX in a tibial muscle (TM). Localization efficiency of GFP⁺ bBMDC was evaluated on serial sections of the AvidinOX- and vehicle-treated (contra lateral limb) TM, 5 days after transplantation. Results show that biotinylated C2C12 cells, once linked to AvidinOX, maintain their proliferation and differentiation capacity, in vitro. Intravenous injection of biotinylated GFP⁺ bone marrow-derived cells leads to their specific and efficient localization in the AvidinOX-pre-treated, but not contra lateral muscle of both naïve and MAVA⁺ mice. The present data suggest a potential use of AvidinOX to improve tissue targeted delivery of biotinylated cells.
EFFECTS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON PLATELET ACTIVATING FACTOR METABOLISM IN NAÏVE HIV-INFECTED PATIENTS: II) STUDY OF THE ABACAVIR/LAMIVUDINE/EFAVIRENZ HAART REGIMEN

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Human Immunodeficiency Virus (HIV)-infected patients are at increased risk for cardiovascular diseases partly due to chronic inflammation. Some antiretroviral drugs and Highly Active Anti-Retroviral Therapy (HAART) regimens seem to be related and amplify this increased risk, especially the ones containing abacavir. Platelet-Activating-Factor (PAF) is a potent inflammatory mediator that is implicated in both cardiovascular diseases and HIV-related manifestations. Our objective is to study the in vivo effect of the abacavir/lamivudine/efavirenz first-line HAART regimen on PAF metabolism in HIV-infected patients. The specific activities of PAF basic biosynthetic enzymes in leukocytes and platelets, PAF-cholinephosphotransferase (PAF-CPT) and lyso-PAF-acetyltransferase (Lyso-PAF-AT), but also those of PAF-basic catabolic enzymes, PAF acetylhydrolase (PAF-AH) in leukocytes and platelets and Lipoprotein-associated-Phospholipase-A\(_{2}\) (LpPLA\(_{2}\)) in plasma, were measured in blood samples of 10 asymptomatic naïve male HIV-infected patients just before and after 1, 3 and 6 months of treatment. CD4 cell counts, viral load and several biochemical markers were also measured in the same blood samples of these patients. The repeated ANOVA measures and the Pearson r criterion were used for studying statistical differences and correlations - partial correlations respectively. Even though viral load was decreased and CD4 cell counts were beneficially increased after treatment with the abacavir/lamivudine/efavirenz regimen, the main enzyme of the remodelling PAF-synthesis that is implicated in pro-atherogenic inflammatory procedures, Lyso-PAF-AT activity, was increased at 3 months of treatment in both leukocytes and platelets, while the main enzyme of PAF-degradation, PAF-AH, was increased as a response only in leukocytes at the 3\(^{rd}\) month. Although the abacavir/lamivudine/efavirenz HAART regimen exhibits very efficient antiretroviral activities, on the other hand it induces an in vivo transient
PROTECTIVE ACTIVITY OF THE ETHANOL EXTRACT OF CYNANCHUM PANICULATUM (BUNGE) KITAGAWA ON TREATING HERPES SIMPLEX ENCEPHALITIS

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To date there has been no valid treatment for herpes simplex encephalitis (HSV). This study explores the protective activity of ethanol extract of Cynanchum paniculatum (bunge) kitagawa for treatment of HSV. Cell models and animal models were established and divided into 4 groups: normal group, virus group, cynanchum paniculatum group and Dexamethasone group. Flow cytometry was employed to detect apoptosis of cell model and TUNEL assay was chosen to detect apoptosis of animal tissues. The survival time of the animal models was observed. ELISA was used to measure TNF-α expression and the Greiss method to measure Nitric Oxide (NO) expression in the mouse brain. As a result, it was found that extract of Cynanchum paniculatum can improve the survival rate of HSV-infected mice. The extract could prevent apoptosis in the neuron cell model and reduce apoptosis rate in brain tissue after HSV infection. With the extract intervention, TNF-α and NO levels in brain tissue were significantly decreased in the animal model. In conclusion, the extract of Cynanchum paniculatum can prevent HSV-inducing impairment in the cell and animal model of HSE.
AN IgE IMMEDIATE REACTION TO THIOCOLCHICOSIDE

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Hypersensitivity reactions due to muscle relaxant drugs may be related either to a nonspecific release of allergic mediators or to allergic reactions induced by the molecules themselves. Rare cases of hypersensitivity reactions have been associated to thiocolchicoside, and no case of IgE-mediated immediate reaction has actually been reported to date. We report the first documented case of immediate anaphylaxis to thiocolchicoside.
SWITCH TO ICATIBANT IN A PATIENT AFFECTED BY HEREDITARY ANGIOEDEMA WITH HIGH DISEASE ACTIVITY: A CASE REPORT


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Icatibant, an antagonist of the bradykinin B2 receptor, was approved for the treatment of acute attacks of hereditary angioedema in the EU in 2008. This paper presents the case of a 65-year-old woman affected by frequent acute attacks of hereditary angioedema who benefitted from a change of therapy to icatibant, following years of treatment with C1-inhibitor.
We describe the case of a 45-year-old woman who had drawn our attention for some recent episodes of transient global amnesia that, upon further examination, resulted from ischemic events caused by multiple arterial thrombosis (bilateral internal carotid occlusion, significant stenosis of the right external carotid, mild stenosis of the right vertebral artery, right anterior cerebral artery occlusion and severe stenosis of the anterior descending coronary artery) due to primary antiphospholipid syndrome. Revascularisation of either carotid was not attempted. A percutaneous intervention in the anterior descending coronary artery stenosis was performed successfully. Due to severe arterial thrombosis, the patient was discharged with only duplex antiplatelet treatment and subcutaneous anticoagulant therapy, since immunotherapy is not indicated in primary APS. The occurrence of transient global amnesia should raise the suspicion of APS.
SIMILAR SERUM LEVELS OF IL-6 AND ITS SOLUBLE RECEPTORS IN PATIENTS WITH HCV-RELATED ARTHRITIS AND RHEUMATOID ARTHRITIS: A PILOT STUDY

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The high serum levels of Interleukin-6 (IL-6) and its soluble receptors (sIL-6r and sgp130), described in the course of Rheumatoid Arthritis (RA), have been linked to the enhanced activity of this cytokine in this disorder. In this study, the serum concentrations of IL-6 and its soluble receptors were determined in a group of patients with HCV-related arthritis (HCVrA), a condition resembling RA in several aspects, and then compared to those found in a sample of subjects affected by RA. Twenty-one patients with HCVrA, 24 patients with RA and 20 healthy subjects (control group) were examined. Different ELISA methods were used for determination of serum concentrations of IL-6, sIL-6r and sgp130. Increased IL-6 serum levels were found in 15 (71%) of the patients with HCVrA and in 16 (62%) of those with RA. Eight (38%) of the patients with HCVrA and 11 (46%) of those with RA denoted high levels of sIL-6r, while sgp130 levels were elevated in 21 (76%) of the patients with HCVrA and in 16 (69%) of those with RA. A significant difference between the median values of sIL-6r and sgp130 levels in the two groups of patients versus controls was found. A mild correlation of these parameters with RF levels was detected in the RA group. Furthermore, in HCVrA patients the serum levels of IL-6, sIL-6r and sgp130 appeared unrelated to HCV viraemia and to levels of transaminases. The enhanced serum levels of IL-6 in HCVrA patients indicate an increased synthesis and hyperactivity of this cytokine in HCVrA, and the substantial similarity of the behaviour of IL-6 and its serum receptors in the two groups of patients suggests common mechanisms with RA, in which the function of IL-6 is central.
Renal-limited vasculitis is a pauci-immune crescentic glomerulonephritis with no signs of systemic involvement, representing one of the most common causes of rapidly progressive glomerulonephritis. The study aims to examine clinical and histological features in twenty-four patients with RLV diagnosed by the Nephrology Department of Sapienza University of Rome, Italy, evaluating the role of these parameters in predicting renal survival. Patients details, clinical and histological features and outcomes were recorded at the time of renal biopsy and over a mean follow-up period of 36±6 months. In our study, serum creatinine at presentation was significantly higher in patients who had a poor outcome than in those who survived with independent renal function (6.3±2.47 mg/dl vs 2.84±2.01 mg/dl, P=0.002). The presence of C3c was found in the area of glomerular fibrinoid necrosis and in small arteries and arterioles with fibrinoid necrosis in 17 patients (P=0.018). In conclusion, serum creatinine at presentation and focal C3c depositions in areas of glomerular and arteriolar fibrinoid necrosis were the best determinants of poor renal outcome, maybe underlining the pathogenic role of alternative pathway activation of complement system but also demonstrating the focal distribution of necrotizing lesions.
HEPATITIS C VIRUS-RELATED ARTHRITIS AND RHEUMATOID ARTHRITIS: COULD THEY BE DIFFERENT ASPECTS OF THE SAME DISEASE?

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The role played by HCV in the genesis of many autoimmune disorders has been reported in several studies. In particular, the onset of arthritis has been described in about 2-3% of HCV infection cases. At present, this HCV-related arthritis is classified as a reactive arthritis, but a real distinction of this form from classical rheumatoid arthritis is often difficult. In this presentation, the Authors distinguish two arthritic forms observed in HCV-related arthritis patients: one, characterized by asymmetrical oligoarticular-involvement, and another, with poly-articular symmetrical involvement. The Authors suggest that the latter can be considered as a form of rheumatoid arthritis, because of the similarity of the main clinical aspects and laboratory findings (rheumatoid factor, anti-cyclic citrullinated peptide antibodies) to those of classical rheumatoid arthritis, which make the two forms indistinguishable. Therefore, HCV could be considered the etiologic agent of a limited number of cases of rheumatoid arthritis.
OCCURRENCE OF SALIVARY GLAND TUMOURS IN TWO PATIENTS TREATED WITH BIOLOGICAL AGENTS

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We report two cases of salivary gland tumors arising in two psoriatic patients treated with an anti-TNF-alpha agent. A clear causal relationship could not be established, but the exceptional onset of a bilateral Warthin’s tumor in one of these patients should be emphasized.
CAN THE ASSOCIATION OF CICLOSPORINE A AND METHOTREXATE MAINTAIN REMISSION/LOW DISEASE ACTIVITY INDUCED BY ETANERCEPT IN EARLY RHEUMATOID ARTHRITIS PATIENTS? EVALUATION BY MAGNETIC RESONANCE IMAGING

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The opportunity to induce remission/low disease activity in Rheumatoid Arthritis (RA) patients has been achieved in recent years by the adoption of more sensitive diagnostic methods [Magnetic Resonance Imaging (MRI), ultrasonography] and early aggressive treatments (combination of biologics and synthetic DMARDs). On the other hand, data are still scarce and contrasting about the management of long-term remission. The aim of this preliminary study is to evaluate whether the association of Methotrexate + Ciclosporine A (MTX + CSA) therapy in early RA (eRA) patients is able to maintain remission/low disease activity and avoid structural progression, evaluated by MRI. Etanercept was suspended in patients who reached remission/low disease activity and CSA+MTX therapy was introduced (T0), all patients continued to receive MTX; at this time MRI showed mild/moderate synovitis and erosions in all the patients; 1-year after (T1), a slight reduction in mean synovitis, bone edema and total score was observed, whereas the erosion score was unchanged. The mean DAS44 remained stable from T0 to T1 and 6/7 patients maintained a low disease activity score. No side effects were reported. These results confirm the good clinical efficacy and safety of the combination therapy CSA+MTX in eRA patients and demonstrate a parallel arrest of structural damage evaluated by MRI 1-year after etanercept suspension.
SATISFACTION WITH ALLERGY TREATMENTS DEPENDS ON SYMPTOM SEVERITY BUT NOT ON ALLERGEN SPECIFICITY IN PATIENTS WITH ALLERGIC RHINITIS

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Allergic rhinitis is characterized by troublesome symptoms that may be particularly severe. Most of rhinitics are dissatisfied with drug treatments. The dissatisfaction level depends on symptoms severity, but not on the type of causal allergen.
POSSIBLE ROLE OF ORAL IBANDRONATE ADMINISTRATION IN OSTEONECROSIS OF THE JAW: A CASE REPORT

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We describe a case of Osteonecrosis of the Jaw (ONJ) that developed in a 65-year-old Caucasian woman with osteopenia and other risk factors who was receiving low doses of oral bisphosphonate therapy (ibandronate, 150 mg monthly). Computed tomography (CT), panoramic radiographs (OPT), ⁹⁹ᵐTc-Sn-MDP scintigraphy, and magnetic resonance imaging (MRI) were performed to study the diseased area; cytological examination also revealed the presence of suppurative material around the area of exposed bone. A diagnosis of bisphosphonate-related osteonecrosis of the jaw complicated by osteomyelitis was made. The patient was prescribed a drug protocol consisting of metronidazole 250 mg 2 times daily, chlorhexidine mouthwashes 3 times daily and chewing exercises for two months. Ibandronate was stopped and replaced with strontium ranelate. The symptoms improved and the patient is still under close follow-up. Assessment of the benefits versus risks is particularly necessary in patients with several risk factors to ascertain their eligibility for treatment with antiresorptive drugs and when this is not possible to choose alternative medications.