ROLE OF TGF-β1 IN IMMUNE REGULATION AND AUTOIMMUNITY
I. Manolova1, E. Alexandrova2, M. Ivanova3 and R. Stoilov3
1Department of Health Care, Medical Faculty, Trakia University – Stara Zagora
2Department of General and Clinical Pathology, Medical Faculty, Trakia University – Stara Zagora
3Clinic of Rheumatology, UMHAT “Sv. Iv. Rilski” – Sofia

Summary. Transforming growth factor-β (TGF-β) belongs to a large family of multifunctional proteins, secreted by a variety of cell types that act as signal molecules in controlling a great number of biological processes. It is a highly pleiotropic cytokine with an important role in maintaining immune homeostasis. TGF-β has a bifunctional role in the immune system. It regulates both proinflammatory and immunosuppressive activities. The latter are realised via controlling activation, proliferation, differentiation and survival of all effector immune cells. Studies in lupus-prone mice and non-autoimmune “wild” type mice have clearly established the key role of this cytokine in the pathogenesis of systemic lupus. In lupus-prone mice, the decreased production of TGF-β and/or the inhibition of its actions via monoclonal antibodies results in immune disregulation and production of autoantibodies, which form immune complexes that elicit immune-mediated inflammation in the target organs. It has been shown that decreased serum levels of TGF-β in patients with systemic lupus are the most distinctive and constant abnormality in the cytokine levels of such patients. Lower serum levels of TGF-β are associated with susceptibility to SLE, as well as activity and organ damage in SLE. A few polymorphic sites in the human TGF-β gene have been identified. For three of the polymorphisms, C-509T, T-869C and G-915C, an association with serum levels of TGF-β has been established, which determines the TGF-β1 as one of the genetic factors contributing to the clinical outcome of SLE.

Key words: autoimmunity, immune regulation, SLE, TGF-β1

OSTEOPOROSIS AND BONE QUALITY – ACHIEVEMENTS, MODERN TECHNOLOGIES, NEWLY EMERGED QUESTIONS AND UNRESOLVED PROBLEMS
Zl. Kolarov1 and R. Nestorova2
1Clinic of Rheumatology, UMHAT “Sv. Iv. Rilski” – Sofia
2Center of Rheumatology “Sv. Irina” – Sofia

Summary. The main qualitative and quantitative characteristics of bone tissue and osteoporosis-related changes are outlined, the metabolic indices and factors are described and the basic achievements in diagnosing and treatment of osteoporosis (OP) are analysed: the structure and function of bone cells, which form and mineralise the bone matrix, bone-turnover mechanisms with the participation of basic pro- and anti-resorptive factors and pathogenetic mechanisms of OP (the RANK/RANKL/OPG system, Wnt and other polypeptides) are clarified, as well as the recent and modern diagnostic methods and guidelines for the treatment of the disease. Newly developed technologies include the use of biomarkers for diagnosis and monitoring of OP, introduction of the FRAX index for evaluation of the 10-year risk of fracturing, therapy with biological agents, such as Prolia (Denosumab). The new questions emerging from the knowledge accumulated to present, are “Are there any other factors and mechanisms of regulation of bone cell differentiation, maturation, activation and apoptosis? Is it possible to treat OP with biological agents, influencing on the Wnt signal path of osteoblasts? Is it possible to have a conceptually different strategy for treating OP? Is it possible to influence on osteoclastic and osteoblastic activity not only with biological, but also with chemical agents? Is there and what is the relation between osteoarthrosis and subchondral OP?” The unresolved problems include: clarification of the role and regulation of cover bone cells; clinically applicable methods for bone quality evaluation; elaboration of the FRAX index; development of prognostic markers for the course, rate of progression and outcome of OP; definition of therapeutic behaviour to patients with pre-menopausal reduction of bone mineral density; elucidation on clinical efficacy and safety of different biological agents for the treatment of OP, such as Odanacatib (MK-0822), glycogen-like peptide 2 (GLP-2), on synthesis of anabolic agents other than PTH, and on clinical significance and efficacy of ronacaleret, as well as on investigations and reimbursement policy in male OP.

Key words: osteoporosis, modern technologies, newly emerged questions, unresolved problems
ORIGINAL ARTICLES

COMPARISON BETWEEN THE BOHAN AND PETER AND TROYANOV CLASSIFICATION CRITERIA IN A GROUP OF PATIENTS WITH MYOSITIS IN THE BULGARIAN POPULATION
D. Kalinova1, E. Ivanova-Todorova2, D. Kurkchiev2, I. Altankova2 and R. Rashkov1
1Clinic of Rheumatology, Medical University – Sofia
2Laboratory of Clinical Immunology, Medical University – Sofia

Summary. Autoimmune myositis (AIM) is a syndrome characterized by chronic muscle inflammation, a result of the involvement of cellular and humoral immune responses and the presence of autoantibodies in the serum of some patients. Autoimmune myositis is diagnosed and classified by using the original Bohan and Peter diagnostic criteria and classification (1975). Presently, it is suggested that the original Bohan and Peter classification criteria should be re-evaluated, because in some cases, they may lead to misclassification of autoimmune myositis. The discovery of myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) has led to a serologic approach that is complementary to the Bohan and Peter classification. Y. Troyanov et al. created a novel classification based on the presence of overlapping clinical features and the test results of different serum autoantibodies (Abs). The aim of the study was to determine the prevalence of serum Abs in patients with autoimmune myositis, to analyse the clinical-serologic correlations between clinical features and different Abs and to classify autoimmune myositis by using the Bohan and Peter classification (1975) and this of Y. Troyanov (2005). Sera were collected from 70 patients with AIM which were classified using the Bohan and Peter classification and the Troyanov clinicoserologic classification. Sera were tested by the Immunoblot test and the enzyme linked immunosorbent assay (ELISA). Associations between clinical manifestations and autoantibodies were analysed by the Chi-square analysis (Fisher's Exact test), as p < 0.05.

One or more autoantibodies were detected in 70% of the patients with autoimmune myositis in this study. The most common Abs were: anti-Ro52 (41%), followed by anti-Ro60 (19%), anti-dsDNA (17%), anti-Jo-1 (16%) Abs. Other Abs were presented in 9% to 1% of the patients. The anti-U1RNP Abs was not detected in any of the patients with autoimmune myositis. We found statistically significant correlations between some clinical features and the detected serum autoantibodies. Polymyositis (PM) was diagnosed in 30% of the patients by using the Bohan and Peter classification; its frequency fell to 10% according to Troyanov classification. Myositis associated with other connective tissue diseases (overlap myositis, OM) was 24%, according to the Bohan and Peter classification, while its frequency was 70%, when using the Troyanov classification. We found that in a great number of the cases in this study, the autoimmune myositis develops within the course of an overlapping rheumatic disease. Overlapping clinical features and positive serum autoantibodies compose the basis of the Troyanov classification criteria, which, therefore, are supposed to be of diagnostic, therapeutic and prognostic value.

Key words: classification should, myositis

ASSOCIATION OF IL12P40 GENE PROMOTER POLYMORPHISM AND SERUM IL-12P40 WITH ANKYLOSING SPONDYLITIS: A PILOT STUDY
I. Manolova1, M. Ivanova2, R. Stoilov2 and S. Stanilova3
1Department of Health Care, Medical Faculty, Trakia University – Stara Zagora
2Clinic of Rheumatology, UMHAT “Sv. Iv. Rilski” – Sofia
3Department of Molecular Biology, Immunology and Medical Genetics, Medical Faculty, Trakia University – Stara Zagora

Summary. The aim of this pilot study was to investigate the effect of IL12Bpro polymorphism on genetic susceptibility to ankylosing spondylitis (AS) and the serum levels of IL-12p40 in the Bulgarian population. 54 patients with AS and 83 healthy controls were genotyped for this polymorphic marker by the allele-specific PCR assay (AS-PCR). Although there were no significant differences in the genotype and allele distribution of IL12Bpro polymorphism between the patients with AS and the healthy controls, a lower frequency of the homozygous genotype 1.1 (16.7%) and a higher frequency of the heterozygous genotype 1.2 (51.8%) were observed among the AS patients, compared with the healthy controls: 24.1% for the homozygous genotype 1.1 and 45.8% for the heterozygous genotype, respectively. The logistic regression analysis has shown that the carriers of IL12Bpro 1.1 are at a 1.5 times lower risk (OR-0.662; 95% CI 0.22÷2.01) of developing AS than the carriers of the homozygous genotype for the wild allele 2. Respectively, the risk of developing AS is 1.5 times higher for the individuals carrying the homozygous genotype 2.2 (OR-1.511; 95% CI 0.5 ÷ 4.64) and almost 2 times higher for these carrying the wild allele 2 in the genotype (1.2+2.2) (OR-1.89; 95% CI
0.72±5.01), compared to the individuals, carrying the homozygous genotype 1.1. The quantitative measurement of the serum IL-12p40 levels has shown that the homozygous genotype 1.1 is associated with elevated levels of IL-12p40, compared with the genotype 2.2 in both healthy subjects and patients with AS, but a statistically significant difference was found only for the patients with AS. In conclusion, our data support the hypothesis that genetic variations in the gene for IL12B, affecting the inducible production of IL-12p40, may contribute to the AS susceptibility in the Bulgarian population.

**Key words:** AS, IL-12p40, gene polymorphism, IL-12p40

---

**PHYSIOTHERAPY AND REHABILITATION TREATMENT OF SJÖGREN’S SYNDROME**

T. Troev, H. Milanova and M. Georgieva
Clinic of Physical and Rehabilitation Medicine, MMA – Sofia

**Summary.** Sjögren’s syndrome (SS) is a chronic inflammatory autoimmune disease characterized by involvement of the exocrine glands. The treatment of SS is based on symptomatic manifestation and prevention of complications. Pathogenetic therapy aims at suppressing the autoimmune process. The application of physical factors offers additional opportunities for maintaining the patient’s general condition, for preventing disability and managing individual symptoms. All means and methods of physical medicine for managing the variety of symptoms of this disease should be considered. A case of the clinical practice with a significantly positive response to physiotherapeutic treatment is presented.

**Key words:** Sjögren’s syndrome, physiotherapy, kinesitherapy, low-frequency pulse magnetic field

---

**CASE REPORTS**

**LUNG CANCER-ASSOCIATED PARANEOPLASTIC DERMATOMYOSITIS: DESCRIPTION OF TWO CLINICAL CASES**

D. Kalinova¹, D. Marinova², Ya. Slavova² and R. Rashkov¹
¹Clinic of Rheumatology, Medical University – Sofia
²Clinical Centre of Pulmonary Diseases, Medical University – Sofia

**Summary.** Dermatomyositis (DM) is a systemic connective tissue disease, characterized with proximal muscle weakness, typical skin rash, increased levels of muscle enzymes, electromyographic changes and characteristic histological data in muscle tissue biopsy. One of the typical features of DM is the connection with different neoplasms. The most common tumours, associated with paraneoplastic DM are these of the lungs, stomach, colon, ovaries and non-Hodgkin lymphoma. The aim of this article was to present two clinical cases of lung cancer-associated paraneoplastic dermatomyositis.

**Key words:** dermatomyositis, cancer, lung, paraneoplastic syndrome
CONTENTS

Treating rheumatoid arthritis to target: recommendations of an international task force .................................. 5

REVIEWS
I. Manolova, E. Alexandrova, M. Ivanova and R. Stoilov. Role of TGF-β1 in immune regulation and autoimmunity ................................................................................................................................. 17
Zl. Kolarov and R. Nestorova. Osteoporosis and bone quality – achievements, modern technologies, newly emerged questions and unresolved problems .................................................................................................................. 24

ORIGINAL ARTICLES
D. Kalinova, E. Ivanova-Todorova, D. Kurkchiev, I. Altankova and R. Rashkov. Comparison between the Bohan and Peter and Troyanov classification criteria in a group of patients with myositis in the bulgarian population ................................................................................................................................................. 31
I. Manolova, M. Ivanova, R. Stoilov and S. Stanilova. Association of IL12p40 gene promoter polymorphism and serum IL-12p40 with ankylosing spondylitis: a pilot study .................................................................................................................................................................................. 39
T. Troev, H. Milanova and M. Georgieva. Physiotherapy and rehabilitation treatment of Sjögren’s syndrome .................................................................................................................................................................................. 45

CASE REPORTS