Thiopyrano[2,3-d]Thiazoles as New Efficient Scaffolds in Medicinal Chemistry

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KEYWORDS: *4-thiazolidinones; [4+2]-cycloaddition; biological activity; thiopyrano[2,3-d] thiazoles.*

This review presents the up to date development of fused thiopyranothiazoles that comprise one of the thiazolidine derivatives classes. Thiazolidine and thiazolidinone-related compounds belong to the widely studied heterocycles from a medicinal chemistry perspective. From the chemical point of view, they are perfect heterodienes to undergo hetero-Diels□Alder reaction with a variety of dienophiles, yielding regio- and diastereoselectively thiopyranothiazole scaffolds. The annealing of thiazole and thiopyran cycles in condensed heterosystem is a precondition for the “centers conservative” creation of the ligand-target binding complex and can promote a potential selectivity to biotargets. The review covers possible therapeutic applications of thiopyrano[2,3-d]thiazoles, such as anti-inflammatory, antibacterial, anticancer as well as aniparasitic activities. Thus, thiopyrano[2,3-d]thiazoles may be used as powerful tools in the development of biologically active agents and drug-like molecules.

Autoantibodies Recognizing Secondary NEcrotic Cells Promote Neutrophilic Phagocytosis and Identify Patients With Systemic Lupus Erythematosus

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KEYWORDS: *autoantibodies; autoimmunity; connective tissue diseases; inflammation; secondary necrosis; systemic lupus erythematosus*

Deficient clearance of apoptotic cells reportedly contributes to the etiopathogenesis of the autoimmune disease systemic lupus erythematosus (SLE). Based on this knowledge, we developed a highly specific and sensitive test for the detection of SLE autoantibodies (AAb) utilizing secondary NEcrotic cell (SNEC)-derived material as a substrate. The goal of the present study was to validate the use of SNEC as an appropriate antigen for the diagnosis of SLE in large

cohort of patients. We confirmed the presence of apoptotically modified autoantigens on SNEC (dsDNA, high mobility group box 1 protein, apoptosis-associated chromatin modifications, e.g., histones H3-K27-me3; H2A/H4 AcK8,12,16; and H2B-AcK12). Anti-SNEC AAb were measured in the serum of 155 patients with SLE, 89 normal healthy donors (NHD), and 169 patients with other autoimmune connective tissue diseases employing SNEC-based indirect enzyme-linked immunosorbent assay (SNEC ELISA). We compared the test performance of SNEC ELISA with the routine diagnostic tests dsDNA Farr radioimmunoassay (RIA) and nucleosome-based ELISA (anti-dsDNA-NcX-ELISA). SNEC ELISA distinguished patients with SLE with a specificity of 98.9% and a sensitivity of 70.6% from NHD clearly surpassing RIA and anti-dsDNA-NcX-ELISA. In contrast to the other tests, SNEC ELISA significantly discriminated patients with SLE from patients with rheumatoid arthritis, primary anti-phospholipid syndrome, spondyloarthropathy, psoriatic arthritis, and systemic sclerosis. A positive test result in SNEC ELISA significantly correlated with serological variables and reflected the uptake of opsonized SNEC by neutrophils. This stresses the relevance of SNECs in the pathogenesis of SLE. We conclude that SNEC ELISA allows for the sensitive detection of pathologically relevant AAb, enabling its diagnostic usage. A positive SNEC test reflects the opsonization of cell remnants by AAb, the neutrophil recruitment to tissues, and the enhancement of local and systemic inflammatory responses.

Hepatitis c and human rights: comparison of legal experience of Ukraine and Georgia

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Wiadomosci Lekarskie 2018;71(2 pt 2):383-388

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KEYWORDS: *funding; health care; hepatitis C; human rights; human rights in patient care; public health*

A comparative legal research of human rights provision in Ukraine and Georgia, in the aspect of combating viral HCV, was conducted. Ukrainian advocacy experience and Georgian strategic litigation experience with regard to human rights and HCV was analyzed. Key international instruments, which lay the conceptual foundations as well as outline the measures, which are directed at human rights in patient care provision and fighting viral hepatitis, were elucidated. Attention was paid to the Global health sector strategy. Viral hepatitis, 2016 - 2021 [1], which, for the first time, defined a global strategy on fighting viral hepatitis, in particular HCV and envisaged the advocacy vectors. The frames of interaction of the human rights in patient care concept and public health, which consists in realization of certain human rights were elucidated and the necessity to embody the human rights in patient care concept into the state policy in the field of public health was determined. It was found out that a common international problem in combating HCV is a deficiency of financial resources, which are necessary for effective fighting the epidemics and guarantee equal access to treatment for every person. The international community outlined five most important spheres, which require investments and will catalyze the measures, which need to be taken in order to fight hepatitis. Analysis of the Ukrainian experience was focused on the issue of donated blood safety and successful advocacy campaigns, which were carried out in order to promote the adoption of programs on prophylactics, diagnostics and treatment of HCV both on national and regional levels. Examples of ensuring the rights of the marginalized groups during HCV treatment, in particular of the people who inject drugs, people living with HIV, participants of the antiterrorist operation were provided. Interesting and important is the experience of Georgia concerning human rights protection in the ECtHR, which has a legal effect for other countries which ratified the Convention for the Protection of Human Rights and Fundamental Freedoms, for instance for Ukraine, where the EctHR judgments are recognized as a source of law.

The increase of efficiency of treatment in patients with non-stable angina pectoris with use of nitrogen oxide donator wzrost skuteczności leczenia chorych z niestabilną dławicą piersiową przy pomocy donorów tlenku azotu

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Wiadomosci Lekarskie 2018;71(2 pt 2):299-302

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KEYWORDS: *arginine aspartate; arginine hydrochloride; endothelial dysfunction; lipid profile of the blood; non-stable angina pectoris*

OBJECTIVE:
Introction: One of the leading pathogenetic factors of CVD is a violation of the function of the endothelium of the vessels, which leads to endothelial dysfunction. The aim: Increasing the efficiency of treatment of patients with NSAP based on the study of the dynamics of clinical picture, blood parametres, CRP, indices of endothelium dependent vasodilatation of the brachial artery with the use of arginine hydrochloride.

PATIENTS AND METHODS:
Materials and methods: The 45 patients with non-stable angina pectoris (NSAP), who were in inpatient treatment in the cardiological department of the Clinical city hospital of emergency care in Lviv, were examined. The average age of patients was 56.8 ± 4.9 years. The patients were divided into 2 groups depending on the treatment. The first group (22 patients) took the common basic therapy, based on the standards of treatment of patients with NSAP. Another group (23 patients) received common standard (basic) treatment plus arginine hydrochloride, as a endothelial protector. The control group included 15 practically healthy individuals. The statistical analysis of the materials was carried out using the Statistica 8.0 program with the definition of the Student's t-criterion.

RESULTS:
Results: When complex treatment of patients with NSAP using arginine hydrochloride improves the clinical picture faster than with basic therapy. After treatment, statistically significant changes in the lipid profile of the blood were observed only in the group of patients who underwent complex therapy with arginine hydrochloride, the level of total cholesterol, LDL cholesterol and atherogenic index decreased, HDL cholesterol increased compared with those before treatment. After the complex treatment, the rate CRP decreased on 40,8% ($p < 0,05$) and on 29,7% ($p > 0,05$) in the basic therapy. After 30 days of treatment in the group of patients with intermittent use of arginine aspartate, a positive trend was observed in 74% of patients, considering that endothelial dysfunction was detected in 95.1% of patients before treatment.

CONCLUSION:
Conclusions: Comprehensive treatment of patients with NSAP using arginine hydrochloride is more effective than basic therapy, as evidenced by faster normalization of the clinical picture of the disease, laboratory blood parameters, and improvement of the function of the endothelium.

Classifications of temporomandibular disorders and patients' examination protocols - comparative analysis by the convenience of their daily use in clinical practice

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Wiadomosci Lekarskie 2018;71(3 pt 2):738-745

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KEYWORDS: *classification; diagnosis; temporomandibular disorders; temporomandibular joint; evaluation protocols*

OBJECTIVE:
Introduction:The problem of temporomandibular disorders (TMD) is relevant in today's world and is considered one of the most common pathologies causing nonodontogenic pain syndromes of maxillofacial region. The morbidity of temporomandibular disorders is 27 to 76% among patients who seek dental care. There is now a significant number of classifications of TMD, however, clinically convenient, morphologically and pathogenetically substantiated classification of temporomandibular joint's (TMJ) conditions has not yet been developed. Therefore, the patient's examination protocols differ substantially. The aim: To analyze and assess the quality of classifications and examination protocols for the patients with suspected TMD.

PATIENTS AND METHODS:
Materials and methods: A comparative analysis of 5 TMD classifications and 3 protocols for the examination of patients with suspected TMDs were performed.

RESULTS:
Review: A comparative analysis of following TMD classifications was conducted: American Academy of Orofacial Pain, Research Diagnostic Criteria for TMD, by B.W.Neville, D.D.Damm, C.M.Allen, J.E.Bouquot, by Christian Köneke, international classification of diseases ICD-10. The analysis of the following protocols for the examination of patients with suspected TMDs was conducted: M. Helkimo index, Hamburg protocol, M. Kleinrok protocol.

CONCLUSION:
Conclusions: Difficulties in interpreting diagnoses by dentists are caused by ambiguities in classifications, a considerable number of clinical entities and their construction principles. Organ principle of structure has proved to be the most convenient for clinical application. The evaluation protocols are cumbersome and duplicate each other. Owing to the lack of a common opinion about the origin and development of TMD, use of the evaluation protocols is based on the experience of dental practitioners.

Prognosis of ischaemic heart disease in patients with newly diagnosed dm type 2 by logistic regression

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KEYWORDS: *IHD; diabetes mellitus type 2; mathematical prediction*

OBJECTIVE: Introduction: Diabetes Mellitus (DM) type 2 is an important medical and social

problem all around the world. One of the most serious and widespread complications of DM type 2 is a damage to the cardiovascular system. The aim was to study the way of how to predict the IHD development in patients with the newly diagnosed DM type 2 by building a mathematical model with the help of statistical method, in particular, a logistic regression, which allows predicting the occurrence of IHD by the levels of proven biochemical and anthropometric indices. This method serves to determine the connection and enables predicting the value of one dependent variable based on the value of other (independent) variables.

PATIENTS AND METHODS:
Materials and methods: We have examined 40 patients with newly diagnosed DM type 2, who at the moment of the study did not have any cardio-vascular pathology. All patients were checked twice (at the moment of examination and 12 months after) for their age, body mass index (BMI), waist / hip ratio, levels of leptin, resistin, sP-selectin, interleukin (IL) -2, IL-6, tumour necrotic factor--α (TNF), glycated haemoglobin (HbA1c), insulin, C-peptide, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), non-esterified fatty acids (NEFA) .

RESULTS:
Results and conclusions: Mathematical prediction allowed finding out the patients with the high tendency to developing an adverse outcome. This information is of great practical importance from a medical, social and economic point of view since it allows the physician to prevent these diseases before their onset.

[Features of the course of irritable bowel syndrome in patients with excess body weight] [Article in Ukrainian]

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Wiadomosci Lekarskie 2018;71(3 pt 2):688-690

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KEYWORDS: *obesity; irritable bowel syndrome; the course; prevalence*

OBJECTIVE:
Introduction: Currently, the diagnosis of irritable bowel syndrome (IBS) is only based on clinical symptoms without clear interpretation and can be interpreted differently, complicating the diagnosis. Therefore, to study features of the prevalence and the course of IBS in patients with excessive body weight / obesity is of particular significance nowadays. The aim of the research is to evaluate the prevalence and the course of IBS in patients with obesity.

PATIENTS AND METHODS:
Materials and methods: Observation results for 120 obese persons who underwent in-patient treatment at various hospital departments in Western Ukraine have been analyzed to evaluate the prevalence of IBS. A thorough collection of complaints, anamnesis of the disease and lifestyle were conducted due to the survey; objective survey data were analyzed. The diagnosis of IBS was made according to Rome IV diagnostic criteria (2016).

RESULTS:
Results: Patients of all groups were gender and age-matched participants. The average body mass index was 33.9 ± 0.83 kg / m². Excessive body weight was revealed in 6 patients (5.0%). Degrees of obesity: (stage I) was diagnosed in 74 patients (61.6%), stage II was determined in

29 patients (24.2%), and stage III - in 11 patients (9,2%). The vast majority of patients (82.5%) complained of fullness or discomfort in the abdomen. Every second obese patient (52.5%) noted periodic bloating. Periodic nausea was recorded in every third patient with obesity (32.5%). Recurrent abdominal pain was determined in 62 (51.7%) of patients during the last 3 months: in females - 38 (61.3%), in males - 24 (38.7%) respectively. The prevalence of diarrhea with IBS compared to IBS with constipation was also noted: 36 (58.1%) versus 26 (41.9%) of cases.

CONCLUSION:
Conclusions: Irritable bowel syndrome was revealed in 51.7% of obese patients. Significant prevalence of combined pathology was noted in females. The prevalence of irritable bowel syndrome with diarrhea was determined.

[Epidemiological features of parasitary invasis in women of reproductive age with disorders of reproductive health] [Article in Ukrainian]

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Wiadomosci Lekarskie 2018;71(3 pt 2):674-677

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KEYWORDS: *ascaris; complicated obstetric anamnesis; infertility; pinworms*

OBJECTIVE:
The aim: The purpose of this study is to analyze the frequency and structure of parasitic lesion in women with reproductive health disorders.

PATIENTS AND METHODS:
Materials and methods: The immune-enzyme method tested immunoglobulins IgG to ascaris, lamblia, toxocara. Determination of the presence of pinworm eggs (sticky tape and perianal scrape method) and ascarid (methods of K.Cato, F.Fueleborna and E.S.Schulman).

RESULTS:
Results: In women with complicated obstetric anamnesis, parasitic invasions occurred in (52.3 ± 5.0)% (X^2 = 34.9, p <0.01; 95% CI = 42.5-62.1). Enterobiasis was detected in (12,0 ± 3,3)% of patients, acarida eggs in (29,3 ± 4,6)%, positive titers of IgG to ascaris - in (11.5 ± 3.2)%, IgG to lamblia in - 7.5%, IgG to toxocara 3.5%, the combined detection - in (11.5 ± 3.2)% of the examined group. In patients of the control group, parasitic invasions were detected in (13.1 ± 3.4)%. The prevalence of parasitic lesion in women with primary infertility (58.0 ± 4.9)% (OR = 8.9; 95% CI = 5.2-15.3; p <0.01), in planning pregnancy (25, 7 ± 4.4)% (OR = 2.3, 95% CI = 1.3-4.0). The most significant aggressive parasite in women with complicated obstetric anamnesis, reproductive loss and infertility is ascariasis (95% CI 6.1-38; p <0.001). In women with parasitic lesion revealed the dominance of pathology of the mammary glands, gastrointestinal tract, acne, pathology of the urinary system, thyroid gland.

CONCLUSION:
Conclusions: The obtained results make it possible to recommend parasite examination in women with infertility and complicated obstetric anamnesis.

Specific nature of changes in main immunohistochemical parameters of neoangiogenesis in patients with psoriasis

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Wiadomosci Lekarskie 2018;71(3 pt 2):658-662

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KEYWORDS: *neoangiogenesis; immunity; psoriasis*

OBJECTIVE:
Introduction: Psoriasis is a skin disease that is accompanied by systemic inflammation and affects about 1 to 5% of the population worldwide. Taking into consideration the data of scientific investigation, at present psoriasis is explained as genetically determined chronic multi factor polysystemic dermatosis. The aim of our research was to determine morphological peculiarities of skin lesions in patients with common psoriasis, investigation of the levels of expression of immunohistochemical markers of vascularization, depending on psoriasis form and severity of the course of pathological processes.

PATIENTS AND METHODS:
Materials and methods: 93 patients with psoriasis aged from 24 to 58 were observed. The control group consisted of 34 practically healthy people of the same age. Skin biopsy with histological evaluation of biopsy materials was performed for all patients.

RESULTS:
Results: Analysis of the condition of vascular bed at different levels of severity of psoriasis course showed that a number of cells at moderate degree of severity (22.65±5.87) was considerably higher than at mild psoriasis (10.09±3.22), and even more numerous than in CG (4.32±2.01). We detected a moderate correlation connection between increased intensity of VEGF expression and amplification of the severity of psoriasis course (r = +0.430) and between increased intensity of MMP-9 marker expression and amplification of the severity of psoriasis course (r = +0.532).

CONCLUSION:
Conclusions: The results of conducted clinical, morphological and immunohistochemical investigations enable to consider importance of neoangiogenesis processes in pathogenesis of this dermatosis and need in elaboration of therapeutic measures with direct influence on this aspect of pathogenesis.

[Effect of preventive treatment on cognitive performance in patients with multiple sclerosis] [Article in Ukrainian]

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Wiadomosci Lekarskie 2018;71(3 pt 2):648-652

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KEYWORDS: *cognitive impairment; glatiramer acetate; multiple sclerosis*

OBJECTIVE:
Introduction: cognitive, emotional and psychopathological changes play a significant role in the clinical picture of multiple sclerosis and influence the effectiveness of drug therapy, working

capacity, quality of life, and the process of rehabilitation of patients with multiple sclerosis. The aim: investigate the changes in cognitive function in patients with multiple sclerosis, such as information processing speed and working memory of patients before and after treatment with immunomodulating drug.

PATIENTS AND METHODS:
Materials and methods:33 patients examined reliably diagnosed with multiple sclerosis who were treated with preventive examinations and treatment from 2012 to 2016. For all patients with multiple sclerosis had clinical-neurological examination (neurological status using the EDSS scale) and the cognitive status was evaluated using the PASAT auditory test. Patient screening was performed before, during and after the therapy. Statistical analysis of the results was performed in the system Statistica 8.0. We used Student's t-test (t), Mann-Whitney test (Z). Person evaluated the correlation coefficients and Spearman (r, R), Wilcoxon criterion (T), Chi-square (X^2).

RESULTS:
Results: The age of patients with multiple sclerosis affects the growth and EDSS scale score decrease PASAT to treatment. Duration of illness affects the EDSS scale score and performance PASAT. Indicators PASAT not significantly decreased throughout the treatment.

CONCLUSION:
Conclusions: glatiramer acetate has a positive effect on cognitive function, information processing speed and working memory patients with multiple sclerosis, which is one of the important components of the therapeutic effect of this drug.

Clinical aspects of gastropathy development in patients with chronic obstructive pulmonary disease

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Wiadomosci Lekarskie 2018;71(3 pt 2):625-627

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KEYWORDS: *chronic obstructive pulmonary disease; gastropathy*

OBJECTIVE:
Introduction: Chronic obstructive pulmonary disease (COPD) is a one of the main reasons of disability and mortality in the world. The essential attention is dedicated to the combination of COPD and erosive/ulcer defects with the haemorrhage risk factor. The aim was to compare gastric acidity and mucoid secretion in patients with chronic obstructive pulmonary disease of gastropathy development.

PATIENTS AND METHODS:
Materials and methods: 94 patients with gastroduodenal erosive and ulcerous defects combined with COPD were examined. More than 50 % of patients (over 20 pack-years) had a long smoking history. Control group including 20 healthy voluntiers.

RESULTS:

Results: The mean age of patients was no difference in both groups. In regards to the severity of disease based on FEV1 30,9 % patients had mild obstruction and 69,1 % had moderate obstruction. Measurement of intragastric pH in patients with COPD and gastropathy showed the tendency of decreasing pH from 1,70±0,05 to 1,52±0,04 ($p<0,05$), while the pepsin level

increased from 0,56±0,05 mg/ml to 0,86±0,07 mg/ml (p<0,01). At the same time the level of NANA decreased in cases of ulcerative defects (p<0,05).

CONCLUSION:

Conclusions: The COPD combination with gastropathy leads to appearance of numerous erosions and ulcers in gastroduodenal zone that can be the reason of bleeding development. Long-term cigarette smoke exposure and high level of H.pylori infectoin are the main cause of gastroduodenal erosive and ulcerative defects in this comorbidities. The presence of erosions and ulcers is accompanied by a significant increase of an acid-peptic factor and a decrease of defense factor.

[Features of exchange of calcium saliva in patients with gastroesophageal reflux disease] [Article in Ukrainian]

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Wiadomosci Lekarskie 2018;71(3 pt 1):561-563

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KEYWORDS: *calcium; gastroesophageal reflux disease; parathormone; saliva*

OBJECTIVE:
Introduction: The pathogenesis of gastroesophageal reflux disease (GERD) is a topical issue of modern gastroenterology. There are a number of scientific papers on changes in the qualitative and quantitative composition of saliva, which triggers a cascade of biochemical reactions, the consequence of which is the destruction of the resistance of the mucous membrane of the esophagus. Calcium is a macro element that provides the normal functioning of cells. Parathormone also regulates the metabolism of calcium in the body. The aim: To study the level of calcium of saliva in patients with GERD before and after 6 months after treatment, to investigate the correlation with the concentration of parathyroid hormone.

PATIENTS AND METHODS:
Materials and methods: The samples of saliva of patients with GERD before and after treatment are analyzed. The content of calcium in saliva was determined by photometric method. To test the level of parathyroid hormone, the Intact-PTH ELISA test was used. The treatment was carried out with pantoprazole doses of 40 mg per day. Normal values of electrolyte levels in human saliva are set on 10 virtually healthy volunteers. Data processing was carried out using Microsoft Excel. Correlations were calculated using the Pearson method.

RESULTS:
Results: 25 samples of saliva have been analyzed: 15 patients with GERD and 10 healthy individuals. Concentration of parathormonone in plasma was consistent with normal values. The concentration of calcium saliva for practically healthy individuals was 2.48 ± 0.07 mmol / L, in patients with GERD before treatment 1.92 ± 0.16 mmol / L, after treatment 2.04 ± 0.07 mmol / L. The correlation coefficient between the level of calcium salivation in patients with GERD and the plasma parathyroid hormone concentration before treatment was 0.21, after treatment 0.73.

CONCLUSION:
Conclusions: The concentration of calcium is statistically significantly reduced in patients with GERD by 22.5% and increased by 10% after treatment. There is a high correlation between the concentration of calcium after treatment and the level of plasma parathyroid hormone.

Influence of risk factors on insulin resistance in patients with overweight and obesity

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Wiadomosci Lekarskie 2018;71(3 pt 1):558-560

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KEYWORDS: *coronary artery disease; atorvastatin; insulin resistance; obesity; type 2 diabetes mellitus*

OBJECTIVE:
Introduction: Obesity is a multifactorial, heterogenic disease, associated with an increased risk of morbidity and mortality due to cardiovascular diseases, diabetes, cancer, chronic liver and kidney diseases. Excessive body weight and obesity are serious medical and social problems, since their incidence is constantly increasing and has reached global epidemic proportions. The aim: Determining the influence of risk factors on insulin resistance level in patients with overweight and obesity.

PATIENTS AND METHODS:
Materials and methods: The study included 127 patients with overweight and obesity. Anthropometric measurement was performed for determination of the degree and type of obesity by WHO and IDF (2015) criteria. The levels of ALT, AST, uric acid, lipids, glucose, insulin, glycated hemoglobin in the blood were measured. HOMA-IR index was calculated and multiple regression method with inclusion of reliable signs was applied.

RESULTS:
Results: By multiple regression method, we identified four signs which, in combined action, affect HOMA-IR index: AST, triglycerides, insulin level and atorvastatin dose. Value of determination coefficient indicates that the level of insulin resistance in overweight and obese patients is by 37% explained by the factors included in regressive model. However, we did not investigate the influence of behavioral risk factors and burdened family history of type 2 diabetes mellitus, which significantly affect insulin resistance level.

CONCLUSION:
Conclusions: We assume that modification of lifestyle and individual approach to pharmacologic correction of dyslipidemia in overweight and obese patients help to avoid the development of insulin resistance, which is a predictor of type 2 diabetes mellitus.

[Clinical and laboratory features of cholelithiasis in patients with type 2 diabetes by gender] [Article in Ukrainian]

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Wiadomosci Lekarskie 2018;71(3 pt 1):534-536

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KEYWORDS: *cholelithiasis; diabetes mellitus; flow*

OBJECTIVE:
Introduction: Today, diabetes is considered a factor that provokes the development of bile duct disease. Cholelithiasis is associated with such risk factors as aging, high body mass index, female sex, genetic predisposition, alcohol abuse, high concentration of triglycerides and cholesterol, low density lipoprotein in blood plasma The aim of the work is to analyze the clinical and laboratory features of the pathology of the gall bladder in patients with type 2 diabetes, depending on the sex.

PATIENTS AND METHODS:
Materials and methods: Complex examination of 126 patients with cholelithiasis and type 2 diabetes mellitus was performed. Diagnosis of chronic cholecystitis was verified on the basis of clinical data, characteristic changes of the wall of the gallbladder according to the data of the echography. In the presence of concretions in the lumen of the gall bladder, bile marijuana was diagnosed. The verification of the diagnosis of diabetes mellitus was based on the determination of carbohydrate balance and glycosylated hemoglobin levels.

RESULTS:
Results: Among the examined patients there were 88 women (69,8%) and 38 men (30,2%). The average age of patients was 61,9 ± 0,9 years. The main complaints revealed in patients with combined pathology were: general weakness, daily fluctuations in blood pressure, abdominal distension, irritability, discomfort in the right hypochondrium, bitter taste in the mouth, heartburn, constipation, vomiting with bile. According to ultrasonography, hepatomegaly was noted in 88 (51,8%) patients. An increase in the size of the gall bladder was found in only 27 (15,9%) patients. The individual biochemical parameters of patients with combined pathology are analyzed.

CONCLUSION:
Conclusions: Established a significant prevalence of female subjects among patients with combined pathology. There were no reliable signs of clinical symptoms and changes in biochemical parameters, depending on sex. A reliable method for diagnosing the changes in the gall bladder in both women and men is ultrasound.

The changes of some bioregulators and gas transmitters in patients with hypertonic disease under the influence of physical loading

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Wiadomosci Lekarskie 2018;71(3 pt 1):513-517

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KEYWORDS: *L-arginine; arterial hypertension; cortisol; hydrogen sulphide; nitric oxide; nitrite-anion; physical loading*

OBJECTIVE:
Introduction: Nowadays arterial hypertension is supposed to be a pathogenetic factor of numerous cardiovascular diseases (CVD) and 18% cases of the preterm death. Due to the data of the American Heart Association in 77% of patients, who had stroke, the arterial pressure overexceeded 140/90 mm Hg. In Ukraine, according to the epidemiologic study more than 1/3 of the population have increased arterial pressure. One of the extremely important aspects of struggle with CVD is diagnosis and prevention of hypertonic disease. The prevalence of arterial hypertension worldwide increases averagely for 3-4% per year that corresponds with the level of a true epidemy. The aim: Was to evaluate nitrosooxidative status, content of hydrogen sulphide and cortisol in blood serum of patients with a II stage arterial hypertension under the conditions of physical loading.

PATIENTS AND METHODS:
Materials and methods: 30 patients with II stage arterial hypertension were examined. Examined patients were exposed to two-stage physical loading using veloergometer with the intensity relevant to 50 and 75 % of the proper maximal oxygen uptake (MOU) of the body.

RESULTS:
Results: In blood serum of patients before and after physical loading the content of TBA-active products, hydrogen sulphide, L-arginine, nitric anion, sum of nitrite-nitrate, cortisol, activity of SOD, catalase and arginase were determined. Significant increase of L-arginine and hydrogen sulphide on the background of the decrease of nitrite-anion and sum of nitrite-nitrate was noted. It may be suggested that in individuals with hypertonic disease under the influence of physical loading synthesis of NO decreases and vasodilatation and vasoprotection occur by means of increase of the hydrogen sulphide level.

CONCLUSION:
Conclusions: The indices of L-arginine, nitrite-anion and H2S in blood serum after physical loading reflect the changes in the system of vasodilatation in patients with arterial hypertension. The parameters of gaseous messengers NO and H2S are the fastest to react to veloergometry on the background of insignificant changes of the level of cortisol, activity of arginase, SOD and catalase in patients with II stage hypertonic disease. Increase of the level of L-arginine and hydrogen sulphide as well as decrease of nitrite-anion level may be considered to be markers of evaluation of immediate changes in patients with arterial hypertension after physical loading.

Evaluation of the peritoneal surface disease severity score (PSDSS) in ovarian cancer patients undergoing cytoreductive surgery and HIPEC: Two pathogenetic types based study

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KEYWORDS: *cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; ovarian cancer; peritoneal carcinomatosis; peritoneal surface disease severity score*

BACKGROUND AND OBJECTIVES:
Clinical experience suggests that cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) play an important role in the management of ovarian cancer. In order to improve patient selection, the peritoneal surface disease severity score (PSDSS) was previously introduced for use in colorectal cancer patients. However, almost no data exist regarding the utility of the PSDSS index in ovarian cancer patients.

METHODS:
A retrospective study of the effectiveness of CRS and HIPEC was carried out in 59 patients with ovarian cancer. The PSDSS was based on three criteria: symptoms, extent of peritoneal dissemination, and primary tumor structure as assessed by histology and biomarker expression.

RESULTS:
The overall survival time for patients with ovarian cancer in PSDSS Stage I was 48 ± 25.3 months. For PSDSS Stage II, the survival time was 26.5 ± 4.7 months. For PSDSS Stage III, it was 15.5 ± 4

months, and for PSDSS Stage IV, it was 6 ± 4.3 months. A multivariate analysis showed that the PSDSS stage was the only independent survival predictor.

CONCLUSIONS:

These data demonstrate that a PSDSS based on two pathogenetic types may be useful for predicting survival outcomes in ovarian cancer patients treated with CRS/HIPEC.

Low amounts of bisecting glycans characterize cerebrospinal fluid-borne IgG

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KEYWORDS: *Bisecting; Cerebrospinal fluid; Glycosylation; Immunoglobulin G; Serum; Sialylation*

Immunoglobulin G (IgG) harbors a conserved N-glycosylation site which is important for its effector functions. Changes in glycosylation of IgG occur in many autoimmune diseases but also in physiological conditions. Therefore, the glycosylation pattern of serum IgG is well characterized. However, limited data is available on the glycosylation pattern of IgG in cerebrospinal fluid (CSF) compared to serum. Here, we report significantly reduced levels of bisected glycans in CSF IgG. Galactosylation and sialylation of IgG4 also differed significantly. Therefore, we propose a common mechanism mediating glycosylation changes of IgG at the transition from serum to CSF in steady state conditions.

Transcription regulatory factor expression in T-helper cell differentiation pathway in eutopic endometrial tissue samples of women with endometriosis associated with infertility

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KEYWORDS: *Foxp3; GATA3; T-bet; T-helper cells; endometriosis; infertility*

Endometriosis is a disease of epidemiological gravity of unknown primary reason. A complex of constitutional factors including the immune system has been considered as its background. The aim of the study was to identify Th1 and Th2 cells as well as the T-regulatory subset in the endometrium of women with endometriosis associated with infertility upon transcription

factors expression. Expression of T-bet, GATA3, and Foxp3 genes was examined using a method of polymerase chain reaction (PCR) in the eutopic endometrial samples of 20 women with endometriosis associated with infertility and 20 women with infertility of tubal origin. An increase in mRNA expression for T-bet and GATA3 with prevailing mRNA level for T-bet and a decrease in Foxp3 expression were observed. In conclusion, the revealed changes in expression of transcription factors may indicate the imbalance between T-helper cells of the Th1 and Th2 type and elimination of regulatory function of T-cells, which can be one of the causes of endometriosis predisposing to the development of infertility associated with this disease.

Glycosylation of random IgG distinguishes seropositive and seronegative rheumatoid arthritis

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KEYWORDS: *ELISA; Immunoglobulin; glycosylation; lectins; rheumatoid arthritis*

The N-glycosylation of human immunoglobulins, especially IgGs, plays a critical role in determining affinity of IgGs towards their effector (pro- and anti-inflammatory) receptors. However, it is still not clear whether altered glycosylation is involved in only antibody-dependent disorders like seropositive rheumatoid arthritis (RA) or also in pathologies with similar clinical manifestations, but no specific autoantibodies like seronegative RA. The clarification of that uncertainty was the aim of the current study. Another study aim was the detection of specific glycan forms responsible for altered exposure of native glycoepitopes. We studied sera from seropositive RA (n = 15) and seronegative RA (n = 12) patients for exposure of glycans in native IgG molecules, followed by determination of specific glycans by capillary electrophoresis with laser-induced fluorescent detection (CE-LIF). Aged-matched groups of normal healthy donors (NHD) and samples of intravenous immunoglobulin IgG preparations (IVIG) served as controls. There was significantly stronger binding of Lens culinaris agglutinin (LCA) and Aleuria aurantia lectin (AAL) lectins towards IgG from seropositive RA compared to seronegative RA or NHD. CE-LIF analysis revealed statistically significant increases in bisecting glycans FA2BG2 (p = .006) and FABG2S1 (p = .005) seropositive RA, accompanied by decrease of bisecting monogalactosylated glycan FA2(6)G1 (p = .074) and non-bisecting monosialylated glycan FA2(3)G1S1 (p = .055). The results suggest that seropositive RA is distinct from seronegative RA in terms of IgG glycan moieties, attributable to specific immunoglobulin molecules present in seropositive disease. These glycans were determined to be bisecting GlcNAc-bearing forms FA2BG2 and FABG2S1, and their appearance increased the availability of LCA and AAL lectin-binding sites in native IgG glycoepitopes.

Indscators of blood lipid profile, acute phase reactions and uric acid in patients with arterial hypertension combined with connective tissue dysplasia

Wiadomosci Lekarskie 2018;71(2 pt 1):356-360

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KEYWORDS: *arterial hypertension; connective tissue dysplasia; methods of examination*

OBJECTIVE:
Introduction:Changes in the cardiovascular system can be divided into 2 groups due to the connective tissue dysplasia (CTD) and changes in the circulatory system, caused by pathological processes that arose on the basis of the connective structures failure. One of the risk factors of arterial hypertension (AH) remaining insufficiently studied is collagen pathology - nondifferentiated connective tissue dysplasia (NCTD). The presence of connective tissue in all organs and systems, the common origin of smooth muscles, blood and lymph from mesenchyma leads to dysplastic changes in any organ and system. NCTD is morphologically characterized by changes in collagen, elastic fibrils, glycoproteins, proteoglycans and fibroblasts, which are based on hereditary mutations of genes encoding the synthesis and spatial organization of collagen, structural proteins and protein-hydrocarbon complexes, enzymes and cofactors to them. The aim was to study external and internal phenotypic signs of CTD, indicators of blood lipid spectrum, acute phase reactions and uric acid in patients with hypertension associated with CTD.

PATIENTS AND METHODS:
Materials and methods: The study implied examination of 52 patients (19 women and 33 men) with AH of the 2-nd stage from 1-st to 3-rd degrees and CTD manifestations, which were on inpatient treatment in the cardiology department of the Lviv City Communal Clinical Emergency Hospital. The average age of patients was 61.14 ± 2.58 years. Patients were divided into 3 groups depending on the degree of hypertension. The first group (n = 5) included patients with AH of the 1-st degree, the second (n = 28) - with AH of the 2-nd degree, the third (n = 19) - with AH of the 3-rd degree. The control group consisted of 25 practically healthy persons. Patients underwent checkup, palpation, percussion, auscultation, laboratory examinations (blood lipid spectrum, CRP, serumukoid content and uric acid), instrumental studies (ECG, echocardiography, DBPM, ultrasound examination of the internal organs and lower limbs vessels, ultrasound examination of the sleep and vertebral arteries, X-ray examination of the bone and articular system), consultation of an ophthalmologist, a neuropathologist, a traumatologist and a dentist.

RESULTS:
Results: In a comparative analysis between the control group and patients with stage II hypertension of 1-3 grades, in 84.6% cases external and internal CTD signs were observed, and in 15.4% cases there were no manifestations. In applying the diagnostic criteria for assessing signs of CTD and stigmata of dysebryogenesis, different numbers of points were defined depending on the severity of the AH. The highest quantity of points was found in patients of the 3-rd group (30,8 ± 0,81), which indicates a significant presence of external signs of CTD in comparison with the 1-st and 2-nd groups of patients (25.2 ± 1.38 and 26.7 ± 0.72), respectively.

CONCLUSION:
Conclusions: The external and internal phenotypic signs of CTD of medium and severe expressiveness degree were revealed, however, most commonly they were observed in patients with hypertension of grade 3. The presence of positive correlations between the levels of TC, HDL-C, LDL-C, AC, UA and TG indicates its direct role in the pathogenesis of hypertension, and the combination with CTD complicates the underlined pathology. Screening of the studied indicators can improve the prognosis of the course and development of cardiovascular complications.

ASIT therapy: advantages and adverse effects. own results and literature data

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Wiadomosci Lekarskie 2018;71(2 pt 1):341-345

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KEYWORDS: *allergen-specific immunotherapy; bronchial asthma; systemic reactions; local reactions*

OBJECTIVE:
Introduction: Allergy is an important medical, social and economic problem nowadays, as it causes disability and patients' quality of life decreases. According to the update data all the existing therapeutic options haven't been used in huge majority of patients. Allergen-specific immunotherapy (ASIT) underuse in particular. One of the reasons for the low frequency of this treatment method using is the fear of systemic and local allergic. The aim of the study was to find out the incidence and severity of adverse reactions in patients receiving subcutaneous and sublingual ASIT.

PATIENTS AND METHODS:
Materials and methods: In conducted research we compared peculiarities of adverse reactions using sublingual and subcutaneous ASIT methods. Criteria for inclusion in the research were age from 18 to 50 years, diagnosed intermittent or persistent BA. The investigation involved 51 patients with combined basic drug therapy and ASIT, which was performed with injected allergens for 38 patients and sublingual allergens - for 13 individuals.

RESULTS:
Results: Local reactions were recorded in five patients (13.16%), who received injected ASIT. In four patients (10.52%), dry rales were observed for a short period after injection of the allergen. Local side effect was observed in one patient (7.69%) during sublingual ASIT.

CONCLUSION:
Conclusions: Adverse reactions, that occur during ASIT, do not pose a threat to patients' lives. However, the therapeutic effect after the year of treatment was significantly better than in patients who used medications only. Modern drugs are safe and, if all the rules are followed, the risk of adverse effects is very low.

Modern specific features and therapy of psoriasis and arthropathic psoriasis courses

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Wiadomosci Lekarskie 2018;71(2 pt 1):322-325

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KEYWORDS: *cytokines; diagnostic; herpesvirus of the 1st and 2nd type; immunity; psoriatic arthritis*

OBJECTIVE:
Introduction:Psoriasis affects about 2% of population. In 30-40% of occurrences arthropathic psoriasis (AP) is diagnosed and it leads to 11-19% of disability cases development. Recent studies have shown that psoriasis is often synergistically combined with herpesvirus of the 1st and 2nd type, which, according to many scientists, determines the severity, frequency of recurrences, and the course of this dermatosis. Recently, new biomarkers, i.e. a system of small ribonucleic microRNA acids, have been described. Their role and interconnection in respect of regulation of congenital and acquired immunity activity in patients with herpesvirus infection at psoriasis has been defined. The article analyses features of anamnesis, clinical, instrumental and laboratory tests related to arthropathic psoriasis, considers the relationship of probable mechanisms of disease aggravation and progression with the definition of a treatment method influencing the dynamics of a disease course. The aim of our work was to improve the diagnostics of AP patients

taking into account some indicators of the immune-endocrine system and features of the disease course to specify their role in AP pathogenesis and to develop the system of integrated therapy of patients whose locomotor system is affected due to psoriasis.

PATIENTS AND METHODS:
Materials and methods: A total of 178 AP patients have been systematically examined. We have examined AP patients with varying severity of process development, generalization and the severity of skin and osseous-articular apparatus damage, the presence of associated pathology. Additional instrumental studies, determination of biochemical, serological parameters and an assessment of stress-induced immune-endocrine system have been conducted in AP patients. The content of trigger cytokines (IL-1β, IL-8, IL-17, IL-22) in blood serum, stress hormones (ACTH, cortisol), cellular and humoral immunity condition (CD3 +, CD4 +, CD8 +, CD16 +, CD22 +, IgM and IgG levels) have been studied.

RESULTS:
Results: The clinical course and characteristic features of AP instrumental tests are extremely versatile as well as the depth of their present study is insufficient. Regardless of the disease duration period, we have detected in blood serum of AP patients probable changes in concentrations of stress-response mediators (decreased parameters of cellular immunity (CD3+, CD4+, CD8+ of T-lymphocytes, CD22+ fraction of B-lymphocytes and compensatory increased CD16+ of T-cells, cytokines - IL-1β, IL-8, IL- 17, IL-22, stress hormones - cortisol, immunoglobulins IgM, IgG, and CIC), which indicate tension of their stress-induced mechanisms even despite occasional clinical stabilization of skin and articular process. We have offered and tested regiments to treat AP patients, which involve differential application within the integrated therapy of nonsteroidal anti-inflammatory medications (Arcoxia 30-60 mg 1 time daily / Naklofen Duo 75 mg daily), disease-modifying medications (Sulfasalazine EH from 500 mg to 2 g daily / Methotrexate 7.5-10 mg/week), lyophilised dialysate of leukocytes.

CONCLUSION:
Conclusions: The analysis of specific features of the AP clinical course and data of integrated studies allows identifying the probability of manifestation or persistence of the pathological psoriatic articular process. The improvement of AP patients diagnostics taking into account some indicators of the immune-endocrine system and specifics of the disease course contributed to the improved therapy and mended quality of life of patients.

Values of the systemic immunity in patients suffering from acne with different clinical course

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Wiadomosci Lekarskie 2018;71(2 pt 1):297-300

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KEYWORDS: *acne; clinical course; systemic immunity*

OBJECTIVE:
Introduction: Acne is chronic recurrent dermatosis, one of the essential skin inflammation in the structure of dermatological pathology, especially in young people of working age, often caused by persistent cicatricial changes in the skin, and affecting negatively the psychoemotional state of patients, their quality of life and working capacity. It has been established by today that the pathogenesis acne is complex and multifactorial, and the changes of immune reactivity of the organism play an important role in its clinical course development. The aim of the article is to determine and analyze the values of the systemic immunity in patients suffering from acne with different clinical course.

PATIENTS AND METHODS:
Materials and methods: 128 patients with acne aged from 18 to 35, among which 74 women (57,8 %) and 54 men (42,2 %) were observed. According to the clinical criteria, 26 patients (20,31%) were diagnosed with comedonal form of acne, 40 patients (31.25%) had papules, 10 people (7.81%) -papular-pustular acne, 29 of the observed (22.65%) had pustules, 9 patients (7.03%) suffered from acne conglobata, and 14 patients (10.94%) were diagnosed with post-acne. The control group consisted of 34 practically healthy people (donors) of the same age.

RESULTS:
Results: Consequently, most of the patients with acne had varying degrees of changes in rates of systemic immunity - the likely reduction in relative and absolute number of total lymphocytes, T-lymphocytes and their subpopulations against the growing number of B lymphocytes and the level of IgM and IgG, which generally indicates the formation in these patients secondary immunodeficiency state of T-link intensified by activation of humoral immunity in response to the development of skin inflammation. The most significant changes in rates of systemic immunity with the depletion of T-cell immunity were found in patients with papular-pustular and pustular acne, and still more significant - in patients with acne conglobate, which justifies differentiated treatment by immunomotropic drugs for these patients.

CONCLUSION:
Conclusion: In patients with acne, changes in systemic immunity indexes that indicate the formation of secondary immunodeficiency state T-cell link, amid an adequate humoral immunity have been found. Relationship between the causes of changes of systemic immunity has been established.

Correlations between lipid metabolism indices in patients with hypertension and hypothyroidism

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Wiadomosci Lekarskie 2018;71(2 pt 1):281-284

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KEYWORDS: *cholesterol; hypertension; hypothyroidism; lipid metabolism; obesity*

OBJECTIVE:
Introduction: Hypertension is a major reason behind morbidity, disability and mortality. Elevated blood pressure is a huge risk factor for cardio-vascular diseases. Almost 90% of hypertension patients have internal comorbidities, in particular hypothyroidism. For now, however, the specificities of the clinical course of hypertension in hypothyroid patients are understudied and the data on lipid metabolism in patients with primary hypothyroidism and hypertension are inconclusive. The study aims at establishing the effect of the lipid metabolism indices in hypertensive patients with hypothyroidism using correlation analysis.

PATIENTS AND METHODS:
Materials and methods: The total of 198 patients with stage 1 and stage 2 hypertension were examined. The patients were divided into two groups based on whether they have hypothyroidism or normal thyroid function.

RESULTS:
Results: The study revealed that in patients with hypertension and hypothyroidism, hypercholesterolemia is associated with hypocoagulation, hyperkalaemia, decreased bilirubin levels and adrenal cortex

activation. Hyperbetalipoproteinemia is linked to the reduced thyroid gland, activation of the lymphocytic component of the inflammatory response, predisposition to hypocoagulation, probable unfavourable acute stress response and development of the eccentric hypertrophy of the left ventricle myocardium. Elevated triglycerides have an effect on the progression of arterial hypertension and are associated with diastolic dysfunction of the left ventricle and hepatic dysfunction.

CONCLUSION:
Conclusion: The combination of hypothyroidism and hypertension is an unfavourable factor in the development and progression of dyslipidaemia, which, in its turn, can cause blood coagulation disorders, adrenal glands activation, cardiac, renal and hepatic damage, and negative adaptive responses.

Oligomannose-Rich Membranes of Dying Intestinal Epithelial Cells Promote Host Colonization by Adherent-Invasive E. coli

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KEYWORDS: *CEACAM6; Crohn's disease; adherent-invasive E. coli; apoptotic cell-derived membranous vesicles; oligomannose glycans*

A novel mechanism is revealed by which clinical isolates of adherent-invasive Escherichia coli (AIEC) penetrate into the epithelial cell layer, replicate, and establish biofilms in Crohn's disease. AIEC uses the FimH fimbrial adhesin to bind to oligomannose glycans on the surface of host cells. Oligomannose glycans exposed on early apoptotic cells are the preferred binding targets of AIEC, so apoptotic cells serve as potential entry points for bacteria into the epithelial cell layer. Thereafter, the bacteria propagate laterally in the epithelial intercellular spaces. We demonstrate oligomannosylation at two distinct sites of a glycoprotein receptor for AIEC, carcinoembryonic antigen related cell adhesion molecule 6 (CEACAM6 or CD66c), on human intestinal epithelia. After bacterial binding, FimH interacts with CEACAM6, which then clusters. The presence of the highest-affinity epitope for FimH, oligomannose-5, on CEACAM6 is demonstrated using LC-MS/MS. As mannose-dependent infections are abundant, this mechanism might also be used by other adherent-invasive pathogens.

Budesonide Suppositories Are Effective and Safe for Treating Acute Ulcerative Proctitis

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KEYWORDS: *Inflammatory Bowel Disease; Mesalazine; RCT; Ulcerative Colitis*

BACKGROUND & AIMS:
Although proctitis is the most limited form of ulcerative colitis, it causes unpleasant symptoms. Topical mesalamine, the standard treatment, is not always effective. We conducted a randomized phase 2 trial to determine the efficacy and safety of 2 doses of a budesonide suppository vs mesalamine suppositories vs combined budesonide and mesalamine suppositories for proctitis.

METHODS:
We performed a prospective, double-blind, double-dummy, multicenter trial in 337 patients with active proctitis to compare the efficacies of 4 different suppository treatments. Patients were randomly assigned to groups given 2 mg budesonide suppositories (2 mg BUS; n = 89 patients), 4 mg BUS (n = 79), 1 g mesalamine suppositories (1 g MES; n = 81), or the combination of 2 mg BUS and 1 g MES (n = 88). The study was performed from November 2013 through July 2015 at 36 study sites in Europe and Russia. The primary end point was the time to resolution of clinical symptoms, defined as the first of 3 consecutive days with a score of 0 for rectal bleeding and stool frequency.

RESULTS:
The mean time to resolution of symptoms in the 4 mg BUS (29.8 days) and combination of 2 mg BUS and 1 g MES (29.3 days) groups resembled that of the standard 1 g MES treatment (29.2 days), but was significantly longer in the 2 mg BUS group (35.5 days). Furthermore, proportions of patients with deep, clinical, and endoscopic remission, as well as mucosal healing, were similar among the 1 g MES, 4 mg BUS, and combination therapy groups, but significantly lower in the group that received 2 mg BUS. No safety signals were observed, and the patients' treatment acceptance was high (67%-85% of patients).

CONCLUSIONS:
In a multicenter randomized trial, we found that the efficacy and safety of 4 mg BUS in treatment of active proctitis did not differ significantly from those of 1 g MES. Budesonide suppositories offer an alternative therapy to mesalamine for topical treatment of proctitis. Clinicaltrialsregister.eu no: 2012-003362-41.

Monodisperse magnetic poly(glycidyl methacrylate) microspheres for isolation of autoantibodies with affinity for the 46 kDa form of unconventional Myo1C present in autoimmune patients

Myronovskij S[1], Nehrych T[2], Negrych N[2], Shorobura M[2], Antonyuk V[1], Stoika R[1], Kit Y[1] [et al.]

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KEYWORDS: *Affinity chromatography; Autoantibody; Autoimmune disease marker; Functionalization; Immunoglobulin M; Magnetic microspheres; Multiple sclerosis; p46/Myo1C protein*

Monodisperse nonmagnetic macroporous poly(glycidyl methacrylate) (PGMA) microspheres were synthesized by multistep swelling polymerization of glycidyl methacrylate, ethylene dimethacrylate and 2-[(methoxycarbonyl)methoxy]ethyl methacrylate (MCMEMA). This was followed (a) by ammonolysis to modify the microspheres with amino groups, and (b) by incorporation of iron oxide (γ-Fe2O3) into the pores to render the particles magnetic. The resulting porous and magnetic microspheres were characterized by scanning and transmission electron microscopy (SEM and TEM), atomic absorption and Fourier transform infrared spectroscopy (AAS and FTIR), elemental analysis, vibrating magnetometry, mercury porosimetry and Brunauer-Emmett-Teller adsorption/desorption isotherms. The microspheres are meso- and macroporous, typically 5 μm in diameter, contain 0.9 mM · g-1 of amino groups and 14 wt.% of iron according to elemental analysis and AAS, respectively. The particles were conjugated to p46/Myo1C protein, a potential biomarker of autoimmune diseases, to isolate specific autoantibodies in the blood of patients suffering from multiple sclerosis (MS). The p46/Myo1C loaded microspheres are shown to enable the preconcentration of minute quantities of specific immunoglobulins prior to their quantification via SDS-PAGE. The immunoglobulin M (IgM) with affinity to Myo1C was detected in MS patients. Graphical abstract Monodisperse magnetic poly(glycidyl methacrylate) microspheres were synthesized, conjugated with 46 kDa form of unconventional Myo1C protein (p46/Myo1C) via carbodiimide (DIC) chemistry, and specific autoantibodies isolated from blood of multiple sclerosis (MS) patients; immunoglobulin M (IgM) level increased in MS patients.

The case of septical form of listeriosis with numerous abscesses of liver

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Przeglad Epidemiologiczny 2018;72(1):53-57

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KEYWORDS: *listeriosis; septic form; liver abscesses*

The article describes the case of a septic form of a listeriosis with multiple abscesses of the liver. Given clinical example illustrates the severe course of listeriosis with the development of septicemia and lesions of internal organs. Despite the adequate etiotropic and pathogenetic treatment for listeriosis meningoencephalitis, there was a lethal outcome of the disease. The polymorphism of clinical manifestations and the range of course variants often make it difficult to diagnose listeriosis, which in turn requires a more thorough examination of patients as well as carrying out all relevant bacteriological and serological tests.

Indicators of phagocytosis in women with acne during comprehensive treatment that included immunotherapy and probiotics

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Wiadomosci Lekarskie 2018;71(1 pt 2):144-147

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KEYWORDS: *acne; autohemotherapy; phagocytosis; probiotic; low-dose birth control pills*

OBJECTIVE:
Introduction: Acne is one of the most common dermatological diseases. It may have a chronic course, leaving permanent marks, and in last years has been tending to have more and more severe clinical course with widespread skin lesions. According to recent studies, the development of acne is due to the combined effect of endogenous and exogenous factors, among which endocrine diseases (quite a significant aspect), disorders of metabolic processes, reduced systemic immunity and phagocytic ability of mononuclear phagocytes and granulocytes at various stages of phagocytosis of pyogenic cocci, which contributes to more severe clinical course, and frequent relapse of this diseases. It was also proved that the intestinal microbiota plays an important role in the formation of homeostasis and immune response. The aim of the studyis to determine the evolution of phagocytosis indices in patients with acne under differentcomprehensive treatments, using oral antibiotics, immunotherapy, probiotics and low-dose birth control pills.

PATIENTS AND METHODS:
Materials and methods: We observed 93 women with acne aged from 18 to 25 years old. In 19 (20,43 %) patients mild acne was diagnosed, in 41 (44.09%) - moderate acne, in 33 (35.48 %) persons - severe acne, 54 (58,06%) persons suffered from acne up to 1 year, 39 (41,93%) - from 1 to 3 years. To assess the state of phagocytosis in patients with acne vulgaris, we determined phagocytic activity (PA) and phagocytic index (PI) of polymorphonuclear leukocytes, nitro blue tetrazolium recovery test (NBT test spontaneous) and NBT-test pyrogenal stimulated by the recognized methods.

RESULTS:
Results: Analysis of the studied parameters of phagocytosis at the end of treatment showed a significant increase in patients of the core group who were administered a comprehensive treatment which included oral antibiotic, probiotic, low-dose birth control pills and autohemotherapy, as compared with the patients of other groups under study.

CONCLUSION:
Conclusions: Using combined therapy for women with acne occurring against the backdrop of a sluggish process of phagocytosis and concomittant intestinal dysbiosis leads to normalization of the leading indices of phagocytosis (PI, PA, NBT tests both spontaneous and stimulated), and enchances their phagocytic activity both during capture and formation of bactericidal activity and in the final stages of phagocytosis justifying the feasibility of a combined use of antibiotics, probiotic, low-dose birth control pills and autohemotherapy in the treatment of acne.

The influence of the manual thrombus aspiration on the short term effectiveness of the percutaneous revascularization in patients with coronary artery thrombosis

Besh DI[1], Besh OM[2], Rafaluk OI[3], Kapustynskyy OO[2] [et al.]

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KEYWORDS: *acute coronary syndrome with ST segment elevation; manual thrombus aspiration; percutaneous coronary intervention; visible coronary thrombosis*

OBJECTIVE:
Introduction: Percutaneous coronary intervention (PCI) is one of the main issues in treatment of acute coronary syndrome with ST segment elevation (STEMI). The manual thrombus aspiration

was believed to improve the results of intervention especially in patients with coronary thrombosis. The aim: To explore the influence of manual thrombus aspiration on the short-termed prognosis after PCI in patients with STEMI and visible coronary thrombosis.

PATIENTS AND METHODS:
Materials and methods: 50 patients with STEMI and visible coronary thrombosis were included for exploration. Main group (MG) consists of 25 patients to whom manual thrombus aspiration was performed and comparison group (CG) of 25 patients whom were performed just conventional PCI.

RESULTS:
Results: In the 84% patients of the MG and in 72% CG was gained TIMI 3 flow grade after the procedure (p=0.5). MBG 3 was reached in similar number of patients from both groups (p=0.37). Comparison of the ejection fraction of the LV and its' wall motion score brought the same results. The trend to better indexes of glomerular filtration rate was observed in the patients of the MG (p=0.18). Need of the balloon angioplasty before stenting was the unique index improved by the manual thrombus aspiration (p=0.02).

CONCLUSION:
Conclisions: No significant advantages of the manual thrombus aspiration usage weren't revealed compearing to conventional PCI in our study in the patients with STEMI and visible coronary thrombosis. At the same time few insignificant trends were reveled. So the more powerful trial is needed to solve this problem.

The influence of the manual thrombus aspiration on the short term effectiveness of the percutaneous revascularization in patients with coronary artery thrombosis

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Variant of rare Hermansky - Pudlak syndrome associated with granulomatous colitis: diagnostics, clinical course and treatment

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Experimental Oncology 2018 Mar;40(1):73-78

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KEYWORDS: *cancer surveillance, Crohn's disease, Hermansky — Pudlak syndrome, HPS, NOD2 and VDR genes mutations, surgical interventions, therapeutic treatment*

AIM:
To study the relationship between the genotype and the phenotype in the patients with Hermansky - Pudlak syndrome (HPS) associated with granulomatous colitis; to monitor clinical course of the disease for adequate treatment, cancer surveillance and genetic counseling.

MATERIALS AND METHODS:
The diagnosis of HPS is established by physical examination, chest X-ray, computed tomography, endoscopic examination with biopsy, and laboratory tests, including histology, baseline laboratory blood, urine and feces tests, determination of ASCA-C and ANCA antibodies using an ELISA. Molecular genetic testing for HPS gene mutations, R702W, G908R, L1007fs and P268S mutations in NOD2 gene, and TaqI variant of the VDR gene were carried out.

RESULTS:
We report 2 cases of HPS from unrelated families. Both were complicated by inflammatory bowel disease with pathologic features of Crohn's disease refractory to antibiotics and corticosteroids. One patient (family 1) with Ashkenazi Jewish ancestry had pathogenic variant of the HPS-4 gene in exon 8, mutation P268S of NOD2 genes and "Tt" genotype of TaqI variant of the VDR gene. Another patient (family 2) carried two mutations P268S and G908R of NOD2 gene, and had a large paraovarian cyst diagnosed. No consistent success with the standard medical therapy, used for treating granulomatous colitis, associated with HPS, in presented cases was achieved. Patients needed surgical interventions at a young age and a long-term surveillance of the probable development of tumors and other complications. Azathioprine at 2 mg/kg/day and mesalazine 3 g/day were used with some positive effect for prevention of Crohn's disease postoperative recurrence.

CONCLUSION:
The occurrence of perianal lesions, the histopathological findings and the results of the molecular genetic analysis confirmed the mutations P268S and G908R of NOD2 gene in these cases suggest that HPS was truly associated with Crohn's disease variant with early onset and severe course. The search for the molecular causes of the disease in some individuals may help in the development of new therapeutic and surgical approaches, as well in the improvement of understanding of premalignant inflammatory conditions in a large bowel.

OCCUPATIONAL HAZARDS AS A RISK FACTOR OF ONSET AND UNFAVORABLE OUTCOME OF ISCHEMIC HEART DISEASE

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Georgian Medical News. 2018 Feb;(Issue):132-141

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Objective -to identify the role of occupational hazards (OH) as a risk factor of onset and unfavorable outcome of coronary artery disease (CAD). Retrospective study included analysis of 307 case reports of CAD patients, including 59 patients with long term history of OH exposure. Prospective study included observation of 244 STEMI patients during their in-patient treatment, including 113 patients with prior exposure to OH. OH were demonstrated to contribute to the risk of CAD, and to be directly involved in atherosclerotic coronary artery (CA) injury, its role being equal to that of the classical risk factors, such as arterial hypertension (AH), dyslipidemia, and diabetes mellitus (DM). As shown by regression analysis, AH, DM, and dyslipidemia primarily promote atherogenesis in second and third order CA, while technogenic xenobiotics - mostly in first and second order CA, including the left CA truncus. History of OH directly affects the degree of stenosis, along with such important factors as LDL cholesterol, HDL cholesterol, triglycerides, and AH. According to Caplan-Meyer curves, OH exposure affects the hospital course of STEMI due to the adverse impact of technogenic xenobiotics leading, which contributes to the main mechanisms of CAD progression. In these patients the activity of systemic inflammation is higher, endothelial dysfunction, and autonomic disbalance and heterogeneity of myocardial repolarization are more profound. More pronounced remodeling of left ventricle, which is apparently due to the pre-existing abnormalities of cardiomyocytes caused by the long term effect of technogenic xenobiotics, significantly impairs the functional condition of myocardium, and accordingly the patient's prognosis. Our data suggest occupational hazards as a risk factor for onset and progression of CAD. Further studies involving this patient category are necessary.

Prevalence of dental erosion among 18-year-old adolescents in the borderland districts of Lviv (Ukraine) and Lublin (Poland)

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Annals of Agricultural and Environmental Medicine 2018 Mar 14;25(1):66-70. doi: 10.5604/12321966.1228948. Epub 2016 Dec 28 (IF=1.116)

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KEYWORDS: *BEWE; Erosive tooth wear; dental erosion*

INTRODUCTION AND OBJECTIVE:
Recent epidemiological studies have shown an association between dental erosion occurrence and changes in lifestyle and dietary habits in both developed and developing countries, and now affects different regions of the world. Furthermore, in current literature, studies have shown that the prevalence of erosive tooth wear has increased particularly among the younger population. The aim of the study was to assess the prevalence and severity of erosive tooth wear among 18-year-old adolescents in the districts of Lviv (Ukraine) and Lublin (Poland).

MATERIAL AND METHODS:
College students (254 subjects) aged 18, living in the Lviv and Lublin districts were examined. Erosive lesions presented in the teeth were assessed on the basis of the BEWE (Basic Erosive Wear Examination) index.

RESULTS:
Among the 137 patients living in the Lublin district, 70 were females and 67 were males, while in the Lviv district, 60 women and 57 men were examined. In both districts, the following numbers of rural patients were examined: 66 in Lublin district and 56 in Lviv district; for urban inhabitants, the numbers were 71 in Lublin and 61 in Lviv. Analysing the BEWE values, it was noted that higher BEWE values, and resulting from them significant differences were observed in both male and female groups living in Lublin, compared with Lviv inhabitants. Based on clinical examination and statistical analysis, the occurrence of lesions of an erosive character in at least one sextant were observed in 59.85% of patients from Lublin district, and in 42.74% of patients from Lviv district.

CONCLUSIONS:
On the basis of the conducted study in the Polish and Ukrainian groups of 18-year-old adolescents living on the borderland, it can be stated that dental erosion is a problem noticeable in both groups of cohorts, but with higher prevalence in the Lublin district.

MicroRNA-15a expression measured in urine samples as a potential biomarker of renal cell carcinoma

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International Urology Nephrology 2018 May;50(5):851-859. doi: 10.1007/s11255-018-1841-x. Epub 2018 Mar 16 (IF= 1.692)

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KEYWORDS: *Biomarker; Diagnosis; MiRNA-15a; Molecular marker; Renal cell carcinoma*

INTRODUCTION:
Currently, there is no accurate diagnostic molecular biomarker for renal cell carcinoma (RCC). The aim of this study was to assess the expression of microRNA-15a (miR-15a) in urine of patients with RCC and to evaluate its potential as a diagnostic molecular biomarker.

MATERIALS AND METHODS:
In total, 67 patients with solid renal tumors were enrolled: clear-cell RCC (ccRCC, n = 22), papillary RCC (pRCC, n = 16), chromophobe RCC (chRCC, n = 14), oncocytoma (n = 8), papillary adenoma (n = 2) and angiomyolipoma (n = 5). MiRNA-15a expression levels measurement in urine were performed using qPCR. Urine of 15 healthy volunteers without kidney pathology was used as control.

RESULTS:
We observed a difference in mean miR-15a expression values in groups of pre-operative patients with RCC, benign renal tumors and healthy persons (2.50E-01 ± 2.72E-01 vs 1.32E-03 ± 3.90E-03 vs 3.36E-07 ± 1.04E-07 RFU, respectively, $p < 0.01$). There was no difference in miR-15a expression between ccRCC, pRCC and chRCC ($p > 0.05$). Direct association between RCC size and miR-15a expression values was obtained (Pearson correlation coefficient-0.873). On the 8th day after nephrectomy, mean expression value in patients with RCC decreased by 99.53% ($p < 0.01$). MiR-15a expression differentiated RCC from benign renal tumors with 98.1% specificity, 100% sensitivity at a cut-off value of 5.00E-06 RFU, with AUC-0.955.

CONCLUSIONS:
MiR-15a expression measured in urine may be used as diagnostic molecular biomarker for RCC.

Antidiabetic effects and erythrocyte stabilization by red cabbage extract in streptozotocin-treated rats

Kanuka O[1], Sybirna N[1] [et al.]

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The protective effect of red cabbage extract (RCE) was evaluated in rats with streptozotocin-induced diabetes, assessing a probable role of this extract in the prevention of erythrocyte impairments associated with a high risk of vascular complications in diabetes. RCE was analyzed by ultrahigh performance liquid chromatography and mass spectrometry, and 11 anthocyanins, 3 hydroxybenzoic acids and 9 hydroxycinnamic acids were identified. Type 1 diabetes was induced by streptozotocin (60 mg kg-1) in Wistar male rats (n = 8 per group). After 7 days of acclimatization, streptozotocin-treated rats were given RCE (800 mg kg-1) or vehicle by intragastric administration for 4 weeks. The RCE treatment lowered blood glucose, and glycated and fetal hemoglobin concentrations and improved glucose tolerance as well as considerably raised serum insulin, proinsulin and C-peptide levels in streptozotocin-treated rats. Simultaneously, RCE improved pancreatic islet morphology, increasing the amount of pancreatic β-cells in diabetic animals. The RCE administration prevented anemia in rats with streptozotocin-induced diabetes, enhanced erythrocyte resistance to acid hemolysis, and normalized reticulocyte production as well as sialic acid content in erythrocyte membranes. The enhanced lectin-induced erythrocyte aggregation in diabetic rats was significantly lowered after the RCE treatment. RCE demonstrated a significant antioxidant effect, decreasing MDA and protein carbonyl contents and increasing catalase and glutathione peroxidase activities in erythrocytes. These results indicate that RCE can be considered as a promising candidate for use as a drug or a food supplement to alleviate diabetes and its vascular complications.

Selenium, selenoprotein P, and Alzheimer's disease: is there a link?

Lysiuk R[1] [et al.]

Free Radical and Biology Medicine 2018 Mar 2. pii: S0891-5849(18)30087-X. doi: 10.1016/j.freeradbiomed.2018.02.030. [Epub ahead of print] (2017 IF=6.020)

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KEYWORDS: *Alzheimer's disease; Amyloid-beta; Brain; Human studies; Model studies; Neurodegeneration; Oxidative stress; Redox regulation; Selenium; Selenoprotein P; Supplementation; Trace elements*

The essential trace element, selenium (Se), is crucial to the brain but it may be potentially neurotoxic, depending on dosage and speciation; Se has been discussed for decades in relation to Alzheimer's disease (AD). Selenoprotein P (SELENOP) is a secreted heparin-binding glycoprotein which serves as the main Se transport protein in mammals. In vivo studies showed that this protein might have additional functions such as a contribution to redox regulation. The current review focuses on recent research on the possible role of SELENOP in AD pathology, based on model and human studies. The review also briefly summarizes results of epidemiological studies on Se supplementation in relation to brain diseases, including PREADViSE, EVA, and AIBL. Although mainly positive effects of Se are assessed in this review, possible detrimental effects of Se supplementation or exposure, including potential neurotoxicity, are also mentioned. In relation to AD, various roles of SELENOP are discussed, i.e. as the means of Se delivery to neurons, as an antioxidant, in cytoskeleton assembly, in interaction with redox-active metals (copper, iron, and mercury) and with misfolded proteins (amyloid-beta and hyperphosphorylated tau-protein).

A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated with neoadjuvant-adjuvant treatment: Final safety, immunogenicity and survival results

Bondarenko I[1], Shparyk Y[2] [et al.]

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KEYWORDS: *Biosimilar; Early breast cancer; Event-free survival; HER2; Safety; Trastuzumab*

BACKGROUND:
The equivalent efficacy between SB3, a proposed trastuzumab biosimilar, and the trastuzumab reference product (TRZ) in terms of the breast pathologic complete response rate after neoadjuvant therapy in patients with early or locally advanced human epidermal growth factor receptor 2-positive breast cancer was demonstrated in the previous report. Here, we report the final safety, immunogenicity and survival results after neoadjuvant-adjuvant treatment.

PATIENTS AND METHODS:
Patients were randomised 1:1 to receive neoadjuvant SB3 or TRZ for 8 cycles concurrently with chemotherapy (4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/cyclophosphamide). Patients then underwent surgery, followed by 10 cycles of adjuvant SB3 or TRZ as randomised. End-points included safety, immunogenicity, event-free survival (EFS) and overall survival through the adjuvant period.

RESULTS:
Of 875 patients randomised, 764 (SB3, n = 380; TRZ, n = 384) completed the study. The median follow-up duration was 437 days in the SB3 group and 438 days in the TRZ group. The incidence of treatment-emergent adverse events was comparable between groups (SB3, 97.5%; TRZ, 96.1%) during the overall study period. Up to the end of study, the overall incidence of antidrug antibody was low in both treatment groups (3 patients each). EFS was comparable between groups with a hazard ratio (SB3/TRZ) of 0.94 (95% confidence interval, 0.59-1.51) and EFS rates at 12 months of 93.7% for SB3 and 93.4% for TRZ.

CONCLUSIONS:
Final safety, immunogenicity and survival results of this study further support the biosimilarity established between SB3 and TRZ.

TRIAL REGISTRATION:
ClinicalTrials.gov (NCT02149524); EudraCT (2013-004172-35).

Features of fracture of prosthetic tooth-endocrown constructions by means of acoustic emission analysis

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KEYWORDS: *Acoustic emission; Ceramics; Composite resin; Endocrown; Fracture; Metal ceramics*

OBJECTIVE:
The study aims at comparing the fracture resistance of different restorative materials used in dental endocrown restorations and respective endocrown restorations under a quasi-static compressive load using acoustic emission (AE) method.

METHODS:
Five restorative materials were used in this study. The restorative materials were manufactured into discs 13mm in diameter and 5mm thick, which were then divided into 5 groups and included into Type 1: Group B: zirconium dioxide (Prettau zirconia); Group C: ceramics (IPS e.max Press); Group D: metal ceramics (GC Initial MC+Nicrallium N2 BCS); Group E: composite resin (Nano Q); Group F: luting cement (RelyX™ U200). Twenty-five extracted human molars were divided

into 5 groups and included into Type 2: Group A: control, no restoration; Group BE: restored by zirconium dioxide endocrowns; Group CE: restored by ceramic endocrowns; Group DE: restored by metal ceramic endocrowns; Group EE: restored by composite resin endocrowns. An increasing load was applied to the center of the samples with a hard steel ball until a fracture occurred. The loading rate was 0.12mm/min. An AE system was used to monitor the fracture of the samples. The load corresponding to the first AE event and the final fracture load were used to evaluate the fracture resistance of the restored teeth. The data were analyzed using ANOVA and Tukey's post hot test (α=0.05).

RESULTS:
A lower threshold of 220μV was selected to exclude spurious background signals. For the initial fracture load of Type 1 samples, Group F (0.029kN)<Group E (0.039kN)<Group D (0.056kN)<Group C (0.253kN)<Group B (intact). The same trend was found for the final fracture load, i.e., Group F (1.289kN)<Group E (1.735kN)<Group D (3.362kN)<Group C (6.449kN)<Group B (intact). For the initial and final fracture load, statistically significant differences ($p<0.05$) were found between group C and the others groups. For the initial fracture load of Type 2 samples, Group EE (0.069kN)<Group DE (0.072kN)<Group CE (0.148kN)<Group BE (2.511kN). For the final fracture load, Group EE (1.533kN)<Group CE (2.726kN)<Group BE (3.082 kN)<Group DE (3.320kN). The initial fracture load of the ceramic samples is somewhat higher than that for the endocrown restorations with the endocrowns made of this material (0.253 and 0.148kN, respectively). At the same time, for the metal ceramic and composite resin samples, the initial fracture loads are somewhat lower than in case of compression of the endocrown restorations with the endocrowns made of these materials (0.056 and 0.072kN; 0.039 and 0.069kN, respectively). The final fracture load of all the samples of the dental materials exceeds the strength of the respective endocrown restorations. The final fracture loads of the endocrown restorations with zirconium dioxide and ceramic endocrowns (3.082 and 2.726kN, respectively) are significantly lower than the final fracture load of the respective endocrown materials (intact and 6.449kN, respectively).

SIGNIFICANCE:
Dental restorations should be made of high-strength materials. Zirconia displayed the highest fracture strength, while composite resin had the lowest fracture strength out of the materials used for the endocrowns. For teeth restored with endocrowns, the use of metal ceramics as endocrown material may lower the risk of failure during clinical use.

Phase III, Randomized, Double-Blind Study Comparing the Efficacy, Safety, and Immunogenicity of SB3 (Trastuzumab Biosimilar) and Reference Trastuzumab in Patients Treated With Neoadjuvant Therapy for Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer

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Purpose This phase III study compared SB3, a trastuzumab (TRZ) biosimilar, with reference TRZ in patients with human epidermal growth factor receptor 2-positive early breast cancer in the neoadjuvant setting (ClinicalTrials.gov identifier: NCT02149524). Patients and Methods Patients were randomly assigned to receive neoadjuvant SB3 or TRZ for eight cycles concurrently with chemotherapy (four cycles of docetaxel followed by four cycles of fluorouracil, epirubicin, and cyclophosphamide) followed by surgery, and then 10 cycles of adjuvant SB3 or TRZ. The primary objective was comparison of breast pathologic complete response (bpCR) rate in the per-protocol set; equivalence was declared if the 95% CI of the ratio was within 0.785 to 1.546 or the 95% CI of the difference was within ± 13%. Secondary end points included comparisons of total pathologic complete response rate, overall response rate, event-free survival, overall survival, safety, pharmacokinetics, and immunogenicity. Results Eight hundred patients were included in the per-protocol set (SB3, n = 402; TRZ, n = 398). The bpCR rates were 51.7% and 42.0% with SB3 and TRZ, respectively. The adjusted ratio of bpCR was 1.259 (95% CI, 1.085 to 1.460), which was within the predefined equivalence margins. The adjusted difference was 10.70% (95% CI, 4.13% to 17.26%), with the lower limit contained within and the upper limit outside the equivalence margin. The total pathologic complete response rates were 45.8% and 35.8% and the overall response rates were 96.3% and 91.2% with SB3 and TRZ, respectively. Overall, 96.6% and 95.2% of patients experienced one or more adverse event, 10.5% and 10.7% had a serious adverse event, and 0.7% and 0.0% had antidrug antibodies (up to cycle 9) with SB3 and TRZ, respectively. Conclusion Equivalence for efficacy was demonstrated between SB3 and TRZ on the basis of the ratio of bpCR rates. Safety and immunogenicity were comparable.

Brief Challenges on Medicinal Plants: An Eye-Opening Look at Ageing-Related Disorders

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Several studies have reported that nature-derived antioxidants may prevent free radicals over-production and therefore control the onset and prevent the exacerbation of different kinds of diseases caused by oxidative stress and redox-derived stressors, including ageing, fundamentally by suppressing the oxidative by-products-mediated degradation. Naturally derived antioxidants exert their anti-ageing action via a panoply of signalling systems, many of which engaging reactive oxygen and nitrogen species scavenging, with the Nrf2/Keap1-ARE system and improving the many survival genes and functions (such as the pathway mTOR/Foxo/SIRT1) able to slow cellular senescence. Most of the research in this field has evaluated the regulative effects and even pathways of herbal extracts with antioxidant property in the ageing process, and various age-

related disorders such as cardiovascular disease, ischaemia-reperfusion injury, coronary and myocardial circulatory perfusion, peripheral vascular resistance, and even neurodegenerative disorders are prevented plant phytochemicals often via their antioxidant potential. A much more complex ability to interact with survival functions makes these compounds successfully active in preventing ageing-related disorders. This report aimed to discuss in more detail some selected medicinal plants including Allium sativum, Aloe vera, Crataegus spp., Cynara scolymus, Eleutherococcus senticosus, Ginkgo biloba, Hippophae rhamnoides, Panax ginseng, Rosmarinus officinalis, Schizandra chinensis, Vitis vinifera and seaweeds in the prevention of ageing-related pathologies. A systematic overview of the relevant information in the antioxidant function of the many herbal products reviewed here for the control of the ageing process is proposed, to provide a new horizon on the design of anti-ageing herbal medicines.

Cardiac autonomic neuropathy: Risk factors, diagnosis and treatment

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KEYWORDS: *Cardiac autonomic neuropathy; Cardiovascular reflex tests; Diabetes mellitus; Heart rate variability; Orthostatic hypotension; Prophylaxis; Risk factors; Screening for cardiac autonomic neuropathy; Treatment*

Cardiac autonomic neuropathy (CAN) is a serious complication of diabetes mellitus (DM) that is strongly associated with approximately five-fold increased risk of cardiovascular mortality. CAN manifests in a spectrum of things, ranging from resting tachycardia and fixed heart rate (HR) to development of "silent" myocardial infarction. Clinical correlates or risk markers for CAN are age, DM duration, glycemic control, hypertension, and dyslipidemia (DLP), development of other microvascular complications. Established risk factors for CAN are poor glycemic control in type 1 DM and a combination of hypertension, DLP, obesity, and unsatisfactory glycemic control in type 2 DM. Symptomatic manifestations of CAN include sinus tachycardia, exercise intolerance, orthostatic hypotension (OH), abnormal blood pressure (BP) regulation, dizziness, presyncope and syncope, intraoperative cardiovascular instability, asymptomatic myocardial ischemia and infarction. Methods of CAN assessment in clinical practice include assessment of symptoms and signs, cardiovascular reflex tests based on HR and BP, short-term electrocardiography (ECG), QT interval prolongation, HR variability (24 h, classic 24 h Holter ECG), ambulatory BP monitoring, HR turbulence, baroreflex sensitivity, muscle sympathetic nerve activity, catecholamine assessment and cardiovascular sympathetic tests, heart sympathetic imaging. Although it is common complication, the significance of CAN has not been fully appreciated and there are no unified treatment algorithms for today. Treatment is based on early diagnosis, life style changes, optimization of glycemic control and management of cardiovascular risk factors. Pathogenetic treatment of CAN includes: Balanced diet and physical activity; optimization of glycemic control; treatment of DLP; antioxidants, first of all α-lipoic acid (ALA), aldose reductase inhibitors, acetyl-L-carnitine; vitamins, first of all fat-soluble vitamin B1; correction of vascular endothelial dysfunction; prevention and treatment of thrombosis; in severe cases-treatment of OH. The promising methods include prescription of prostacyclin analogues, thromboxane A2 blockers and drugs that contribute into strengthening and/or normalization of Na+, K+-ATPase (phosphodiesterase inhibitor), ALA, dihomo-γ-linolenic acid (DGLA), ω-3 polyunsaturated fatty acids (ω-3 PUFAs), and the simultaneous prescription of ALA, ω-3 PUFAs and DGLA, but the future investigations are needed. Development of OH is associated

with severe or advanced CAN and prescription of nonpharmacological and pharmacological, in the foreground midodrine and fludrocortisone acetate, treatment methods are necessary.

FANCM and RECQL genetic variants and breast cancer susceptibility: relevance to South Poland and West Ukraine

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KEYWORDS: *Breast cancer predisposition; FANCM; Familial breast cancer; Gene panel testing; RECQL*

BACKGROUND:
FANCM and RECQL have recently been reported as breast cancer susceptibility genes and it has been suggested that they should be included on gene panel tests for breast cancer predisposition. However, the clinical value of testing for mutations in RECQL and FANCM remains to be determined. In this study, we have characterised the spectrum of FANCM and RECQL mutations in women affected with breast or ovarian cancer from South-West Poland and West Ukraine.

METHODS:
We applied Hi-Plex, an amplicon-based enrichment method for targeted massively parallel sequencing, to screen the coding exons and proximal intron-exon junctions of FANCM and RECQL in germline DNA from unrelated women affected with breast cancer (n = 338) and ovarian cancer (n = 89) from Poland (n = 304) and Ukraine (n = 123). These women were at high-risk of carrying a genetic predisposition to breast and/or ovarian cancer due to a family history and/or early-onset disease.

RESULTS:
Among 427 women screened, we identified one carrier of the FANCM:c.1972C > T nonsense mutation (0.23%), and two carriers of the frameshift insertion FANCM:c.1491dup (0.47%). None of the variants we observed in RECQL were predicted to be loss-of-function mutations by standard variant effect prediction tools.

CONCLUSIONS:
Our study of the Polish and Ukrainian populations has identified a carrier frequency of truncating mutations in FANCM consistent with previous reports. Although initial reports suggesting that mutations in RECQL could be associated with increased breast cancer risk included women from Poland and identified the RECQL:c.1667_1667 + 3delAGTA mutation in 0.23-0.35% of breast cancer cases, we did not observe any carriers in our study cohort. Continued screening, both in research and diagnostic settings, will enable the accumulation of data that is needed to establish the clinical utility of including RECQL and FANCM on gene panel tests.

Efficacy and safety of frontline rituximab, cyclophosphamide, doxorubicin and prednisone plus bortezomib (VR-CAP) or vincristine (R-CHOP) in a subset of newly diagnosed mantle cell lymphoma patients medically eligible for transplantation in the randomized, phase 3 LYM-3002 study

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***KEYWORDS**: Bortezomib; frontline; mantle cell lymphoma; phase 3*

This post-hoc subanalysis of the LYM-3002 phase 3 study assessed the efficacy and safety of substituting vincristine in rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHOP; n = 42) for bortezomib (VR-CAP; n = 38) in a subgroup of 80 mantle cell lymphoma (MCL) patients aged < 60 years who did not receive stem cell transplantation (SCT) despite medical eligibility. Complete response (CR)/unconfirmed CR (CRu) rates were 67 vs. 39% (odds ratio 3.69 [95% CI(confidence interval): 1.31, 10.41]; p = .012). After 40 months median follow-up, median progression-free survival by independent radiology committee with VR-CAP vs. R-CHOP was 32.6 vs. 12.0 months (hazard ratio (HR) 0.59 [95% CI: 0.31, 1.13]; p = .108); median overall survival was not reached vs. 47.3 months (HR 0.81 [95% CI: 0.33, 1.96]; p = .634). Adverse events included neutropenia (92/76%), thrombocytopenia (70/10%) and leukopenia (65/50%). VR-CAP represents a potential alternative to R-CHOP in combined and/or alternating regimens for younger, SCT-eligible MCL patients.

Amaranth oil reduces accumulation of 4-hydroxynonenal-histidine adducts in gastric mucosa and improves heart rate variability in duodenal peptic ulcer patients undergoing Helicobacter pylori eradication

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***KEYWORDS:** 4-hydroxynonenal; Helicobacter pylori; Peptic ulcer; amaranth oil; heart rate variability; oxidative stress*

Helicobacter pylori-induced oxidative stress in gastric mucosa (GM) is a milieu for the development of chronic gastritis, duodenal peptic ulcer (DPU), gastric cancer, and a number of extragastric diseases. Because our previous study revealed the accumulation of the protein adducts of lipid peroxidation product 4-hydroxynonenal (HNE) in GM, which persists after eradication of H. pylori, the aim of the study was to test whether Amaranth oil supplementation

in addition to standard anti-Helicobacter treatment could prevent such accumulation of HNE in GM in H. pylori-positive DPU patients. Seventy-five patients were randomly split into two groups: group 1 - standard treatment (n = 39) and group 2 - standard treatment with additional supplementation of 1 ml of concentrated oil from amaranth seeds (Amaranthus cruenthus L., n = 36). Clinical analysis, including endoscopy with biopsies from antrum and corpus of the stomach were performed before and after the treatment, as was heart rate variability (HRV) recorded, as parameter of systemic, extragastric pathophysiological alterations in DPU patients. Improvement of clinical, endoscopic and histologic manifestations, and successful ulcer healing were observed in both the groups. Moreover, supplementation of amaranth oil in addition to standard anti-H. pylori treatment significantly reduced accumulation of HNE-histidine adducts in GM and increased HRV in DPU patients ($p < .05$). Therefore, standard treatments of DPU require additional therapeutic approaches, in accordance with integrative medicine principles, aiming to reduce persistence of oxidative stress, as was successfully done in our study by the use of amaranth oil.

Differential diagnosis of the small renal masses: role of the apparent diffusion coefficient of the diffusion-weighted MRI

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KEYWORDS: *Apparent diffusion coefficient; Diffusion-weighted imaging; MRI; Renal cell carcinoma; Small renal masses*

INTRODUCTION:
Renal cell carcinoma (RCC) accounts for approximately 3% of adult malignancies and more than 90% of neoplasms arising from the kidney. Uninformative percutaneous kidney biopsies vary from 10 to 23%. As a result, 7.5-33.6% of partial nephrectomies in patients with small renal masses (SRM) are performed on benign renal tumors. The aim of this study was to assess the feasibility of the apparent diffusion coefficient (ADC) of the diffusion-weighted imaging (DWI) of MRI, as RCC imaging biomarker for differentiation of SRM.

METHOD:
Adult patients (n = 158) with 170 SRM were enrolled into this study. The control group were healthy volunteers with normal clinical and radiologic findings (n = 15). All participants underwent MRI with DWI sequence included.

RESULTS:
Mean ADC values of solid RCC (1.65 ± 0.38 × 10-3 mm2/s) were lower than healthy renal parenchyma (2.47 ± 0.12 × 10-3 mm2/s, $p < 0.05$). There was no difference between mean ADC values of ccRCC, pRCC and chRCC (1.82 ± 0.22 × 10-3 vs 1.61 ± 0.07 × 10-3 vs 1.46 ± 0.09 × 10-3 mm2/s, respectively, p = ns). An inverse relationship between mean ADC values and Fuhrman grade of nuclear atypia of solid ccRCCs was observed: grade I-1.92 ± 0.11 × 10-3 mm2/s, grade II-1.84 ± 0.14 × 10-3 mm2/s, grade III-1.79 ± 0.10 × 10-3 mm2/s, grade IV-1.72 ± 0.06 × 10-3 mm2/s. This was significant ($p < 0.05$) only between tumors of I and IV

grades. Significant difference ($p < 0.05$) between mean ADC values of solid RCCs, benign renal tumors and renal cysts was observed (1.65 ± 0.38 × 10-3 vs 2.23 ± 0.18 × 10-3 vs 3.15 ± 0.51 × 10-3 mm2/s, respectively). In addition, there was a significant difference ($p < 0.05$) in mean ADC values between benign cysts and cystic RCC (3.36 ± 0.35 × 10-3 vs 2.83 ± 0.21 × 10-3 mm2/s, respectively).

CONCLUSION:
ADC maps with b values of 0 and 800 s/mm2 can be used as an imaging biomarker, to differentiate benign SRM from malignant SRM. Using ADC value threshold of 1.75 × 10-3 mm2/s allows to differentiate solid RCC from solid benign kidney tumors with 91% sensitivity and 89% specificity; ADC value threshold of 2.96 × 10-3 mm2/s distinguishes cystic RCC from benign renal cysts with 90% sensitivity and 88% specificity. However, the possibility of differentiation between ccRCC histologic subtypes and grades, utilizing ADC values, is limited.

Development of Predictive QSAR Models of 4-Thiazolidinones Antitrypanosomal Activity Using Modern Machine Learning Algorithms

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KEYWORDS: *Antitrypanosomal activity; QSAR; Structure-activity relationships; Thiazolidinones*

This paper presents novel QSAR models for the prediction of antitrypanosomal activity among thiazolidines and related heterocycles. The performance of four machine learning algorithms: Random Forest regression, Stochastic gradient boosting, Multivariate adaptive regression splines and Gaussian processes regression have been studied in order to reach better levels of predictivity. The results for Random Forest and Gaussian processes regression are comparable and outperform other studied methods. The preliminary descriptor selection with Boruta method improved the outcome of machine learning methods. The two novel QSAR-models developed with Random Forest and Gaussian processes regression algorithms have good predictive ability, which was proved by the external evaluation of the test set with corresponding Q2ext =0.812 and Q2ext =0.830. The obtained models can be used further for in silico screening of virtual libraries in the same chemical domain in order to find new antitrypanosomal agents. Thorough analysis of descriptors influence in the QSAR models and interpretation of their chemical meaning allows to highlight a number of structure-activity relationships. The presence of phenyl rings with electron-withdrawing atoms or groups in para-position, increased number of aromatic rings, high branching but short chains, high HOMO energy, and the introduction of 1-substituted 2-indolyl fragment into the molecular structure have been recognized as trypanocidal activity prerequisites.

Corrigendum to "European contribution to the study of ROS: A summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS)" [Redox Biol. 13 (2017) 94-162]

Kaminskyy D[1], Semen K[1], Yelisyeyeva O[1] [et al.]

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***KEYWORDS**: Reactive oxygen species, Reactive nitrogen species, Redox signaling, Oxidative stress, Antioxidants, Redox therapeutics*

The European Cooperation in Science and Technology (COST) provides an ideal framework to establish multidisciplinary research networks. COST Action BM1203 (EU-ROS) represents a consortium of researchers from different disciplines who are dedicated to providing new insights and tools for better understanding redox biology and medicine and, in the long run, to finding new therapeutic strategies to target dysregulated redox processes in various diseases. This report highlights the major achievements of EU-ROS as well as research updates and new perspectives arising from its members. The EU-ROS consortium comprised more than 140 active members who worked together for four years on the topics briefly described below. The formation of reactive oxygen and nitrogen species (RONS) is an established hallmark of our aerobic environment and metabolism but RONS also act as messengers via redox regulation of essential cellular processes. The fact that many diseases have been found to be associated with oxidative stress established the theory of oxidative stress as a trigger of diseases that can be corrected by antioxidant therapy. However, while experimental studies support this thesis, clinical studies still generate controversial results, due to complex pathophysiology of oxidative stress in humans. For future improvement of antioxidant therapy and better understanding of redox-associated disease progression detailed knowledge on the sources and targets of RONS formation and discrimination of their detrimental or beneficial roles is required. In order to advance this important area of biology and medicine, highly synergistic approaches combining a variety of diverse and contrasting disciplines are needed.

Transcription factor c-Myb inhibits breast cancer lung metastasis by suppression of tumor cell seeding

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Metastasis accounts for most of cancer-related deaths. Paracrine signaling between tumor cells and the stroma induces changes in the tumor microenvironment required for metastasis. Transcription factor c-Myb was associated with breast cancer (BC) progression but its role in metastasis remains unclear. Here we show that increased c-Myb expression in BC cells inhibits spontaneous lung metastasis through impaired tumor cell extravasation. On contrary, BC cells

with increased lung metastatic capacity exhibited low c-Myb levels. We identified a specific inflammatory signature, including Ccl2 chemokine, that was expressed in lung metastatic cells but was suppressed in tumor cells with higher c-Myb levels. Tumor cell-derived Ccl2 expression facilitated lung metastasis and rescued trans-endothelial migration of c-Myb overexpressing cells. Clinical data show that the identified inflammatory signature, together with a MYB expression, predicts lung metastasis relapse in BC patients. These results demonstrate that the c-Myb-regulated transcriptional program in BCs results in a blunted inflammatory response and consequently suppresses lung metastasis.

Immunogenicity, efficacy and safety of Nuwiq® (human-cl rhFVIII) in previously untreated patients with severe haemophilia A-Interim results from the NuProtect Study

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KEYWORDS: *FVIII inhibitors; Human-cl rhFVIII; Nuwiq®; haemophilia A; previously untreated patients*

INTRODUCTION:
Nuwiq® (Human-cl rhFVIII) is a fourth generation recombinant FVIII, produced in a human cell line, without chemical modification or protein fusion. No inhibitors developed in studies with Nuwiq® in 201 previously treated patients with haemophilia A (HA). The immunogenicity, efficacy and safety of Nuwiq® in previously untreated patients (PUPs) with severe HA are being assessed in the ongoing NuProtect study.

METHODS:
The study, conducted across 38 centres worldwide, is evaluating 110 true PUPs of all ages and ethnicities enrolled for study up to 100 exposure days (EDs) or 5 years maximum. The primary objective is to assess the immunogenicity of Nuwiq® (inhibitor activity ≥0.6 BU) using the Nijmegen-modified Bethesda assay at a central laboratory.

RESULTS:
Data for 66 PUPs with ≥20 EDs from a preplanned interim analysis were analysed. High-titre (HT) inhibitors developed in 8 of 66 patients after a median of 11.5 EDs (range 6-24). Five patients developed low-titre inhibitors (4 transient). The cumulative incidence (95% confidence interval) was 12.8% (4.5%, 21.2%) for HT inhibitors and 20.8% (10.7%, 31.0%) for all inhibitors. During inhibitor-free periods, median annualized bleeding rates during prophylaxis were 0 for spontaneous bleeds and 2.40 for all bleeds. Efficacy was rated as "excellent" or "good" in treating 91.8% of bleeds. Efficacy of surgical prophylaxis was "excellent" or "good" for 8 (89%) procedures and "moderate" for 1 (11%). No tolerability concerns were evident.

CONCLUSION:
These interim data show a cumulative incidence of 12.8% for HT inhibitors and convincing efficacy and tolerability in PUPs treated with Nuwiq® .

Chemical Composition of Selected Commercial Herbal Remedies in Relation to Geographical Origin and Inter-Species Diversity

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KEYWORDS: *Essential elements; Herbal remedies; Statistical evaluation; Total flavonoids*

Infusions prepared from medicinal herbs that are rich in flavonoids are very popular herbal remedies in societies of Eastern Europe. Therefore, the content of essential elements together with total flavonoids was analyzed in 65 commercially available samples of herbal drugs originating from Ukraine, Romania, and Belarus. The results showed that metallic elements (in mg kg-1 d.w.) have occurred in the following order: Fe > Mn > Zn > Cu, both for total and water-extractable species. Total flavonoids were determined in the range from 10.0 to 191.8 mg g-1 d.w. Several significant correlations have been found between the analytes, especially among water-extractable Fe with other metals, and total flavonoids and Fe, Zn, and Mn. Analysis of variance has revealed significant differences among studied samples due to their origin from different countries, especially between Belarussian samples and others. Differences owing to belonging to various plant species were also found, as it was noticed in the case of Polygoni aviculare herba in comparison with other botanical plant species. Moreover, multivariate statistical techniques, such as cluster analysis (CA) and principal component analysis (PCA) were used to gather herbal drugs based on similarity of chemical composition. CA grouped the samples into clusters with similar level of elements and total flavonoid contents, and PCA has indicated Hyperici herba, Tiliae flores, and Crataegi fructus as herbal remedies with close concentration of studied elements and flavonoids.

Матеріал підготувала,
в.о. зав. відділу навчальної літератури

Хрипко Ольга Богданівна