

CROATIAN INTERNATIONAL PUBLICATIONS

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Kurelac I, Lepej SZ, Grljic I, Gorenec L, Papic N, Dusek D, Barsic B, Vince A. Chemokine CXCL10 at week 4 of treatment predicts sustained virological response in patients with chronic hepatitis C. *J Interferon Cytokine Res.* 2012; 32(8):386-91.

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The aim of this study was to analyze the predictive value of CXCL9, CXCL10, and CXCL11 concentrations before and after 4 and 12 weeks of treatment with pegylated interferon- α 2b and ribavirin in patients with chronic hepatitis C infected with the hepatitis C virus genotype 1. The study included 46 adult patients (29 women and 17 men). Chemokine quantification in the serum was performed at baseline and after 1, 3, and 6 months of treatment by enzyme immunoassay. Chemokine responses were compared in patients achieving a sustained virological response to treatment (SVR, $n=26$) and the non-SVR group ($n=20$). The differences in the CXCL9 and CXCL10 concentrations between the SVR and non-SVR groups were statistically significant. A multivariate analysis showed a significant association between treatment failure and higher concentrations of CXCL10. A higher predictive value of CXCL10 concentrations after 4 weeks of treatment compared to pretreatment values has been found (area under the curve 0.9288 and 0.7942, respectively, $P=0.016$). CXCL10 concentrations above 250 pg/mL 4 weeks after the start of treatment were independently associated with non-SVR. In conclusion, the results of this study have shown that CXCL10 concentrations at the time of a rapid viral response (4 weeks) are better predictors of achieving SVR compared to baseline levels. Additionally, this study suggests an important role of CXCL9 as a biomarker of SVR in patients with chronic hepatitis C.

Lovrić M, Božina N, Hajnšek S, Kuzman MR, Sporiš D, Lalić Z, Božina T, Granić P. Association Between Lamotrigine Concentrations and ABCB1 Polymorphisms

in Patients With Epilepsy. *Ther Drug Monit.* 2012; 34(5):518-25.

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BACKGROUND: Epilepsy is treated with a variety of anti-convulsants that are often used concomitantly. Therefore, therapeutic drug monitoring is often necessary. Along with clinical and environmental factors, genetic predisposition has been recognized to be relevant for interindividual variability in drug response. Polymorphic transporter proteins such as P-glycoprotein significantly influence pharmacokinetics and bioavailability of many structurally unrelated drugs. The aim of the study was to evaluate the impact of polymorphisms in the P-glycoprotein-encoding gene ABCB1 (C1236T, G2677T/A, C3435T) on antiepileptic drug disposition. **METHODS:** We recruited 222 patients with epilepsy who were prescribed lamotrigine in monotherapy or polytherapy. Lamotrigine plasma concentrations were analyzed and compared with ABCB1 gene variants. The ABCB1 genotyping was performed by real-time polymerase chain reaction methods. The therapeutic drug monitoring was performed by high-performance liquid chromatography-diode array detector (DAD) and immunoassay. **RESULTS:** A significant correlation was confirmed between lamotrigine concentration and additional drugs ($P < 0.001$). In the whole group, statistical analysis showed correlations between lamotrigine concentrations and ABCB1 C1236T variants: 10.1 and 6.5 $\mu\text{mol/L}$ for CC versus CT + TT, respectively ($P = 0.021$), and for dose corrected lamotrigine 0.068 and 0.053 $\mu\text{mol}\cdot\text{L}\cdot\text{mg}$, for CC versus CT + TT, respectively ($P = 0.017$). Analysis of a specific haplotype showed that 1236C-2677G-3435C carriers had higher lamotrigine concentrations than 1236T-2677G-3435T carriers ($P < 0.001$), followed by 1236T-2677T-3435C carriers ($P < 0.001$). **CONCLUSIONS:** ABCB1 C1236T, G2677T/A, C3435T

polymorphisms have an influence on lamotrigine serum concentrations.

Bradamante M, Turčić P, Stambuk N, Konjevoda P, Aralica G, Alerić I, Kozmar A. Cytoprotective Effects of β -Melanocortin in the Rat Gastrointestinal Tract. *Molecules*. 2012; 17(10):11680-92.

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Recently discovered anti-inflammatory and immunomodulatory properties of melanocortin peptides led to the conclusion that they might serve as new anti-inflammatory therapeutics. The purpose of this work was to examine the effectiveness of β -melanocortin (β -MSH) in two experimental models: ethanol-induced gastric lesions and TNBS (2,4,6-trinitrobenzenesulfonic acid)-induced colitis in male Wistar rats. Three progressive doses of β -MSH were used: 0.125, 0.250 and 0.500 mg/kg. Our results suggest that β -MSH acts as a protective substance in the gastric lesions model, which can be seen as a statistically significant reduction of hemorrhagic lesions at all three doses, compared to the control group. The most efficient dose was 0.250 mg/kg. Statistically significant reduction in mucosal surface affected by necrosis and the reduction of overall degree of inflammation in the colitis model indicates an anti-inflammatory effect of β -MSH at a dose of 0.250 mg/kg. The results justify further research on β -MSH peptide and its derivatives in the inflammatory gastrointestinal diseases, and point out the possibility of using β -MSH in studies of digestive system pharmacology.

Katičić M, Antoljak N, Kujundžić M, Stamenić V, Skoko Poljak D, Kramarić D, Stimac D, Strnad Pešikan M, Samija M, Ebling Z. Results of national colorectal cancer screening program in Croatia (2007-2011). *World J Gastroenterol*. 2012; 18(32):4300-7.

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AIM: To study the epidemiologic indicators of uptake and characteristic colonoscopic findings in the Croatian National Colorectal Cancer Screening Program. **METHODS:** Colorectal cancer (CRC) was the second leading cause of cancer mortality in men ($n = 1063$, 49.77/100 000), as well as women ($n = 803$, 34.89/100 000) in Croatia in 2009.

The Croatian National CRC Screening Program was established by the Ministry of Health and Social Wel-

fare, and its implementation started in September, 2007. The coordinators were recruited in each county institute of public health with an obligation to provide fecal occult blood testing (FOBT) to the participants, followed by colonoscopy in all positive cases. The FOBT was performed by hypersensitive guaiac-based Hemognost card test (Biognost, Zagreb). The test and short questionnaire were delivered to the home addresses of all citizens aged 50-74 years consecutively during a 3-year period. Each participant was required to complete the questionnaire and send it together with the stool specimen on three test cards back to the institute for further analysis. About 4% FOBT positive cases are expected in normal risk populations. A descriptive analysis was performed. **RESULTS:** A total of 1 056 694 individuals (born between 1933-1945 and 1952-1957) were invited to screening by the end of September 2011. In total, 210 239 (19.9%) persons returned the envelope with a completed questionnaire, and 181 102 of them returned it with a correctly placed stool specimen on FOBT cards. Until now, 12 477 (6.9%), FOBT-positive patients have been found, which is at the upper limit of the expected values in European Guidelines for Quality Assurance in CRC Screening and Diagnosis [European Union (EU) Guidelines]. Colonoscopy was performed in 8541 cases (uptake 66%). Screening has identified CRC in 472 patients (5.5% of colonoscoped, 3.8% of FOBT-positive, and 0.26% of all screened individuals). This is also in the expected range according to EU Guidelines. Polyps were found and removed in 3329 (39% of colonoscoped) patients. The largest number of polyps were found in the left half of the colon: 64% (19%, 37% and 8% in the rectum, sigma, and descendens, respectively). The other 36% were detected in the proximal part (17% in the transverse colon and 19% in ceco-ascending colon). Small polyps in the rectum (5-10 mm in diameter), sigmoid and descending colon were histologically found to be tubular adenomas in 60% of cases, with a low degree of dysplasia, and 40% were classified as hyperplastic. Polyps of this size in the transverse or ceco-ascending colon in almost 20% had a histologically villous component, but still had a low degree of dysplasia. Polyps sized 10-20 mm in diameter were in 43% cases tubulovillous, and among them, 32% had areas with a high degree of dysplasia, especially those polyps in the ceco-ascending or transverse part. The characteristics of the Croatian CRC Screening National Program in the first 3 years were as follows: relatively low percentage of returned FOBT, higher number of FOBT-positive persons but still in the range for population-based programs, and higher number of pathologic findings (polyps and cancers). **CONCLUSION:** These results suggest a need for intervention strategies that in-

clude organizational changes and educational activities to improve awareness of CRC screening usefulness and increase participation rates.

Mitrović M, Arapović J, Traven L, Krmpotić A, Jonjić S. Innate immunity regulates adaptive immune response: lessons learned from studying the interplay between NK and CD8(+) T cells during MCMV infection. *Med Microbiol Immunol.* 2012; 201(4):487-95.

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Natural killer (NK) cells play a crucial role in early immune response against cytomegalovirus infection. A large and mounting body of data indicate that these cells are involved in the regulation of the adaptive immune response as well. By using mouse cytomegalovirus (MCMV) as a model, several groups provided novel insights into the role of NK cells in the development and kinetics of antiviral CD8(+) T cell response. Depending on infection conditions, virus strain and the genetic background of mice used, NK cells are either positive or negative regulators of the CD8(+) T cell response. At present, there is no unique explanation for the observed differences between various experimental systems used. In this review we discuss the mechanisms involved in the interplay between NK and CD8(+) T cells in the early control of MCMV infection.

Laskarin G, Persic V, Miškulin R, Ruzic A, Zaputovic L. Can we assess an acute myocardial infarction in patients with acute coronary syndrome according to diagnostic accuracy of heat shock proteins? *Med Hypotheses.* 2012; 79(5):592-4.

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Heat shock proteins (HSPs) have changed very little with evolution, suggesting that they play important role(s) in cellular survival. Specifically, HSPs protect cells from induced cell death. Their expression is triggered by heat or other stress, such as ischemia. HSPs provide protection against protein denaturation, although they slightly differ with respect to group affiliation. Release of HSPs from necrotic and ischemic cardiomyocytes into the intercellular space and plasma may correlate with the intensity of the

pro-inflammatory response observed during and immediately after myocardial infarction. We hypothesized that the plasma concentration of particularly inducible forms of HSPs from different groups (HSP 90, HSP 70, HSP 60 and/or HSP 20) can be used as early specific markers for diagnosing myocardial infarction in patients with acute coronary syndrome. Our hypothesis is supported by the following data: (I) HSP expression occurs very early after acute coronary events; (II) HSP concentrations increase rapidly in the peripheral blood; (III) HSP concentrations correlate with markers of myocardial necrosis and pro-inflammatory biochemical parameters. The magnitude of the increase in plasma HSP concentrations over initial concentrations during the period of highest sensitivity and specificity of the assay could be important for early detection of myocardial infarction and distinguishing it from unstable angina. We suggest that these parameters, along with close observation of patients with chest pain, will assist providers who must differentiate between acute myocardial damage and other organ diseases.

Grubic Z, Stingl K, Zunec R. Heterogeneity of HLA-DRB1*04 alleles and haplotypes in the Croatian population. *Tissue Antigens.* 2012; 80(3):219-23.

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Analysis of allele distribution at the HLA-DRB1*04 gene, as one of the frequent ones among Croatians, and their HLA-A-B-DRB1 haplotypes in the Croatian population was performed in this study. Using LABType® SSO and PCR-SSP method, 11 DRB1*04 subtypes were observed, of which DRB1*04:01 was the most frequent (28.0%) followed by DRB1*04:02 (26.3%), DRB1*04:03 (22.3%), and DRB1*04:04 (14.2%). The significant haplotypes (with highest P value) for given DRB1*04 allele were the following combinations: HLA-B*15:01-DRB1*04:01, HLA-B*38:01-DRB1*04:02, HLA-B*35:03-DRB1*04:03, HLA-B*35:03-DRB1*04:08, HLA-B*14:01-DRB1*04:04, and HLA-B*49-DRB1*04:05. Marked differences in the distribution of our most frequent haplotypes of HLA-B-DRB1*04 (HLA-B*38:01-DRB1*04:02 and HLA-B*15:01-DRB1*04:01) were found in comparison to other European populations investigated so far. Additionally, comparison of HLA-A-B-DRB1*04 haplotypes showed that although there are similarities in the haplotype structure between our and other populations, there are also noteworthy differences. In summary, the identification of conserved and unusual DRB1*04 haplotypes in

the present study of Croats should have important clinical implications for donor-recipient matching in the hematopoietic stem cell transplantation program, help in the understanding of HLA polymorphisms in different European populations, and also prove to be very useful in the determination of possible susceptibility genes involved in HLA-DRB1*04-associated diseases.

Sarac H, Markeljevic J, Mokrovic G, Erdeljic V, Bozina N, Cicin-Sain L. Platelet serotonin in primary Sjögren's syndrome: Level and relation with disease activity. J Neuroimmunol. 2012; 251(1-2):87-9.

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Primary Sjögren's syndrome (pSS) is chronic autoimmune disorder of unknown etiopathogenesis. In line with the concept of neuroimmunohormonal dysregulation in in-

flammatory rheumatic diseases, the aim of this study was to investigate platelet serotonin level (PSL) in patients with pSS and its relation with the activity and duration of the disease. Significantly lower PSL in pSS patients (N=61) was shown as compared to healthy controls (N=103). No correlation was found between PSL and the actual disease activity assessed by the recently developed EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). Results suggest involvement of the serotonin system in the pathogenesis of pSS.