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

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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 Q^2_{ext} =0.812 and Q^2_{ext} =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.

Key Words: Antitrypanosomal activity, QSAR, Structure-activity relationships, Thiazolidinones

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.]
Redox Biology 2017 Oct 26. pii: S2213-2317(17)30747-4. doi: 10.1016/j.redox.2017.10.001 (IF=6.337) (5-Year IF=6.899) Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.

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.

Key words: Reactive oxygen species Reactive nitrogen species Redox signaling Oxidative stress Antioxidants Redox therapeutics

A Helicobacter pylori-associated insulin resistance in asymptomatic sedentary young men does not correlate with inflammatory markers and urine levels of 8-iso-PGF2-α or 1,4-dihydroxynonane mercapturic acid

Cherkas A[1,2], Golota S[3], Abrahamovych O[1], Krupak V[4], Bugiichyk V[1,5], Yatskevych O[1], Pliatsko M[1][et al.]

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A potential contribution of H. pylori contamination to low-grade inflammation, oxidative stress (OS) and insulin resistance as well as correlations between these parameters in asymptomatic sedentary males was analysed. We enrolled 30 apparently healthy asymptomatic young subjects (18 H. pylori negative and 12 positive) and measured whole blood glucose, glycated haemoglobin, insulin, C-peptide, cortisol, aldosterone, testosterone, thyroid stimulating hormone, C-reactive protein, interleukins 6 and 10, TNF-alpha and comet assay. As markers of OS, we used urine levels of iso-PGF_2-α and 1,4-dihydroxynonane mercapturic acid (DHN-MA). Twofold elevation of fasting insulin level and HOMA index in H. pylori-positive subjects ($p < .05$) was shown. Inflammatory parameters and monocyte DNA damage, urine levels of DHN-MA and iso-PGF2-α did not show significant differences between the groups. The early stage of H. pylori-triggered metabolic derangements in sedentary subjects include development of insulin resistance in H. pylori-positive subjects; however, there is no evidence of systemic inflammatory and OS-related changes.

Key words: *Helicobacter pylori; inflammation; insulin resistance; oxidative stress; sedentary lifestyle.*

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. Oncogene advance online publication, 30 October 2017; doi:10.1038/onc.2017.392.

Flavonoids as detoxifying and pro-survival agents: What's new?

Lysiuk R[1][et al.]
Food and Chemical Toxicology 2017 Oct 24;110:240-250. doi: 10.1016/j.fct.2017.10.039 (IF=3.778) (5-Year IF=3.628)
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The role of flavonoids in the survival machinery of cells has come in the spotlight due to the recent evidence of their effect on the relationship mitochondria-ER stress-proteasome, including the intracellular mechanisms of autophagy and apoptosis. Numerous experimental animal investigations and even human clinical studies have highlighted the major role of these natural compounds in the economy of life and their deep relationship with autotrophic organisms in the evolutionary space. Their role as anti-oxidant and oxidative stress preventive molecules has to date been investigated extensively in the literature. Despite this great amount of promising evidence, many concerns, however, remain, most of which dealing with biochemistry, bioavailability, pharmacokinetics, and interaction of flavonoids with gut microbiome, issues that make difficult any good attempt to introduce these molecules in the human healthcare systems as possible, encouraging therapeutic substances. This review tries to address and elucidate these items.

Key words: *Anti-oxidants; Detoxification; Flavonoids; Oxidative stress response; Plant extracts.*

Hydrogen Sulfide Releasing 2-Mercaptoacrylic Acid-Based Derivative Possesses Cytoprotective Activity in a Small Intestine of Rats with Medication-Induced Enteropathy

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Small intestinal injury is known to be one of the most commonly appearing pathologies, resulting in the use of medications such as: nonsteroidal anti-inflammatory drugs (NSAIDs), antitumor drugs and angiotensin-converting enzyme (ACE) inhibitors. The principal objective of this study is to evaluate the action of a novel mercaptoacrylic acid derivative able to release H_2S on parameters of NO-synthase system and oxidative stress. Inducing enteropathy, three types of

medications were used: indomethacin, an NSAID (35 mg/kg); methotrexate, an antitumor drug (10 mg/kg); and enalapril, an ACE inhibitor (2 mg/kg/day). 2-[(4-chlorophenyl-carbamoyl)-methyl]-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-acrylic acid (2C3DHTA) was introduced based on the background of medication-induced enteropathy (10 mg/kg/day). The survey showed that malondialdehyde (MDA) concentration, myeloperoxidase (MPO) activity, superoxide dismutase (SOD), catalase, and NO-synthases (NOS) were determined in the small intestinal mucosa. The increase in inducible NO-synthase (iNOS) activity was due to indomethacin and methotrexate administration. Constitutive NO-synthase (cNOS) activity was decreased by an ACE-inhibitor. The cytoprotective effect was demonstrated by 2C3DHTA, which returned iNOS activity to its control level and increased cNOS activity. The enterotoxic action of studied medication was accompanied by the development of oxidative stress manifested, activity of MPO was increased. MPO activity and manifestations of oxidative stress were decreased by 2C3DHTA. Effects of 2C3DHTA can be explained by the action of H_2S, released from this compound in the gastrointestinal (GI) system.

Key words: *2-mercaptoacrylic acids; enteropathy; hydrogen sulfide; small intestine*

Targeted massively parallel sequencing characterises the mutation spectrum of PALB2 in breast and ovarian cancer cases from Poland and Ukraine

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Institute of Obstetrics and Emergency Medicine, University of Rzeszow, Rzeszow, Poland.

Loss-of-function germline mutations in the PALB2 gene are associated with an increase of breast cancer risk. The purpose of this study was to characterise the spectrum of PALB2 mutations in women affected with breast or ovarian cancer from South-West Poland and West Ukraine. 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 PALB2 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. Targeted-sequencing identified two frameshift deletions: PALB2:c.509_510del; p.R170Ifs in three women affected with breast cancer and PALB2:c.172_175del;p.Q60Rfs in one woman affected with ovarian cancer. A number of other previously described missense (some predicted to be damaging by PolyPhen-2 and CADD) and synonymous mutations were also identified in this population. This study is consistent with previous reports that PALB2:c.509_510del and PALB2:c.172_175del are recurrent mutations associated with breast cancer predisposition in Polish women with a family history of the disease. Our study contributes to the accumulating evidence indicating that PALB2 should be included in genetic testing for breast cancer susceptibility in these populations to enhance risk assessment and management of women at high-risk of developing breast cancer. This data could also contribute to ongoing work that is assessing the possible association between ovarian cancer risk and PALB2 mutations for which there is currently no evidence.

Key words: *Breast cancer; Genetic susceptibility; Massively parallel sequencing; Ovarian cancer; PALB2*

Anticancer properties of 4-thiazolidinone derivatives depend on peroxisome proliferator-activated receptor gamma (PPARγ)

Kaminskyy DV[1], Kryshchyshyn AP[1], Pinyazhko OR[2], Lesyk RB[1]
European Journal of Medicine Chemistry 2017 Dec 1;141:162-168. doi: 10.1016/j.ejmech.2017.09.071 (IF=4.519) (5-Year IF=4.187)
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Peroxisome proliferator-activated receptors (PPARs) play an important role in numerous chronic diseases such as diabetes, obesity, atherosclerosis and cancer, and PPAR modulators are among the approved drugs and drug-candidates for their treatment. The aim of this study was to elucidate the involvement of PPARs in the mechanism of cytotoxic and pro-apoptotic action of novel anticancer 4-thiazolidinone derivatives (Les-2194, Les-3377, Les-3640) and approved 4-thiazolidinones (Rosiglitazone, Pioglitazone) towards the human squamous carcinoma (SCC-15) cell line. Experiments with 4-thiazaolidinone derivatives and PPAR-specific siRNA were conducted and PPARα, PPARβ and PPARγ mRNA expression was studied. Moreover, after PPARα, PPARβ and PPARγ siRNA gene silencing, cell viability, cell metabolism and caspase-3 activity were measured. The results showed a decrease of mRNA expression of the studied PPARs in SCC-15 cells treated with 10 and 50 μM Les-2194, Les-3377 and Les-3640. PPARγ knockdown protected the cells from the cytotoxic effect of the tested compounds (50 μM). It was established that novel anticancer 4-thiazolidinone derivatives act mainly through the PPARγ pathway in SCC-15 cells. Our results suggest that all studied compounds act as PPARs agonists. Interestingly, silencing of PPARγ gene increases the expression of PPARα, PPARβ mRNA in SCC-15 cells. The anticancer potential of new studied compounds was more expressed as compared to Rosiglitazone and Pioglitazone.

Key words: *Cytotoxicity; PPARs; SCC-15; Thiazolidinone; Thiazolothiopyranes*

Recent developments with rhodanine as a scaffold for drug discovery

Kaminskyy D[1], Kryshchyshyn A[1], Lesyk R[1]
Expert Opin Drug Discov. 2017 Dec;12(12):1233-1252. doi: 10.1080/17460441.2017.1388370
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INTRODUCTION*:* Rhodanines, as one of the 4-thiazolidinones subtypes, are recognized as privileged heterocycles in medicinal chemistry. The main achievements include the development of drug-like molecules with numerous biological activities as well as approved drugs. Among rhodanines, 5-ene-rhodanines are of special interest, and are often claimed as pan assay interference compounds due to Michael acceptor functionality. Areas covered: Herein, the synthetic protocols for rhodanines and their transformation are reviewed. Biological activity is briefly discussed as well as biotargets, mode of actions and optimization directions. Furthermore, the utilization of 5-ene-rhodanines in Michael additions are discussed while both pro and contra arguments have been outlined within medicinal chemistry application. Expert opinion: Rhodanines remain privileged heterocycles in drug discovery. They are accessible building blocks for optimization and transformation into related heterocycles, simplified analogues and fused heterocycles with a thiazolidine framework. Michael acceptor functionality, as well as the thesis about low selectivity towards biotargets of rhodanines, must be confirmed experimentally and it cannot be based on just the presence of conjugated α,β-unsaturated carbonyl. Moreover, the positive aspects of Michael acceptors must be considered as well as their multitarget properties. New criteria for target affinity must be found. In conclusion, rhodanines are generally not problematic per se.

Key words: 4-thiazolidinone; Michael acceptor; PAINS; Rhodanine

Lysosome-Targeting Amplifiers of Reactive Oxygen Species as Anticancer Prodrugs

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Cancer cells produce elevated levels of reactive oxygen species, which has been used to design cancer specific prodrugs. Their activation relies on at least a bimolecular process, in which a prodrug reacts with ROS. However, at low micromolar concentrations of the prodrugs and ROS, the activation is usually inefficient. Herein, we propose and validate a potentially general approach for solving this intrinsic problem of ROS-dependent prodrugs. In particular, known prodrug 4-(N-ferrocenyl-N-benzylaminocarbonyloxymethyl)phenylboronic acid pinacol ester was converted into its lysosome-specific analogue. Since lysosomes contain a higher concentration of active ROS than the cytoplasm, activation of the prodrug was facilitated with respect to the parent compound. Moreover, it was found to exhibit high anticancer activity in a variety of cancer cell lines (IC50 =3.5-7.2 μm) and in vivo (40 mg kg-1 , NK/Ly murine model) but remained weakly toxic towards non-malignant cells (IC50 =15-30 μm).

Key words**:** *aminoferrocene; cancer; lysosomes; prodrugs; reactive oxygen species*

5-Ene-4-thiazolidinones - An efficient tool in medicinal chemistry

Kaminskyy D[1], Kryshchyshyn A[1], Lesyk R.[2]
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The presented review is an attempt to summarize a huge volume of data on 5-ene-4-thiazolidinones being a widely studied class of small molecules used in modern organic and medicinal chemistry. The manuscript covers approaches to the synthesis of 5-ene-4-thiazolidinone derivatives: modification of the C5 position of the basic core; synthesis of the target compounds in the one-pot or multistage reactions or transformation of other related heterocycles. The most prominent pharmacological profiles of 5-ene derivatives of different 4-thiazolidinone subtypes belonging to hit-, lead-compounds, drug-candidates and drugs as well as the most studied targets have been discussed. Currently target compounds (especially 5-en-rhodanines) are assigned as frequent hitters or pan-assay interference compounds (PAINS) within high-throughput screening campaigns. Nevertheless, the crucial impact of the presence/nature of C5 substituent (namely 5-ene) on the pharmacological effects of 5-ene-4-thiazolidinones was confirmed by the numerous listed findings from the original articles. The main directions for active 5-ene-4-thiazolidinones optimization have been shown: i) complication of the fragment in the C5 position; ii) introduction of the substituents in the N3 position (especially fragments with carboxylic group or its derivatives); iii) annealing in complex heterocyclic systems; iv) combination with other pharmacologically attractive fragments within hybrid pharmacophore approach. Moreover, the utilization of 5-ene-4-thiazolidinones in the synthesis of complex compounds with potent pharmacological application is described. The chemical transformations cover mainly the reactions which involve the exocyclic double bond in C5 position of the main core and correspond to the abovementioned direction of the 5-ene-4-thiazolidinone modification.

Key words: 5-Ene-4-thiazolidinones; Biological activity; Synthesis

Flexible Nanoholey Patches for Antibiotic-Free Treatments of Skin Infections

Dumych T[1], Paryzhak S[1], Vovk V[1], Bilyy RO[1] [et al.]
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doi: 10.1021/acsami.7b12949 (IF=7.504)
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Despite the availability of different antibiotics, bacterial infections are still one of the leading causes of hospitalization and mortality. The clinical failure of antibiotic treatment is due to a general poor antibiotic penetration to bacterial infection sites as well as the development of antibiotic-resistant pathogens. In the case of skin infection, the wound is covered by exudate, making it impermeable to topical antibiotics. The development of a flexible patch allowing a rapid and highly efficient treatment of subcutaneous wound infections via photothermal irradiation is presented here. The skin patch combines the near-infrared photothermal properties of a gold nanohole array formed by self-assembly of colloidal structures on flexible polyimide films with that of reduced graphene oxide nanosheets for laser-gated pathogen inactivation. In vivo tests performed on mice with subcutaneous skin infection and treated with the photothermal skin patch show wound healing of the infected site, while nontreated areas result in necrotic muscular fibers and bacterial infiltrate. No loss in efficiency is observed upon multiple use of these patches during in vivo experiments because of their robustness.

Key words: *bacteria ablation; gold nanoholes; in vivo treatment; photothermal therapy; polyimide; reduced graphene oxide; wound infection*

Comparison of using different bridge prosthetic designs for partial defect restoration through mathematical modeling

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EJD European Journal of Dentistry 2017 Jul-Sep;11(3):345-351. doi: 10.4103/ejd.ejd_72_17
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OBJECTIVE: To analyze the stress-strain states of bone and abutment teeth during the use of different prosthetic designs of fixed partial dentures with the use of relevant mathematical modeling principles.

MATERIALS AND METHODS: The use of Comsol Multiphysics 3.5 (Comsol AB, Sweden) software during the mathematical modeling of stress-strain states provided numerical data for analytical interpretation in three different clinical scenarios with fixed dentures and different abutment teeth and demountable prosthetic denture with the saddle-shaped intermediate part.

STATISTICAL ANALYSIS USED: Microsoft Excel Software (Microsoft Office 2017) helped to evaluate absolute mistakes of stress and strain parameters of each abutment tooth during three modeled scenarios and normal condition and to summarize data into the forms of tables.

RESULTS: In comparison with the fixed prosthetic denture supported by the canine, first premolar, and third molar, stresses at the same abutment teeth with the use of demountable denture with the saddle-shaped intermediate part decreased: at the mesial abutment tooth by 2.8 times, at distal crown by 6.1 times, and at the intermediate part by 11.1 times, respectively, the deformation level decreased by 3.1, 1.9, and 1.4 times at each area.

CONCLUSIONS: The methods of mathematical modeling proved that complications during the use of fixed partial dentures based on the overload effect of the abutment teeth and caused by the deformation process inside the intermediate section of prosthetic construction.

Key words: Dental rehabilitation; mathematical modeling; prosthetic bridges design

Diagnosis and treatment of gastroesophageal reflux disease complicated by Barrett's esophagus

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Pol Przegl Chir. 2017 Aug 31;89(4):29-32. doi: 10.5604/01.3001.0010.3908
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The aim of the study was to evaluate the effectiveness of a diagnostic and therapeutic algorithm for gastroesophageal reflux disease complicated by Barrett's esophagus in 46 patients.

MATERIALS AND METHODS: A diagnostic and therapeutic algorithm for complicated GERD was developed. To describe the changes in the esophagus with reflux esophagitis, the Los Angeles classification was used. Intestinal metaplasia of the epithelium in the lower third of the esophagus was assessed using videoendoscopy, chromoscopy, and biopsy. Quality of life was assessed with the Gastro-Intestinal Quality of Life Index. The used methods were modeling, clinical, analytical, comparative, standardized, and questionnaire-based. Results and their discussion. Among the complications of GERD, Barrett's esophagus was diagnosed in 9 (19.6 %), peptic ulcer in the esophagus in 10 (21.7 %), peptic stricture of the esophagus in 4 (8.7 %), esophageal-gastric bleeding in 23 (50.0 %), including Malory-Weiss syndrome in 18, and erosive ulcerous bleeding in 5 people. Hiatal hernia was diagnosed in 171 (87.7 %) patients (sliding in 157 (91.8%), paraesophageal hernia in 2 (1.2%), and mixed hernia in 12 (7.0%) cases). One hundred ninety-five patients underwent laparoscopic surgery. Nissen fundoplication was conducted in 176 (90.2%) patients, Toupet fundoplication in 14 (7.2%), and Dor fundoplication in 5 (2.6%). It was established that the use of the diagnostic and treatment algorithm promoted systematization and objectification of changes in complicated GERD, contributed to early diagnosis, helped in choosing treatment, and improved quality of life.

CONCLUSIONS: Argon coagulation and use of PPIs for 8-12 weeks before surgery led to the regeneration of the mucous membrane in the esophagus. The developed diagnostic and therapeutic algorithm facilitated systematization and objectification of changes in complicated GERD, contributed to early diagnosis, helped in choosing treatment, and improved quality of life.

Key words: Barrett's esophagus; complications; gastroesophageal reflux disease

ESVM guidelines - the diagnosis and management of Raynaud's phenomenon

Chraim A[1][et al.]
Vasa: Europian Journal of Vascular Medicine 2017 Oct;46(6):413-423.
doi: 10.1024/0301-1526/a000661
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Regarding the clinical diagnosis of Raynaud's phenomenon and its associated conditions, investigations and treatment are substantial, and yet no international consensus has been published regarding the medical management of patients presenting with this condition. Most knowledge on this topic derives from epidemiological surveys and observational studies; few randomized studies are available, almost all relating to drug treatment, and thus these guidelines were developed as an expert consensus document to aid in the diagnosis and management of Raynaud's phenomenon. This consensus document starts with a clarification about the definition and terminology of Raynaud's phenomenon and covers the differential and aetiological diagnoses as well as the symptomatic treatment.

Key words: *Raynaud's; hand arm vibration; systemic sclerosis; vasospasm*

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

Dubey L[1] [et al.]
Haemophilia. 2017 Aug 16. doi: 10.1111/hae.13320 (IF=3.569)
Western Ukrainian Specialized Children's Medical Centre, Lviv, Ukraine.

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® .

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

2017 update of the WSES guidelines for emergency repair of complicated abdominal wall hernias

Gerych I[1] [et al.]
World Journal of Emergency Surgery 2017 Aug 7;12:37. doi: 10.1186/s13017-017-0149-y. eCollection 2017 (IF=2.282)
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Emergency repair of complicated abdominal wall hernias may be associated with worsen outcome and a significant rate of postoperative complications. There is no consensus on management of complicated abdominal hernias. The main matter of debate is about the use of mesh in case of intestinal resection and the type of mesh to be used. Wound infection is the most common complication encountered and represents an immense burden especially in the presence of a mesh. The recurrence rate is an important topic that influences the final outcome. A World Society of Emergency Surgery (WSES) Consensus Conference was held in Bergamo in July 2013

with the aim to define recommendations for emergency repair of abdominal wall hernias in adults. This document represents the executive summary of the consensus conference approved by a WSES expert panel. In 2016, the guidelines have been revised and updated according to the most recent available literature.

Key words: *Abdominal wall hernia; Biologic mesh; Bowel resection; Contaminated wound; Emergency surgery; Hernia repair; Incarcerated hernia; Infected field; Mesh repair; Strangulated hernia*

A Multicentre Study on the Efficacy, Safety and Pharmacokinetics of IqYmune®, a Highly Purified 10% Liquid Intravenous Immunoglobulin, in Patients with Primary Immune Deficiency

Kostyuchenko L[1][et al.]
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This multicentre, open-label, prospective, single-arm study was designed to evaluate the efficacy, pharmacokinetics, and safety of IqYmune®, a highly purified 10% polyvalent immunoglobulin preparation for intravenous administration in patients with primary immunodeficiency. IqYmune® was administered to 62 patients (aged 2-61 years) with X-linked agammaglobulinemia or common variable immune deficiency at a dose from 0.22 to 0.97 g/kg every 3 to 4 weeks for 12 months with an infusion rate up to 8 mL/kg/h. A pharmacokinetic study was performed at steady state between the 8th and the 9th infusion. A single case of serious bacterial infection was observed, leading to an annualized rate of serious bacterial infections/patient (primary endpoint) of 0.017 (98% CI: 0.000, 0.115). Overall, 228 infections were reported, most frequently bronchitis, chronic sinusitis, nasopharyngitis and upper respiratory tract infection. The mean annualized rate of infections was 3.79/patient. A lower risk of infections was associated with an IgG trough level > 8 g/L (p = 0.01). The mean annualized durations of absence from work or school and of hospitalization due to infections were 1.01 and 0.89 days/patient, respectively. The mean serum IgG trough level before the 6th infusion was 7.73 g/L after a mean dose of IqYmune® of 0.57 g/kg. The pharmacokinetic profile of IqYmune® was consistent with that of other intravenous immunoglobulins. Overall, 15.5% of infusions were associated with an adverse event occurring within 72 h post infusion. Headache was the most common adverse event. In conclusion, IqYmune® was shown to be effective and well tolerated in patients with primary immunodeficiency.

Key words: *Clinical trials; IVIg; Immunoglobulins*

Partial Characterization of Tick-Borne Encephalitis Virus Isolates from Ticks of Southern Ukraine

Vynograd NO[1][et al.]
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Tick-borne encephalitis (TBE) is the most common tick-borne viral infection in Eurasia; thousands of human cases are annually reported from several European countries. Several tick species are vectors of the tick-borne encephalitis virus (TBEV), while TBE appears to be spreading from the Eurasian continent westward to Europe. Fifteen study sites were chosen from five territories of southern Ukraine, including Odessa, Mykolaiv, Kherson Oblast, the Autonomous Republic of Crimea, and Sevastopol. Tick collection was performed in spring season of three

consecutive years (1988-1990) using either flagging technique or direct collection of specimens feeding on cattle. A total of 15,243 tick imagoes and nymphs were collected from nine species, including Dermacentor marginatus, D. reticulatus, Haemaphysalis parva, H. punctata, Hyalomma marginatum, Ixodes ricinus, Rhipicephalus bursa, R. rossicus, and R. sanguineus, pooled in 282 monospecific samples. Supernatant of grinded pool was used for inoculation to suckling mice for virus isolation. Eight TBEV isolates were identified from ticks among six study sites. Ticks showed a minimum infection rate from 0.11% to 0.81%. Phylogenetic analysis of the envelope (E) protein gene of seven isolates, assigned all to the European subtype (TBEV-Eu) showing a maximum identity of 97.17% to the "Pan" TBEV-Eu reference strain. Compared to 104 TBEV-Eu isolates they clustered within the same clade as the Pan reference strain and distinguished from other TBEV-Eu isolates. Amino acid sequence analysis of the South Ukrainian TBEV-Eu isolates revealed the presence of four amino acid substitutions 67 (N), 266 (R), 306 (V), and 407 (R), in the ectodomains II and III and in the stem-anchor region of the E protein gene. This study confirmed TBEV-Eu subtype distribution in the southern region of Ukraine, which eventually overlaps with TBEV-FE (Far Eastern subtype) and TBEV-Sib (Siberian subtype) domains, showing the heterogeneity of TBEV circulating in Ukraine.

Key words: *Ukraine; envelope protein; nucleotide sequencing; phylogenetic analysis; tick-borne encephalitis virus*

European contribution to the study of ROS: A summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS)

Kaminskyy D[1], Semen K[1], Yelisyeyeva O[1][et al.]
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The European Cooperation in Science and Technology (COST) provides an ideal framework to establish multi-disciplinary 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.

Key words: *Antioxidants; Oxidative stress; Reactive nitrogen species; Reactive oxygen species; Redox signaling; Redox therapeutics*

Registries on peritoneal surface malignancies throughout the world, their use and their options

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AIM:
The treatment of peritoneal surface malignancies ranges from palliative care to full cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy, HIPEC. Ongoing monitoring of patient recruitment and volume is usually carried out through dedicated registries. With multiple registries available worldwide, we sought to investigate the nature, extent and value of existing worldwide CRS and HIPEC registries.

METHODS:
A questionnaire was sent out to all known major treatment centres. The questionnaire covers: general purpose of the registry; inclusion criteria in the registry; the date the registry was first established; volume of patients in the registry and description of the data fields in the registries. Finally, the population size of the catchment area of the registry was collected.

RESULTS:
Twenty-seven questionnaires where returned. National databases are established in northwest European countries. There are five international general databases. Most database collect data on patients who have undergone an attempt to CRS and HIPEC. Two registries collect data on all patients with peritoneal carcinomatosis regardless the treatment. Most registries are primarily used for tracking outcomes and complications. When correlating the number of cases of CRS and HIPEC that are performed to the catchment area of the various registry, a large variation in the number of performed procedures related to the overall population was noted, ranging from 1.3 to 57 patients/million year with an average of 15 patients/1 million year.

CONCLUSIONS:
CRS and HIPEC is a well-established treatment for peritoneal surface malignancies worldwide. However, the coverage as well as the registration of treatment procedures differs widely. The most striking difference is the proportion of HIPEC procedures per capita which ranges from 1.3 to 57 patients per million. This suggests either a difference in patient selection, lack of access to HIPEC centres or lack of appropriate data collection.

Key words: *HIPEC; peritoneal surface malignancy; registration study.*

Altered glycan accessibility on native immunoglobulin G complexes in early rheumatoid arthritis and its changes during therapy

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The goal of this study was to investigate the glycosylation profile of native immunoglobulin (Ig) G present in serum immune complexes in patients with rheumatoid arthritis (RA). To accomplish this, lectin binding assays, detecting the accessibility of glycans present on IgG-containing immune complexes by biotinylated lectins, were employed. Lectins capturing fucosyl residues (AAL), fucosylated tri-mannose N-glycan core sites (LCA), terminal sialic acid residues (SNA) and O-glycosidically linked galactose/N-acetylgalactosamine (GalNac-L) were used. Patients with

recent-onset RA at baseline and after 3-year follow-up were investigated. We found that native IgG was complexed significantly more often with IgM, C1q, C3c and C-reactive protein (CRP) in RA patients, suggesting alterations of the native structure of IgG. The total accessibility of fucose residues on captured immune complexes to the respective lectin was significantly higher in patients with RA. Moreover, fucose accessibility on IgG-containing immune complexes correlated positively with the levels of antibodies to cyclic citrullinated peptides (anti-CCP). We also observed a significantly higher accessibility to sialic acid residues and galactose/GalNAc glyco-epitopes in native complexed IgG of patients with RA at baseline. While sialic acid accessibility increased during treatment, the accessibility of galactose/GalNAc decreased. Hence, successful treatment of RA was associated with an increase in the SNA/GalNAc-L ratio. Interestingly, the SNA/GalNAc-L ratio in particular rises after glucocorticoid treatment. In summary, this study shows the exposure of glycans in native complexed IgG of patients with early RA, revealing particular glycosylation patterns and its changes following pharmaceutical treatment.

Key words: *Aleura aurantia; GalNAc-L; Sambucus nigra; immune complex; lectin ELISA; rheumatoid arthritis*

A blind spot on the global mental health map: a scoping review of 25 years' development of mental health care for people with severe mental illnesses in central and eastern Europe

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Just over 25 years have passed since the major sociopolitical changes in central and eastern Europe; our aim was to map and analyse the development of mental health-care practice for people with severe mental illnesses in this region since then. A scoping review was complemented by an expert survey in 24 countries. Mental health-care practice in the region differs greatly across as well as within individual countries. National policies often exist but reforms remain mostly in the realm of aspiration. Services are predominantly based in psychiatric hospitals. Decision making on resource allocation is not transparent, and full economic evaluations of complex interventions and rigorous epidemiological studies are lacking. Stigma seems to be higher than in other European countries, but consideration of human rights and user involvement are increasing. The region has seen respectable development, which happened because of grassroots initiatives supported by international organisations, rather than by systematic implementation of government policies.

Nanoscale Observation of Dehydration Process in PHEMA Hydrogel Structure

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One of the most important field of interest in respect to hydrogel materials is their capability to water storage. The problem mentioned above plays an important role regarding to diffusion of fluid media containing nanoparticles, what is very useful in biomedical applications, such as artificial polymeric implants, drug delivery systems or tissue engineering.In presented work, dehydration process in hydrogels used in ophthalmology as intraocular lenses was observed. Before measurements studied materials were immersed in deionized water and saline solution to obtain equilibrium swelling state. Studies of the dehydration process were carried out by use of

gravimetric analysis, Fourier-Transform Infrared and Positron Annihilation Lifetime Spectroscopy. Obtained results revealed changes in hydrogen bonding structure and free volume holes induced by saline solution ingredients.

Key words: *Dehydration; FTIR; Free volume; Hydrogen bonding; PALS; PHEMA*

Light-Curing Volumetric Shrinkage in Dimethacrylate-Based Dental Composites by Nanoindentation and PAL Study

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Light-curing volumetric shrinkage in dimethacrylate-based dental resin composites Dipol® is examined through comprehensive kinetics research employing nanoindentation measurements and nanoscale atomic-deficient study with lifetime spectroscopy of annihilating positrons. Photopolymerization kinetics determined through nanoindentation testing is shown to be described via single-exponential relaxation function with character time constants reaching respectively 15.0 and 18.7 s for nanohardness and elastic modulus. Atomic-deficient characteristics of composites are extracted from positron lifetime spectra parameterized employing unconstrained x3-term fitting. The tested photopolymerization kinetics can be adequately reflected in time-dependent changes observed in average positron lifetime (with 17.9 s time constant) and fractional free volume of positronium traps (with 18.6 s time constant). This correlation proves that fragmentation of free-volume positronium-trapping sites accompanied by partial positronium-to-positron traps conversion determines the light-curing volumetric shrinkage in the studied composites.

Key words: *Composites; Filler; Light curing; Nanoindentation; Positron annihilation; Trapping*

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