Abbreviations: DILI; drug-induced liver injury, mtDNA; mitochondrial DNA,

235 Evaluation of the risk of Denosumab-Associated Hypocalcaemia

A. Krahenbule[1], A. Morel[1], L. Aubert[1], B. Azzouz[1], **T. Trenque**

[1]*Regional Center of Pharmacovigilance and Pharmacoepidemiology, Reims, France*

Background: Denosumab is a human monoclonal antibody working through inhibition of RANK-ligand osteoclast-mediated bone resorption. As such, it is used to prevent complications of osteoporosis, bone metastasis and giant cells tumors. However, a trade-off from this action is an increased risk of occurrence of denosumab-associated hypocalcaemia (DAH), which can lead to serious complications.
Objective: The present study aimed to evaluate the risk of hypocalcaemia associated with the intake of denosumab.
Method: All cases of adverse drug reactions including hypocalcaemia with denosumab reported to the French Pharmacovigilance Database from 1985 to the 31st of March 2017 were reviewed. Demographic and medical information were analyzed. Renal failure, a known risk factor for DAH, also was documented. The association between reported cases of hypocalcaemia and denosumab use was assessed using Reporting Odds Ratio (ROR) with 95% confidence interval.
Results: 543 cases of hypocalcemia were collected in the database of which 53 with denosumab. Patients had a mean age of 70.36 years, males and females were represented in similar proportions (27 females, 25 males and 1 unknown). Concerning risk factors, renal failure was identified in 22 cases (41.5%) and severe renal failure (defined as a renal creatinine clearance inferior to 30 ml/min) in 7 cases (13.2%). Hypocalcaemia was significantly associated with the use of denosumab, ROR = 191.93 [142.04-259.33].
Conclusion: This study, performed on a large national pharmacovigilance database, implies the existence of a very significant risk of hypocalcaemia associated with the use of denosumab. Hypocalcaemia is a known side effect of denosumab, however, the extreme value of ROR found in this study implies its potential underestimation. Hypocalcaemia can lead to serious complications and a risk-benefit ratio assessment, as well as close monitoring of patients under denosumab, especially if they suffer from renal failure, is strongly recommended.

236 Evaluation of the first EU-wide social media ADR awareness week: 7–11 November 2016

M. Jadeja[1]

[1]*MHRA, London, UK*

Background: A Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action project survey found only four EU National Competent Authorities (NCAs) used social media to promote ADR reporting [1]. A key deliverable from this SCOPE awareness levels topic, led by the Medicines and Healthcare products Regulatory Agency (MHRA), was to develop a media toolkit to support NCAs promote suspected ADR reporting nationally. Underreporting is a known limitation of spontaneous ADR reporting systems and is linked to awareness levels.
Objective/Aim: To develop and run an EU-wide social media campaign to increase ADR reporting by 5% using SCOPE materials and measure its effectiveness to provide insight into future campaigns [2].
Methods: SCOPE developed a media toolkit of campaign collateral for NCAs consisting of animations and infographics [3,4]. The ADR awareness week took place between 7 and 11 November 2016. To support NCAs, a template press release; campaign guide; and a running plan were developed and shared. NCAs were able to adapt to suit these to their own needs. The campaign plan was developed and led by MHRA and formalised via the Heads of Medicines Agency Working Group for Communications Professionals (HMA WGCP). Participation was encouraged through SCOPE meetings and HMAWGCP. Social media channels used: LinkedIn, Facebook, YouTube, Twitter and websites. Audiences included patients, public and healthcare professionals. Participating NCAs monitored campaign impact and reported their findings to MHRA, including changes reporting compared to a baseline.
Results: 21 NCAs participated with common ADR messages. SCOPE produced 24 different versions of tailored collateral in different languages for NCAs and stakeholders such as the European Medicines Agency, the European Commission and patient organisations. Between 15 NCAs there was a 13% increase in suspected ADR reporting (1056 reports). The campaign reached 2562,071 people; 337,781 viewed animation; 22,584 likes, clicks, retweets and shares. A multitude of stakeholders were engaged to disseminate messages. Feedback on what worked well and improvements were analysed. All respondents indicated it was worthwhile running.
Conclusion: The SCOPE ADR awareness week campaign was a significant success despite being the first of its kind. Recommendations include consideration of more frequent social media use and further working together between NCAs to make this an annual ADR awareness week at a global level to encourage suspected ADR reporting for an improved and a larger data pool for signal detection.
Further sources of information/References:

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237 Mechanisms of Chemotherapy-Induced Diarrhoea

S. French[1], A. Davies[1], M. Pirmohamed[1]

[1]*University of Liverpool, Liverpool, UK*

Background: Lower gastrointestinal toxicity—which presents clinically as diarrhoea and colitis—is a prevalent adverse event occurring during chemotherapeutic treatment. In addition to decreasing treatment efficacy and patient quality of life, it contributes to the economic burden on the NHS due to patient hospitalization and subsequent complications. Tyrosine kinase inhibitors are a broad class of chemotherapeutic agents for which this is a major problem. For example Bcr-Abl inhibitors used for the treatment of chronic myeloid leukaemia induce diarrhoea with a frequency of 70 and 25% for bosutinib and imatinib, respectively [1]. However, the mechanistic basis of this remains poorly understood.
Objective/Aim: Determine the processes involved in Bcr-Abl inhibitor-induced diarrhoea
Methods: Caco-2 (human colorectal cancer) cells, which differentiate into monolayers of polarised enterocytes, were utilized as an *in vitro* model.

Cells were seeded into transwells which enable changes in paracellular permeability to be determined by measuring electrical resistance and flux of FITC-dextran, a fluorescently labelled polysaccharide, across the monolayer. Changes in gene expression, protein levels and protein localization were studied using RTqPCR, immunoblotting and immunocytofluorescence, respectively.

Results: Sub-apoptotic concentrations of bosutinib increased paracellular permeability of Caco-2 monolayers to ions and FITC-dextran (ANOVA, $p < 0.0001$), whilst imatinib was less effective at inducing this change (ANOVA, $p < 0.001$). Bosutinib decreased protein levels (ANOVA, $p < 0.05$), but not RNA levels, of cell junction protein E-cadherin—a transmembrane protein already implicated in tyrosine kinase inhibitor-induced diarrhoea [2,3]. In addition, mislocalization of E-cadherin was observed after bosutinib treatment. These changes were not seen for imatinib. As ER stress is involved in E-cadherin degradation induced by another tyrosine kinase inhibitor (erlotinib) [3], the role of ER stress in bosutinib-induced E-cadherin decrease was investigated. However, no increase in ER stress markers were detected after bosutinib or imatinib treatment.

Conclusion: Decreased intestinal barrier integrity, potentially mediated by E-cadherin degradation, is likely an important factor in the aetiology of bosutinib-induced diarrhoea. This information will provide useful for identification and development of better treatments for this gastrointestinal adverse event.

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238 Whole exome sequencing in individuals with statin-induced myopathy

K.M. Bloch[1], D. Carr[1], M. Pirmohamed[1], A. Morris[1], C. Maroteau[2], N. Eriksson[3], M. Wadelius[3], C. Palmer[2], A. Alfirevic[1]

[1]University of Liverpool, Liverpool, UK, [2]Dundee University, Dundee, UK, [3]Uppsala University, Uppsala, Sweden

Background: Statins are widely used lipid-lowering drugs that are effective in reducing cardiovascular disease risk. Although they are safe and effective in the majority of patients, they can cause muscle toxicity. The clinical spectrum of statin-induced myotoxicity varies from asymptomatic elevations of creatine kinase (CK), to muscle pain or weakness with raised CK levels and rhabdomyolysis. The precise mechanisms underlying statin myotoxicity are unknown, but several hypotheses have been suggested including alterations in myocyte membrane cholesterol, depletion of isoprenoids, depletion of ubiquinone or coenzyme Q10 and genetics such as a strong association between simvastatin-associated myopathy and the common polymorphisms in *SLCO1B1,* a solute carrier organic anion transporter has been identified [1].

Objective: The objective of the study is to try to identify genetic risk factors that are responsible for statin-induced myopathy.

Methods: We standardized nomenclature (SRM1-SRM6) and phenotypic definitions of statin-induced muscle toxicity [2] and recruited 779 Caucasian patients on statins (Table 1). Most of our patients were on simvastatin (N = 511; 66%) and atorvastatin (N = 201; 26%). We performed exome sequencing in 779 patients; 245 with statin-induced toxicity (SRM3-SRM6) and 534 tolerant controls. DNA libraries from each sample were pooled for exome capturing using the SureSelect v5 all-exon probe set (Illumina). Sequencing was performed with paired-end 2×125 base reads on the Illumina HiSeq 2500 platform. The data was aligned to indexed reference genome hg19/GRCh37 using BWA, indel realignment, base quality score recalibration and variant calling were performed using Genome Analysis Toolkit (GATK) v.3.5 HaplotypeCaller. The single variant and gene-based analyses were performed using EPACTS.

Results and Conclusion: We have identified IPO9, CELF2, SIN3A and DOCK1 as top significant genes. Future work will include validation of the findings and a collaborative meta-analysis of whole exome sequencing with the US cohort.

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	Mild (SRM 3)	Severe (SRM4, SRM5)	Autoimmune (SRM 6)	TOTAL
Case	146	91	8	245
Control	NA	NA	NA	534
TOTAL	146	91	8	779

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239 A Description of New Safety Signals Detected and Assessed by PRAC at EU level in 2014–2016

A. Mahalean[1], **A. Farcas[1]**

[1]Drug Information Research Center, University of Medicine and Pharmacy, Cluj-Napoca, Romania

Background: Safety monitoring of all drugs throughout their entire life-cycle, in order to assure that the benefit-risk balance remains positive, is mandatory in order to protect the public health. New potential risks or changes in known risks arising from different sources are evaluated through the signal management process. At EU level the Pharmacovigilance Risk Assessment Committee (PRAC) is mandated to assess signals and make recommendations for action following the signal assessment.

Objective: To describe all new signals detected and assessed at EU level in 2014–2016.

Methods: Publicly available data on signals assessment and prioritization from PRAC meeting minutes for the period January 2014-December 2016 were collected, analyzed and classified according to predefined criteria (e.g. drug evaluated, type of signal, signal source, PRAC final recommendation).

Results: 190 new signals for 157 drugs/drugs associations/therapeutic classes, were evaluated by PRAC in this study's timeframe. 122 new signals