1000

Prenatal and Infant Exposure to Acid-Suppressive Medications and Allergic Diseases in Children: A Nationwide Cohort Study with Sibling-Matched Analysis

Dr Yunha Noh[1], Han Eol Jeong[1], Ahhyung Choi[1], Eun-Young Choi[1], Björn Pasternak[2], Hedvig Nordeng[3], Mette Bliddal[4], Kenneth Man[5], Ian Wong[5], Dong Keon Yon[6], Ju-Young Shin[1]

[1]Sungkyunkwan University, South Korea, [2]Karolinska Institutet, Sweden, [3]University of Oslo, Norway, [4]University of Sourthern Denmark, Denmark, [5]University College London, UK, [6]Kyung Hee University College of Medicine, South Korea

Aim/Objective: Existing data have indicated positive associations of childhood allergic disease with acid-suppressive medication (ASM) use in fetal and early life; however, no study to date has accounted for confounding by indications or within-familial factors. We evaluated the association of prenatal or infant exposure to ASM with the risk of allergic disease in children.

Methods: Using Korea's mother-child linked healthcare database, we included women who gave live birth during 2008-2018 and their children. ASM exposure was defined as having ≥1 PPI or H2RA prescriptions, during pregnancy and the first six months of life, for prenatal and infant exposure analyses, respectively; the reference was unexposed. Study outcomes were composite and individual outcomes for allergic disease (asthma, allergic rhinitis, atopic dermatitis, and food allergy) in children and followed up to 13 years of age. Hazard ratios (HR) were estimated using Cox proportional hazard model in propensity score (PS) matching and sibling analysis to control potential clinical and unmeasured within-familial confounders.

Results: Prenatal exposure analyses included 3,904,536 mother-child pairs; 881,639 (22.6%) were prenatally exposed to ASMs. Adjusted HRs were 1.01 (95% CI 1.01-1.02) for allergic disease overall (individual outcomes ranged 1.02-1.03) in PS-matched analyses; all outcomes were statistically non-significant in sibling analyses. Infant exposure analyses included 2,923,120 mother-child pairs; 69,124 (2.4%) were exposed to ASMs during infnacy. Adjusted HRs were 1.05 (1.04-1.07) for allergic disease overall (asthma [1.12, 1.10-1.14], allergic rhinitis [1.02, 1.01-1.03], atopic dermatitis [1.05, 1.02-1.08], and food allergy [1.32, 1.11-1.58]) in PS-matched analyses; asthma risks (1.17, 1.12-1.22) remained significantly increased in sibling analyses.

Conclusion: Our findings suggest no association between prenatal exposure to ASMs and allergic disease in offspring. However, we found a positive association of asthma with infant exposure to ASM, implying that ASMs should be used in children only when clearly indicated.

Keywords: Acid-suppressive drugs, allergic disease, pregnancy, infancy

1001

Association Between Prenatal Exposure to Sedatives and Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder

Miss Adrienne Chan[1,2,3], Le Gao[2], Prof Louise M Howard[4], Prof Emily Simonoff[5], Prof Dave Coghill[6], Dr Patrick Ip[7,9], Dr Wallis CY Lau[2,3,8], Prof Katja Taxis[1], Prof Ian CK Wong[2,3,8], Dr Kenneth KC Man[2,3,8]

[1]Groningen Research Institute of Pharmacy, Unit of PharmacoTherapy, Epidemiology and Economics, University of Groningen, The Netherlands, [2]Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, [3]Laboratory of Data Discovery for Health, Hong Kong Science Park, Hong Kong, [4]Section of Women's Mental Health, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [5]Department of Child and Adolescent Psychiatry, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, United Kingdom, [6]Departments of Paediatrics and Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, VIC Australia, [7]Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong[8], Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom, [9]Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong

Aim/Objective: To evaluate the association between prenatal sedative use and the risk of adverse birth and neurodevelopmental outcomes.

Methods: This cohort study included children born between 2001 and 2018 in Hong Kong. Primary analyses compared gestationally exposed and gestationally nonexposed individuals to estimate the odds ratios of preterm birth and small for gestational age, and hazard ratios of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) through logistic/Cox proportional hazards regression, using propensity score fine stratification to address confoundings. Sibling-matched analyses and complementary negative controlled analyses were applied to address the effect of unmeasured confounding and confounding by indication.

Results: The cohorts included 533 445, 532 342, and 379 188 pairs of mother-child records for preterm birth and small for gestational age analyses, ASD analysis, and ADHD analysis respectively. Of the exposed children, 280/2281 (12.3%), 43/2281 (1.9%), 108/2274 (4.7%), and 117/1481 (7.9%) had preterm birth, small for gestational age, ASD, and ADHD respectively. The weighted odds ratio (wOR) was 1.10 (95%CI: 0.97-1.25) for preterm birth and 1.03 (95%CI: 0.76-1.39) for small for gestational age while the weighted hazard ratio (wHR) was 1.40 (95%CI: 1.13-1.73) for ASD and 1.15 (95%CI: 0.94-1.40) for ADHD, when comparing gestationally exposed with gestationally nonexposed individuals. Sibling-matched analysis showed no association between gestationally exposed individuals with their gestationally unexposed siblings for all outcomes (preterm birth-wOR: 0.84, 95%CI: 0.66-1.06; small for gestational age-wOR: 1.02, 95%CI: 0.50-2.09; ASD-wHR: 1.10, 95%CI: 0.70-1.72; ADHD- wHR: 1.04, 95%CI: 0.57-1.90). Similarly, no significant differences were observed when comparing children who were gestationally exposed to sedatives with children whose mothers were exposed to sedatives before but not during pregnancy for all outcomes.

Conclusion: Our findings do not support a causal relationship between prenatal sedative exposure and preterm birth, small for gestational age, ASD, or ADHD.

1002

Levothyroxine treatment among pregnant woman and risk of seizure/epilepsy in children: a population-based cohort study

Miss Grace Menggin Ge[1], Dr. Kenneth K.C. Man[1,2], Mr Edmund C.L. Cheung[1], Dr. Patrick Ip[3], Dr. Wing Cheong Leung[4], Prof. Annie W.C. Kung[5], Dr. Ching-Lung Cheung[1], Prof. Ian C.K. Wong[1,2]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong,Hong Kong, [2]Research Department of Practice and Policy, UCL, School of Pharmacy, London, United Kingdom,United Kingdom, [3]Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong,Hong Kong, [4]Department of Obstetrics and Gynecology, Kwong Wah Hospital, Hong Kong,Hong Kong, [5]Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong,Hong Kong

Background: The risk of offspring seizure/epilepsy and prenatal exposure to levothyroxine remains unclear. This study aims to evaluate the association between levothyroxine treatment among pregnant women and the risk of seizure/epilepsy in their offspring.

Methods: We conducted a population-based cohort study including children born between January 2001 to January 2018 with a follow-up to December 2020, using data from Hong Kong Clinical Data Analysis and Reporting System. Exposure was defined as maternal levothyroxine treatment during pregnancy. Hazard ratios (HRs) with 95% confidence intervals (CIs) were evaluated to assess the association between maternal levothyroxine use during pregnancy and seizures in children using the propensity score fine-stratification weighting and Cox proportional hazards regression model.

Results: Among 528,343 included mother-child pairs, 3,044 children were born from mothers exposed to levothyroxine during pregnancy. A significantly increased risk of seizure was observed in children of the gestational exposed group compared with the gestational unexposed group (weighted HR [wHR]: 1.13, 95%CI: 1.03, 1.24). Similarly, an increased risk of seizure was found when comparing the gestational exposed group with euthyroid mothers who had no history of thyroid-related diagnosis or prescriptions (wHR: 1.14, 95%CI: 1.04, 1.24). However, no significant difference was observed between the gestational exposed group and those previously exposed to levothyroxine but had stopped during pregnancy (wHR: 0.92, 95%CI: 0.62, 1.35). No significant difference was observed in the sibling matched analysis either (wHR: 0.99, 95%CI: 0.61, 1.60).

Conclusions: Our results do not support a causal association between maternal levothyroxine treatment during pregnancy and seizure/epilepsy in children. The observed increased risk is likely to be confounded by maternal thyroid disease itself. The findings support the current guidelines on the safe use of levothyroxine treatment during pregnancy.

1003

The Influence of COVID-19 Pandemic on the Utilization Pattern of Childhood Vaccines in a South Indian Community.

Dr Merrin Mathew[1], Dr. Juny Sebastian[1]
[1]*JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru., Mysuru, India*

Background: Worldwide, countries launched immunization programmes to deliver selected vaccines to the targeted beneficiaries, especially focusing on vulnerable populations (pregnant women, infants and children) who are at a high risk of diseases preventable by vaccines. Today we witness more public concerns about vaccines as compared to the pre-pandemic era.

Aim: To compare the utilization pattern of childhood vaccines before and after pandemics (COVID-19).

Methodology: A comparative study was conducted on the utilization pattern of routine childhood immunization before and after the COVID-19 pandemic. The data were collected through the immunization registry maintained in the immunization center (study site). The study included all the pediatric (< 18 years) vaccine beneficiaries immunized from the study site. The study was conducted in two different phases i.e., Phase I: May November 2019 (before Covid-19) and Phase II: November 2021 – May 2022 (after Covid-19). The vaccine uptake in the year 2018 was also collected from the registry and was considered as the base year for comparing the two phases.

Results: Pre-pandemic study period includes 1,728 vaccine beneficiaries, while in the post-pandemic study period includes 1,147 vaccine beneficiaries. The study found out significant statistical decline in the utilization pattern of routine childhood vaccination (covered in the Expanded Programme on Immunization [EPI]) in the community. Whereas, other optional vaccines (which are not covered in EPI) especially the influenza vaccine show an increased uptake among the community in the post-pandemic phase.

Conclusion: The impact of pandemics on the community towards the attitude on childhood vaccination can be significantly drawn out from the study. The introduction of new COVID-19 vaccines and various circulating myths about immunization brought so many concerns in our society. The core reasons should be treated from the root to bypass mass vaccine hesitancy.

Keywords: Optional vaccines, Pre/post-pandemic phase, Public concerns, Routine childhood immunization

1004

Systematic Comparison of Drug Information Resources for Recommendations on Drug Use in Pregnancy

Mr Atiqulla Shariff[1], Dr. Srikanth Malavalli Siddalingegowda[1], Dr. Sathvik Belagodu Sridhar[2], Mr. Parth Patel[1], Ms. Vaishakhi Shetty[1], Ms. Muskan Singh[1], Ms. Aashka Thakur[1], Ms. Anjali Pradhan[1]
[1]JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, India, [2]RAK College of Pharmacy, RAK Medical & Health Sciences University, Ras Al-Khaimah, United Arab Emirates

Aim/Objective: To assess the consistency of information related to drug use in pregnancy among six drug information resources.

Methods: We selected fifty drugs frequently used in pregnancy and six drug information resources available at the study site. The recommendations documented in each drug information resource on drug use in pregnancy were carefully reviewed. The reviewed information was categorized as reassuring, cautionary, suggesting avoidance, inconclusive, contradicting, and no specific recommendation. Fleiss Kappa (k) score was estimated using SPSS (version 24.0, IBM, Armonk, New York, USA) to measure the consistency in documented information among the drug information resources.

Results: Six drug information resources, namely; Medscape.com, Medsafe.govt.nz, Brigg's Drugs in Pregnancy and Lactation; A Reference Guide to Fetal and Neonatal Risk, 12th edition (DPL), United Kingdom's Teratology Information Service at uktis.org (UKTIS), UpToDate®, and Portable Emergency Physician Information Database (PEPID©) were reviewed for the recommendation related to drug use in pregnancy. Medscape.com, UpToDate®, and PEPID© had the highest (100%), whereas UKTIS had the least (62%) scope score in providing information on drug use in pregnancy. Cautionary was the most frequent pregnancy risk category documented by Medsafe.govt.nz (28/45), Medscape.com (19/50), UKTIS (15/31), UpToDate® (16/50), and PEPID© (36/50). Reassuring was the most frequent (31/48) pregnancy risk category reported by DPL. The intersource reliability test revealed Fleiss' kappa score of 0.074, indicating poor consistency among the drug information resources concerning information on drug use in pregnancy.

Conclusion: Inconsistencies in the information provided by the drug information resources pose challenges to the safe use of drugs in pregnancy. Therefore, developing an evidence-based list of pregnancy risk categories and re-categorizing the drugs accordingly by consolidating the information from the most commonly used drug information resources will help guide rational drug use in this special population.

Keywords: Consistency, Drug information resources, Pregnancy risk categories, Rational drug use

1005

Beta-blockers reducing acute exacerbation of COPD among COPD with AF patients: evaluation in different severity of COPD

Ms ShanJu lin[1], Co-author Xin-Min Liao[2], Co-author Cheng-Han Lee[3], Yu-Ching Chang[4], Co-author Nai-Yu Chen[1,5], Corresponding author Ching-Lan Cheng[1,4,6]

[1]School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [2]Division of Pulmonary Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, [3]Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University,Taiwan, [4]Health Outcome Research Center, National Cheng Kung University,Taiwan, [5]Department of Pharmacy, Kaohsiung Veterans General Hospital,Taiwan, [6]Department of Pharmacy, National Cheng Kung University Hospital,Taiwan

Aim/Objective: Acute exacerbation (AE) associated with beta-blocker (BB) in patients with Chronic obstructive pulmonary disease (COPD) and atrial fibrillation (AF) remains controversy. We aimed to assess the risk of AE in different severity COPD with AF patients compared to calcium channel blocker (CCB).

Methods: We conducted a retrospective cohort study with new user design, active comparison, using Taiwan's National Health Insurance Data (2009-2018). We enrolled patients with prevalent COPD and incident AF. The index date was the first prescription date of BB or CCB after AF diagnosis. Outcome was AE-related emergency room visits or hospitalizations. COPD severity was classified to mild and severe group by prior exacerbation history. We used multivariable Cox proportional hazard model to estimate hazard ratio (HR) and the 95 % confidence interval (CI). Sensitivity analysis including propensity score matching (1:1) and subgroup analysis.

Results: The study enrolled 13,462 patients. Compared to CCB group, BB group was younger and consisted of more mild COPD patients. After 1-year follow-up, the incidence rate of AE is 13 patients per 100 person-years in BB group, and 31 patients in CCB group. The study revealed using BB reduced risk of AE (aHR= 0.76, 95%CI 0.69-0.84). When stratifying by COPD severity, BB group still reduced risk of AE compared with CCB group in mild COPD (aHR=0.73, 95%CI 0.64-0.84), but not in severe COPD cases (aHR=0.94, 95%CI 0.77-1.15). After propensity score matching, we found same results among 4493 matched pairs (aHR= 0.78, 95%CI 0.70-0.87). Results showed consistent protective effect in subgroup analysis, even in patients without heart failure and myocardial infraction.

Conclusion: Further study on long term risk of AE in severe COPD patients with AF who exposure BB is needed and lung function monitoring is particularly warranted in these patients.

#COPD #AF #beta-blocker #AECOPD

1006

Comparative risk of hip fracture in older adults initiating suvorexant versus z-drugs: Results from the LIFE study in Japan

Mr Motohiko Adomi[1], Megumi Maeda[2], Fumiko Murata[2], Haruhisa Fukuda[2]
[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, United States, [2]Department of Health Care Administration and Management, Kyushu University Graduate School of Medical Sciences, Japan

Objective: There are only few studies reporting the comparative safety of hypnotics with different mechanisms among older adults. This retrospective cohort study aims to evaluate the risk of femur fracture in community-dwelling older adults initiating z-drugs, nonbenzodiazepine hypnotics, versus those initiating suvorexant, dual orexin receptor antagonist.

Methods: We used a claims database built in the LIFE study consisting of 1.5 million beneficiaries in Japan. People aged 65 years and older were included in the study. The exposure was defined as new-use of z-drugs (eszopiclone, zolpidem, or zopiclone) or suvorexant. The outcome was set as hospitalization due to femur fracture within 30 days of exposure initiation. We estimated inverse probability of treatment weights from 28 pre-specified covariates, including comorbidities and comedications. Cox proportional hazards model was fitted to the weighted pseudo-population to estimate the hazard ratio of outcome. As sensitivity analyses, we narrowed the outcome definition, requiring surgical procedure to be recorded during the hospitalization to minimize misclassification of the outcome. We also expanded the follow-up periods to 365 days and allowed any type of fracture.

Results: We identified 54,471 z-drugs new-users and 16,244 suvorexant new-users. In the main analysis with 30 days follow-up, there were 53 (0.10%) and 22 (0.14%) femur fractures among z-drugs new-users and suvorexant new-users, with an adjusted hazard ratio of 1.04 (95% CI: 0.64-1.69). In the sensitivity analysis with 365 days follow-up, there were 402 (0.74%) and 147 (0.90%) femur fractures in each group, with similar hazard ratio of 0.98. Other sensitivity analyses were also in line with the main result.

Conclusion: This study shows that the z-drugs new-users have comparable safety profile to suvorexant new-users regarding femur fracture and any types of fracture. This finding may contribute to the update of guidelines of insomnia treatment.

Keywords: Hypnotics, Femur fracture, Administrative Claims, Comparative safety

1007

Real-world use of and adherence to anti-diabetic medications in older patients in Japan; the Shizuoka Study

Hiraku Kumamaru[1,2], Shiori Nishimura[1,2], Shun Kohsaka[1,3], Satoshi Shoji[1,3], Hiroyuki Yamamoto[1,2,4], Eiji Nakatani[1], Yoshiki Miyachi[1], Hiroaki Miyata[1,2,4]

[1]Shizuoka Graduate University of Public Health, Shizuoka, Japan, [2]Department of Healthcare Quality Assessment, The University of Tokyo Graduate School of Medicine, Tokyo, Japan, [3]Deparment of Cardiology, Keio University School of Medicine, Tokyo, Japan, [4]Department of Health Policy and Management, Keio University School of Medicine, Tokyo, Japan

Aim/Objective: The findings from recent large-scale clinical trials has altered the guideline recommendations for medical treatments for type 2 diabetes mellitus (T2DM). We aimed to assess the medication use pattern and adherence to these medications in an understudied elderly population in Japan.

Methods: Using Shizuoka Kokuho Database, a prefectural administrative claims database, we identified patients ≧65 year old with prior diagnosis of T2DM who initiated non-insulin anti-diabetic medications between April 2014 and October 2020. We summarized their medication use pattern by fiscal year and age-group. We also evaluated the adherence to biguanides, dipeptidyl peptidase-4 inhibitors (DPP4i), and sodium glucose co-transporter 2 inhibitors (SGLT2i) during the 365 days after the initiation using the proportion of days covered (PDC), and estimated the percentage of patients with PCD≧80%. Patients were censored at disenrollment from the municipal government insurance plan (including death). In this analysis, switching to another anti-diabetes drug was considered as discontinuation.

Results: We identified 41,430 T2DM treatment initiators during the study period. DPP4i was dominantly prescribed as initial treatment (68.4% in 2014, and 65.4% in 2020), and the use of SGLT2i (3.7% in 2014 to 8.6% in 2020) and biguanides (4.3% in 2014 to 11.3% in 2020) increased over time. The increase was most prominent among relatively young patients aged 65-74 (SGLT2i: 1.0% in 2014 to 11.8% in 2020). GLP-1 was rarely used (<0.5%) as initial treatment throughout the study period. The adherence to DPP4i was high across age groups (PCD≧80% in 67.6% for 65-74; 69.5% for 75-84; 69.3% for 85-). The adherence to SGLT2i was lower, especially in the oldest age-group (60.6% for 65-74; 59.0% for 75-84; 48.9% for 85-).

Conclusion: While the use of SGLT2i is increasing, its adherence may be suboptimal especially among the older patients. Reasons for discontinuation should be fully explored for treatment strategy development.

1008

Reduction of Potentially Inappropriate Medications using PIM-Taiwan Criteria in Elderlies in Long-Term Care Facilities in the Northern Area of Taiwan

Yen-Ju Hsieh[1], Ming-Neng Shiu[1]
[1]*National Yang Ming Chiao Tung University, Faculty of Pharmacy, Taipei, Taiwan*

Objectives: To identify whether medication reviews using PIM-Taiwan criteria (2018) is an effective intervention to reduce PIM use in the elderly in long-term care facilities (LCFs) in Taiwan. Moreover, to evaluate whether more precise recommendations increase physicians' acceptation rates, thus leading to more effective intervention.

Methods: We conducted a cluster randomized control trial with visiting physicians as clusters in 10 LCFs in Taiwan between 2021.12 and 2022.06. Recommendations to avoid PIMs are given to the visiting physicians in the intervention(1) group; in the intervention(2) group more precise recommendations for the alternative medications are given. Differences in the number of PIMs prescribed before and after the intervention are estimated, and the difference of the differences stated before is also estimated between the intervention(1) and intervention(2) groups. The difference in the recommendations acceptation percentage between the two groups is also estimated.

Results: There is only a slight decrease in the number of PIMs prescribed in the intervention(2) group (RR 0.93, 95% CI 0.63-1.37), while there is no decrease in the number of PIMs prescribed in the intervention(1) group (RR 1.00, 95% CI 0.69-1.46). However, there is a slight increase in the percentage of recommendations accepted by the physicians between the intervention(1) and intervention(2) groups (0.0% vs. 7.4%).

Conclusion: Our study is the first to investigate the effect of medication reviews in residential care settings in Taiwan to reduce PIM use. Medication review using PIM-Taiwan criteria (2018) in LCFs in Taiwan is not an effective intervention. However, we should not only focus on the quantitative decrease in PIM use but concentrate on the clinical outcomes of using the PIM treatment. Monitoring the signs and symptoms of the adverse events related to the PIMs may be a more effective way.

Keywords: Potentially Inappropriate Medication, Residential Facilities, Deprescription, Medication Review

1009

Anticholinergic Burden and Risk of Acute Cardiovascular Events in Elderly Patients: A Population-based Case Crossover Study

Wei-Ching Huang[1], Avery Shuei-He Yaung[1], Daniel Hsiang-Te Tsai[1], Edward Chia-Cheng Lai[1]
[1]*School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Science, National Chen Kung University, Tainan, Taiwan*

Aim/Objective: To evaluate the association between anticholinergic burden and risk of acute cardiovascular events among the elderly patients in Taiwan.

Methods: This was a case-crossover study analyzing Taiwan National Health Insurance Database. We selected the case patients aged 65+ years hospitalized for acute cardiovascular events, including myocardial infarction, stroke, conduction disorders, dysrhythmias, or cardiovascular death, from 2011 to 2018. We used disease risk score matching to select control patients without an event for a control-crossover analysis. We also conducted case-case-time-control analysis by selecting future cases with events within 60-180 days after the matched event date. We defined hazard period as 0-30 day before the event date, and randomly selected a 30-day period between 60 and 180 days before the event date as referent period. We used German Anticholinergic Burden Scale (GABS) and classified GABS into 3+, 1-2, and 0 scores. We performed conditional logistic regression to compare the score differences between hazard and referent period.

Results: We identified a total of 317,446 cases. The average age was 78.4 (SD 0.01). The case-crossover analysis indicated GABS 1-2 points (OR, 5.39; 95% CIs, 5.27-5.50) and 3+ points (OR, 16.75; 16.38-17.13) were associated with higher risk of acute cardiovascular events, comparing with GABS score 0. We also selected 263,916 control patients and 248,579 future cases for adjustments of the time trend. The results remained consistent after adjustments by control-crossover analysis (GABS 1-2 points OR, 4.84; 4.69-4.99; GABS 3+ points OR, 13.58; 13.16-14.01) and case-case-time-control analysis (GABS 1-2 points, OR, 3.89; 3.77-4.02; GABS 3+ points, OR, 10.35; 10.03-10.67).

Conclusion: We found elderly patients with high anticholinergic burden was associated with the increased risk of acute cardiovascular events. The finding warrants closing monitoring for those with high anticholinergic burden to avoid unintended outcomes.

Keywords: Anticholinergic burden, cardiovascular event, elderly patients.

1010

Benign prostatic hyperplasia medication and the risk of delirium: A population-based self-controlled case series

Sheng-Yung Chang[1], Chin-Yao Shen[1], Edward Chia Cheng Lai[2]

[1]NCKU Institute of Clinical Pharmacy and Pharmaceutical Sciences, Tainan City, Taiwan, [2]National Cheng Kung University Hospital, Tainan City, Taiwan

Aim: To evaluate the association between medications for benign prostatic hyperplasia (BPH) and risk of delirium in elderly patients.

Methods: We conducted a self-controlled case series (SCCS) study by using Taiwan's National Healthcare Insurance Database (NHID). We included elderly patients aged 65+ years who diagnosed with BPH between 2012 to 2018, and with a record of alpha blockers (AB) or 5-alpha reductase inhibitors (5ARI) prescription and delirium diagnosis. We pre-defined 5 periods based on AB or 5ARI treatment, including pre-treatment, early treatment (1-7 days), treatment (8+ days), post-treatment (1-14 days after drug discontinuation) and non-treatment periods. We performed conditional Poisson regression model to compare the incidence rate among different periods, with adjustment of calendar year. We conducted sensitivity analyses to examine the result robustness, including stratification by age groups (65-74, 75-84 and 85+), settings (inpatient or outpatient department), and additional exclusion of patients who died or receiving prostate transurethral resection.

Results: We included 16,896 patients receiving AB and 2,976 patients receiving 5ARI for this SCCS. Comparing with non-treatment period, the IRRs for early treatment, treatment and post- treatment periods were 3.42 (95%CI, 3.01, 3.88), 2.90 (2.77, 3.04), 3.59 (3.30, 3.89) for AB and 1.64 (1.03, 2.62), 1.59 (1.41, 1.79), 2.43 (1.88, 3.13) for 5ARI. We observed high IRRs for the pre- treatment periods for AB (IRRs 12.81; 95%CI, 11.93, 13.75) and 5ARI (4.96; 3.70, 5.94). The results of sensitivity analyses were consistent to the main analysis.

Conclusion: The findings may suggest urinary retention was associated with delirium in elderly patients with BPH because high risk was observed in the pre-treatment period. The risk magnitude was largely reduced after treatment but still higher than non- treatment period, suggesting a close monitoring is still required until patients has recovered to baseline status.

Keywords: adrenergic alpha-antagonists, 5-alpha reductase inhibitors, delirium, benign prostatic hyperplasia

1011

The Risk of Prostatic Hyperplasia with Concomitant Use of Warfarin and Statin: a population-based cohort study

Hehyun Won[1], Hui-Eon Lee[2], Na-Young Jeong[3], Nam-Kyong Choi[2,3]

[1]Ewha Womans University, Seoul, South Korea, [2]Ewha Womans University, Department of Industrial Pharmaceutical Science, College of Pharmacy, Seoul, South Korea, [3]Ewha Womans University, Department of Health Convergence, College of Science and Industry Convergence, Seoul, South Korea

Aim/Objective: There were reports of prostatic hyperplasia after concomitant use of statin and warfarin in the Korea adverse events reporting system database. We evaluated the association between concomitant administration of warfarin and statin and the risk of prostatic hyperplasia from population-based data.

Methods: We conducted a retrospective cohort study using a National Health Insurance Sample Cohort Database from 2004 to 2009. We included the male adult patients aged over 50 years who were prescribed statin from 2005 to 2008. Concomitant users were classified as the exposed group and those who only statin users were classified as the non-exposed group. Concomitant user was defined as a patient who was prescribed warfarin and statin for more than one day. We performed 1:1 propensity score (PS) matching between the groups. The patients diagnosed with prostatic hyperplasia, prostate and bladder cancer, and resected prostate a year before the index date (first prescribing date) were excluded. The primary outcome was an occurrence of prostatic hyperplasia from the index date to 1 year. Hazard ratios (HRs) for risk of prostatic hyperplasia between the concomitant users and only statin users were calculated by Cox's proportional-hazards regression.

Results: A total of 22,825 patients were taking only statin and 456 patients were taking statin and warfarin concomitantly. After PS matching, the most frequent age group was 60-69 years old in both exposed and un-exposed group. Of the 456 patients in the exposed group, 85 were diagnosed with prostatic hyperplasia, and 85 of the 456 patients in the unexposed group were diagnosed with prostatic hyperplasia. HRs with concomitant use were 1.09 (95% CI 0.81 to 1.47) for prostatic hyperplasia.

Conclusion: There was no significant association of prostatic hyperplasia in concomitant user of warfarin and statin. However, continuous motoring is needed.

Key words: Concomitant use, Warfarin and Statin, Prostatic hyperplasia

1012

Comparative safety of SARS-COV-2 Vaccination in pediatric population: Using WHO international database

Mr Donghyuk Kim[1], Comparative safety of SARS-COV-2 Vaccination in pediatric population: Using WHO international database In-Sun Oh[1,2], Comparative safety of SARS-COV-2 Vaccination in pediatric population: Using WHO international database Ju-Young Shin[1,2,3]

[1]Department of Biohelath Regulatory Science, Sungkyunkwan University, Suwon, South Korea, [2]School of Pharmacy, Sungkyunkwan University, Suwon, South Korea, [3]Department of Clinical Research Design & Evaluation, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, South Korea

Aim/Objective: Some concerns regarding COVID-19 vaccine-associated serious adverse events (AEs) have emerged in pediatric population. We aimed to analyze comparative safety of COVID-19 vaccine use in pediatric population compared with other age groups.

Methods: In this observational, pharmacovigilance study, we used VigiBase, WHO's global individual case safety report database, to compare reporting of potential serious risks in pediatric population vaccinated against COVID-19 with that in other age groups who received COVID-19 vaccine. Potential serious risks of COVID-19 vaccine were determined as myocarditis/pericarditis, multisystem inflammatory syndrome, anaphylaxis, and febrile seizure. We included AE reports of COVID-19 vaccine available data with age group and classified them into pediatric population (<18 years) and other age groups (≥18 years). Then, we conducted a disproportionality analysis to estimate reporting odds ratios (ROR) for each risk. Subsequently, adjusted ROR with 95% confidence interval was calculated by multivariable logistic regression with sex, region, and reporting period.

Results: Of 2,426,533 reports after COVID-19 vaccination in all age groups, we identified 78,503 reports in pediatric individuals who received COVID-19 vaccines (40,944 [52.2%] females; 61,016 [77.7%] aged 12-17 years; 47,537 [60.6%] America). Higher reporting odds for all four risks were identified in pediatric population; myocarditis/pericarditis (2,565 reports in pediatrics vs 20,734 reports in other age groups, aROR 2.81; 95% CI 2.7-2.93), anaphylaxis (509 vs 12,673, 1.34; 1.23-1.47) and febrile seizure (31 vs 212, 5.06; 3.43-7.46), especially for multisystem inflammatory syndrome (119 vs 10, 267.18; 95% CI 138.89-513.98).

Conclusion: Based on our disproportionality analysis, there is need to closely monitor and manage inflammation-related AEs when vaccinating pediatric groups, even though reporting bias may exist. Also, further studies are needed to confirm the causation between COVID-19 vaccine and AEs in pediatric population.

Keywords: Covid-19 vaccine, Pediatric population, Adverse Events

1013

Safety of COVID-19 Vaccines in Pregnancy: A Vigibase Analysis

Miss Dayeon Kang[1], Ahhyung Choi[2], Ju-Young Shin[1,2,3]
[1]Department of Biohealth Regulatory Science, Sungkyunkwan University, Suwon, South Korea, [2]School of Pharmacy, Sungkyunkwan University, Suwon, South Korea, [3]Department of Clinical Research Design & Evaluation, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, South Korea

Aim/Objective: There is limited evidence on the safety of COVID-19 vaccination during pregnancy. Thus, we aimed to evaluate the association between exposure to COVID-19 vaccine and adverse pregnancy outcomes using the WHO's international pharmacovigilance database VigiBase.

Methods: We conducted a case/non-case study using VigiBase to identify potential associations of adverse pregnancy outcomes with COVID-19 vaccine. Cases were defined based on the SMQ of "pregnancy and neonatal topics" and non-cases were defined as all other adverse events. We included all physician reports with COVID-19 vaccine as the suspected cause between January 5, 2021 and April 24, 2022. Using the full database as the comparator group, reporting odds ratios (RORs) with 95% confidence intervals (CIs) were estimated by logistic regression, adjusting for maternal age, region, and reporting year.

Results: Among 731 reports with COVID-19 vaccines in pregnant women, we identified 275 reports associated with pregnancy and neonatal topics. Overall, "termination of pregnancy and risk of abortion" had higher reporting odds in COVID-19 vaccine (n= 15, adjusted ROR (aROR) 1.93; [95% CI 1.14-3.26]). However, we did not find disproportionalities for "pregnancy, labour and delivery complications and risk factors" (n= 249, aROR 0.49), and "congenital, familial and genetic disorders" (n= 6, aROR 0.48). When "termination of pregnancy and risk of abortion" was further analyzed at preferred term level, stillbirth was associated with COVID-19 vaccine (aROR 4.25; [95% CI 1.67-10.84]), although the absolute number of reports was relatively low (n= 5).

Conclusion: We identified a significant disproportionate reporting association between exposure to COVID-19 vaccine during pregnancy and "termination of pregnancy and risk of abortion". However, considering the Weber effect and unavailability of the timing of exposure during pregnancy, continuous surveillance is warranted to confirm the safety of COVID-19 vaccine during pregnancy.
Keywords: COVID-19 vaccine; pregnancy; adverse pregnancy outcomes; Vigibase

1014

Serious adverse effects after COVID-19 vaccination in Japan: Analysis using administrative claims data linked with vaccination registry

Yoshinori Takeuchi[1,2], Dr. Masao Iwagami[3,4], Dr. Sachiko Ono[5], Dr. Hideo Yasunaga[6]
[1]Division of Medical Statistics, Department of Social Medicine, Faculty of Medicine, Toho University, Tokyo, Japan, [2]Department of Biostatistics, School of Public Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [3]Department of Health Services Research, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan, [4]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK, [5]Department of Eat-loss Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [6]Department of Clinical Epidemiology & Health Economics, School of Public Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Aim/Objectives: To examine risks of serious adverse effects after COVID-19 vaccination.

Design: A cohort study and self-controlled case series (SCCS) using an administrative claims database linked with COVID-19 vaccination registry in an urban city of Japan.

Setting: National or late elder's health insurance system between March 2021 and December 2021.
Exposures: First and second doses of any COVID-19 vaccinations (mRNA vaccines accounting for >99%)
Main outcome measures: Hospitalization with acute myocardial infarction, appendicitis, bell's palsy, disseminated intravascular coagulation, immune thrombocytopenia, pulmonary embolism, hemorrhagic stroke, ischemic stroke, and venous thromboembolism

Statistical analysis: For the cohort study, we estimated incidence rate ratios (IRRs) within 21 days after each COVID-19 vaccination dose compared with non-exposure periods by Poisson models adjusting for the subjects' sex, age, and Charlson comorbidity index. We also estimated adjusted incidence rate differences (IRDs) by the existence method. For the SCCS, we estimated within-subject IRRs by conditional Poisson models. We fitted separate statistical models for each outcome.

Results: We identified 196,693 enrollees (male: 93,337, mean [standard deviation] age: 61.2 [23.1] years old) with 146,763 first-dose and 143,182 second-dose vaccinations. No statistically significant signals were found in any doses of both study designs, except for the second dose on hemorrhagic and ischemic stroke in the SCCS analysis: IRR 1.80 (95% confidence interval (CI) 1.11–2.92) for hemorrhagic stroke and IRR 1.39 (95%CI 1.08–1.79) for ischemic stroke. In the cohort analysis, IRR and IRD (period after the second dose vs. non-exposure period) were 1.24 (95%CI 0.78–1.96) and 0.13 (95%CI -0.16–0.42)/10000 person-days for hemorrhagic stroke, and 1.23 (95%CI 0.97–1.55) and 0.41 (95%CI -0.14–0.96) for ischemic stroke, respectively.

Conclusion: Safety signals of the second-dose COVID-19 vaccinations on hemorrhagic and ischemic strokes were suggested only in the SCCS analysis, which should be confirmed by further studies.
Keywords: cohort study, self-controlled case series, signal, vaccine safety

1015

Adverse Events Following COVID-19 Vaccines: An active surveillance study

Dr Juny Sebastian[1], Dr Mandyan Dhati Ravi[2], Dr Chethak K B[2]
[1]JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, Mysuru, India, [2]JSS Medical College & Hospital, JSS Academy of Higher Education and Research, Mysuru, India

Objective: This study aimed to evaluate the Adverse Events (AEs) following COVID-19 vaccinations in a tertiary care hospital.

Materials and methods: An active vaccine safety surveillance study was conducted among the COVID-19 Vaccine beneficiaries from an immunization center in South India. All the enrolled study population were followed for identification of AEFIs through two telephonic follow-ups, which was held during 8 Days ± 2 days of and 28 Days ± 2 days of immunization. Collected data were analyzed and categorized by severity and seriousness. The causality assessment team performed causality assessment of the AEFIs using the World Health Organization's causality assessment algorithm. Bivariate analysis was performed to identify the predictors of AEFI among the study population.

Results: Out of the total 13,190 COVID -19 vaccine beneficiaries during the study period, 10,662 (80.83%) were enrolled for the study. A total of 1347 study population developed 886 AEFIs with an incidence rate of 8.3%. A total of 1197 AEFIs with COVISHIELD vaccine and 86 AEFIs with COVAXIN was expected as per its respective fact sheets. Most of the AEFIs (87.69%) were observed with the system organ class of 'General disorders and administration site conditions'. 83.66% of events had a consistent causal association to immunization, where as 14.92% events were coincidental. 1.34% of the AEs had inconsistent causal association to immunization and those might be potential signals. Female gender (P Value 0.0010), age groups of 40-49 years (P Value 0.0033) & 50 -59 years (0.0041), presence of comorbid conditions (P Value 0.0010) were the identified predictors of AEFIs.

Conclusion: Active vaccine Safety Surveillance studies are the best methods to identify and report AEs associated with any newly introduced vaccines. Also, safety monitoring helps the Health care professional to scientifically convince the beneficiaries on their safety concerns which helps to improve the vaccine acceptance.

1016

COVID-19 vaccine-induced interstitial lung disease in WHO pharmacovigilance database: case/non-case study

Mr Min-Taek Lee[1,2], Seung-Hun You[1,2], Sewon Park[1,2], Jeong-Yeon Kim[1,2], Dal Ri Nam[1,2], Ju Won Lee[1,2], Jongmin Lee[1,2], Hyeon Ji Lee[1,2], Prof Sun-Young Jung[1,2]

[1]College of Pharmacy, Chung-Ang University, South Korea, [2]Department of Global Innovative Drugs, The Graduate School of Chung-Ang University, South Korea

Interstitial lung disease (ILD) has been reported after administration COVID-19 vaccines. The safety information on COVID-19 vaccine-induced-ILD is unknown. The objective was to identify characteristics of vaccine-related-ILD reports and to assess signal of increased risk of ILD associated with COVID-19 vaccines using World Health Organization (WHO) pharmacovigilance database (VigiBase).

This study used VigiBase until March 2022. We defined vaccines using both the Anatomical Therapeutic Chemical code, substance information in VigiBase and the product type information in WHODrug. The COVID-19 vaccines were categorized into RNA-, and viral-vaccines. We identified ILD using standardized medical dictionary for regulatory activities (MedDRA) Queries (SMQ) narrow search (39 perferred terms). We applied descriptive analysis to identity demographic characteristics of vaccine-related-ILD. We adopted case/non-case approach to assess the association between the COVID-19 vaccines and ILD. Each case was matched to four non-cases by age group and gender. Conditional logistic regression analysis was used to estimate reporting odds ratio (ROR) with 95% confidence interval (CI).

The VigiBase contains 21,691,785 reports until Mar 2022. There were 4,149,402 vaccine-related reports, of which 4,971 were reported for ILD. The majority of reported vaccine-related with ILD were ≥ 75 years (26,2%, 1,301 reports), and 3,521 report (70.8%) were reported from Americas. Among vaccine-related reports, we identified 4,971 cases of ILD and 19,884 non-cases. The adjusted RORs (aRORs) of ILD reported for COVID-19 vaccines were 1.63 (95% CI, 1.48-1.78) and 1.21 (95% CI, 1.08-1.36) compared with all other vaccines and influenza vaccines, respectively. According to COVID-19 vaccine type, the aROR of RNA-COVID-19 vaccines were 1.59 (95% CI, 1.47-1.71), and that of viral-COVID-19 vaccines was 0.90 (95% CI, 0.80-1.01) compared with all other vaccines.

Our study shows that COVID-19 vaccines was associated with an increased reporting in ILD using case/non-case approach. The COVID-19 vaccine-related ILD should be monitored carefully, particularly in RNA-based COVID-19 vaccines.

1017

Immune-Related Adverse Events after COVID-19 vaccination among patients with autoimmune diseases using World Health Organization VigiBase

Miss Seohyun Kim[1], Sungho Bea[2], Ju-Young Shin[3]
[1]Department of Biohealth Regulatory Science, SungKyunKwan University, Suwon, South Korea, [2]School of Pharmacy, SungKyunKwan University, Suwon, South Korea, [3]Department of Clinical Research Design & Evaluation, Samsung Advanced Institute for Health Sciences & Technology, SungKyunKwan University, Seoul, South Korea

Aim/Objective: Hyperactivity of autoimmunity can be triggered by vaccination in patients with autoimmune diseases. Yet there is lack of data on the new-onset autoimmune disorders following COVID-19 vaccination. This study aimed to explore immune-related safety events (irAEs) among patients with autoimmune diseases after COVID-19 vaccination.

Methods: All COVID-19 vaccines-associated irAEs were extracted from World Health Organization VigiBase between Jan 1967 and Apr 2022. We evaluated the signals for possible irAEs, which lists have been suggested by the FDA and EMA. Futhermore, we also included MedDRA SMQ “Immune-mediated/Autoimmune Disorders” to define potential signals of irAEs. Individual case safety reports (ICSRs) of patients with autoimmune diseases were compared with the ICSRs of the general population. We assessed the time-to-onset of irAEs following COVID-19 vaccination. We then conducted a disproportionality analysis to determine the safety signal by using reporting odds ratio (ROR) with 95% confidence intervals (CI).

Results: Among 56,601 ICSRs of irAE 708 ICSRs were identified from patients with autoimmune diseases. The majority of ICSRs were female (71%), and age of 45-64 (30%). The median time-to-onset of irAEs was 12 days (IQR 3-22). Most irAEs recommended by regulatory authorities were identified as signals (Addison's disease ROR 10.26, [95% CI 4.49-23.49]; psoriasis 1.81, [1.43-2.30]; sarcoidosis 1.87, [1.13-3.11]; scleroderma 2.78, [1.06-7.29]; systemic lupus erythematosus 6.88, [5.73-8.27]; Sjogren's syndrome 4.37, [2.70-7.09]). Although ankylosing spondylitis was not included in the AE list by authorities, it was also detected as a signal among patients with autoimmune diseases (ROR 11.07, [95% CI 8.25-14.76]).

Conclusion: Several irAEs were more likely to be observed among patients with autoimmune diseases compared with the general population. This study suggests the need for additional surveillance and management for the patients, who were more likely to be vulnerable to immune-related adverse events following COVID-19 vaccination.

Keywords: Autoimmune disease, COVID-19 vaccine, VigiBase, Signal detection

1018

Comparative effectiveness of Nucleos(t)ide Analogues-based treatments for Hepatitis B Virus-related Hepatocellular Carcinoma after curative therapies: Systematic review and network meta-analysis

Miss Yu-Han Huang[1], Chung-Yu Chen[1]
[1]*Master Program in Clinical Pharmacy, School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan*

Objective: To evaluate comparative effectiveness of different nucleos(t)ide analogues (NAs)-based treatments on patients with HBV-related hepatocellular carcinoma (HCC) patients after curative therapies by network meta-analysis of cohort studies.

Methods: The PubMed, EMBASE, and Cochrane Library databases were searched for eligible studies from inception to May 2022. Eligible studies were cohort studies including adult patients with HBV-related HCC after curative therapies, comparing effectiveness of nucleos(t)ide analogues-based treatments, and reporting the outcomes of 3-, and 5-year recurrence-free survival (RFS) and overall survival (OS). The rank plots based on the surface under cumulative ranking values were performed.

Results: Twelve cohort studies with 5362 patients and 6 different nucleos(t)ide analogues-based treatments were included. Network meta-analysis indicated that sequential therapy ((Odds ratio(OR)) RFS: 9.43 [2.74-19.91]; OS: 10.65 [2.23-19.28]), and tenofovir disoproxil fumarate (OR RFS: 1.89 [1.78-4.56]; OS: 3.36 [1.20-9.28]) presented significantly beneficial effects compared to standard of care on 3-year RFS and OS. As for 5-year RFS and OS, sequential therapy (OR RFS: 3.25 [1.83-14.50]; OS: 6.34 [1.96-22.04]), tenofovir disoproxil fumarate (OR RFS: 2.87 [1.80-12.26]; OS: 4.97 [1.82-13.93]), and adefovir (OR RFS: 2.01 [1.03-3.89]; OS: 2.37 [1.03-5.49]) had significant better prognosis than standard of care. Surface under cumulative ranking values identified sequential therapy (rank first), tenofovir disoproxil fumarate (rank second) and adefovir (rank third) as the top three best treatments for RFS and OS.

Conclusions: Sequential therapy with Entecavir and Peg-IFNα is superior to other monotherapies, which could be recommended as the first-line treatment therapy for patients with HBV-related HCC after curative therapies. TDF is the optimal first-line treatment selection considering its beneficial effects on recurrence-free survival and overall survival among the monotherapies.

Keywords: hepatitis B virus; hepatocellular carcinoma; nucleos(t)ide analogues; network meta-analysis

1019

Fanconi syndrome associated with anticancer drugs: A disproportionality analysis in a spontaneous reporting database

Miss Rifa Shareen[1], Fanconi syndrome associated with anticancer drugs: A disproportionality analysis in a spontaneous reporting database Subeesh Viswam[1], Fanconi syndrome associated with anticancer drugs: A disproportionality analysis in a spontaneous reporting database Roopa Acharya[1], Fanconi syndrome associated with anticancer drugs: A disproportionality analysis in a spontaneous reporting database Amulya Bhatkal[1]

[1]*Manipal College of Pharmaceutical Sciences, MAHE., Manipal, India*

Objectives: To investigate association between fanconi syndrome and anticancer drugs through disproportionality analysis in the FDA Adverse Event Reporting System (FAERS) Database.

Methods: The case/non-case retrospective disproportionality analysis was performed in a publicly available FAERS database using OpenVigil 2.1(2014Q1-2021Q3). The preferred term defined by MEDRA v24 used for the study was “Fanconi syndrome” and all the anticancer drugs were included. Reporting odds ratio (ROR) was used as the analysis data mining algorithm. The threshold for a positive signal was considered as ROR-1.96SE>1 with a minimum of 3 reports.

Results: 707 cases of fanconi syndrome were identified from FAERS database, of which 122(17.25%) reports were associated with anticancer drugs. Among them, highest number of cases reported were due to alkylating agents(n=77) and platinum agents(n=62). Ifosfamide accounted for 68 cases and doxorubcin for 41 cases. Olaratumab showed the highest positive signal of ROR 422.172 (208.148, 856.265) followed by ifosfamide of ROR 130.565 (102.074, 167.01). On gender stratification, anticancer drugs were found to have a higher ROR value of 8.884 (6.704, 11.775) times for females compared to males [ROR 5.342 (4.06, 7.027)]. Most of the cases were reported from the United States(n=73). Population’s median age was found to be 33.

Conclusions: On analysis, the data identified signals for fanconi syndrome are associated with the use of anticancer drugs, but more research with a superior epidemiological study design of a defined population is required to validate these findings.

1020

Myelodysplastic syndrome transformation associated with the use of antineoplastic agents: A disproportionality analysis in a spontaneous reporting database

Miss Amulya Bhatkal[1], Roopa Acharya B[1], Rifa Shareen[1], Lipin Lukose[1], Gursimran Kaur[1], Subeesh K Viswam[1]
[1]*Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, India*

Background: Myelodysplastic syndrome is a group of myeloid hematopoietic malignant disorders with a potential to turn into Acute Myeloid Leukemia in patients with high-risk features at diagnosis - this phenomenon is termed Myelodysplastic Syndrome Transformation - and carries a poor prognosis.

Objectives: To detect the possible safety signal of antineoplastic agents associated with myelodysplastic syndrome transformation through disproportionality analysis in the FDA Adverse Event Reporting System (FAERS) Database

Methodology: The case/non-case retrospective disproportionality analysis was performed in a publicly available FAERS database using OpenVigil 2.1(2014Q1-2021Q3). The preferred term defined by MedDRA v24 used for the study was 'myelodysplastic syndrome transformation' and all anti-neoplastic drugs were screened for possible association with
myelodysplastic syndrome transformation. Proportional Reporting Ratio (PRR) and Reporting Odds Ratio (ROR) were used as the measure of disproportionality. The threshold for a positive signal was considered as ROR- 1.96SE>1 and PRR>2 with an associated chi-square value of 4 or more.

Results: The FAERS database identified a total of 842 cases of myelodysplastic syndrome transformation, out of which 449 (53.32%) were associated with antineoplastic agents. Pyrimidine antagonists accounted for 153 (34.07%), Immunomodulatory agents for 132 (29.39%), purine antagonists for 43 (9.57%), folate antagonists for 41 (9.13%), anthracycline antibiotics for 37 (8.24%), miscellaneous agents for 29 (6.45%), and alkylating agents for 14 (3.11%) cases of myelodysplastic syndrome transformation. Highest number of cases were associated with lenalidomide (n=127) followed by azacytidine (n=106). Highest signal strength was found to be with arsenic trioxide [ROR 581.572(376.384,898.618)] followed by azacytidine [ROR 405.698(323.397,508.944)]. On gender stratification, we found that the signal strength (ROR58.099[(38.411, 87.878)] and 39.755[(28.57, 55.318)] respectively) was greater for females than males.

Conclusions: Our analysis of spontaneous reporting data identified signals for myelodysplastic syndrome transformation with antineoplastic drugs and more research with superior epidemiological studies is required to validate these findings.

1021

Palbociclib and Ribociclib Use in Stage IV Breast Cancer Females: A Comparative Retrospective Observational Study

Mohamed Izham Mohamed Ibrahim[1], Ms Nour Hisham Al-Ziftawi[1], Dr Shereen Elazzazy[2], Dr Mohamed Fasihul Alam[3], Professor Asrul Shafie[4], Dr Anas Hamad[1,2], Dr Salha Bbujassoum[2]

[1]Department of Clinical Pharmacy & Practice, College of Pharmacy, QU Health, Qatar University, Doha, Qatar, [2]National Center for Cancer Care and Research, Hamad Medical Corporation, Doha, Qatar, [3]Department of Public Health, College of Health Sciences, QU Health, Qatar University, Doha, Qatar, [4]School of Pharmaceutical Sciences, Universiti Sains Malaysia, Malaysia

Objective: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are indicated in the first-line treatment of hormonal receptor-positive and HER-2 negative (HR+/HER2- negative) advanced breast cancer. Although phase III randomized controlled trials (RCTs) proved their clinical efficacy, there are no observational studies to date to validate the clinical findings of the existing RCTs.

Thus, this study evaluated and compared the clinical effectiveness and safety profiles of palbociclib and ribociclib in Qatar.

Methodology: A retrospective observational study was carried out on HR+/HER-2 negative stage IV breast cancer patients receiving palbociclib or ribociclib in Qatar. Clinical data were collected from the National Center for Cancer Care and Research (NCCCR) from January 2017 to December 2019 using Cerner ® system. The primary outcomes were progression-free survival (PFS) and overall-survival (OS) generated by Kaplan Meier curves. In addition, the safety profiles of both of the two medications were also evaluated.

Results: The data of 108 exclusive patients who met the research criteria were included in the final analysis. There was no statistically significant difference in PFS between the palbociclib and ribociclib groups; PFS time was 17.85 versus 13.55 months, respectively ($p > 0.05$). Similarly, there was no statistically significant difference in terms of OS between the two medications, 29.82 versus 31.72 months, respectively ($p>0.05$). Adverse events ratios were equivalent between the palbociclib and ribociclib groups. Neutropenia was the most common side-effect in the study population accounting for 59.3% of the patients.

Conclusions: In summary, this study found that both treatment strategies have similar efficacy and safety profiles.

1022

Drug-repositioning of beta-blockers for bladder cancer: a disproportionality inverse signal analysis in spontaneous reporting database

Mr Lipin Lukose[1], Ms. Gursimran Kaur[1], Ms. Roopa Acharya[1], Ms. Rifa Shareen[1], Ms. Amulya Bhatkal[1], Ms Gouri Nair[1], Dr. Subeesh Viswam[1]
[1]*Department of Pharmacy Practice, Manipal college of Pharmaceutical Sciences, MAHE, Manipal/Udupi, India*

Objective: To identify potential drug-repositioning of beta-blockers by inverse associations identified through disproportionality analysis in the FDA Adverse Event Reporting System (FAERS) database.

Methods: The case/non-case retrospective disproportionality analysis was performed in the publicly available FAERS database using OpenVigil 2.1(2004Q1-2022Q1). OpenVigil is a tool for extracting medication safety reports and generating new ideas based on pharmacovigilance data. The preferred term used for the study was “bladder cancer” and the drugs included were beta-blockers. The effect of beta-blockers on co-administration with pioglitazone, a drug known to cause bladder cancer was also measured. Reporting odds ratio (ROR) was used as a measure for disproportionality. A value of ROR+1.96SE<1 and ≥5 cases was considered as a threshold for inverse signal.

Results: FAERS database had a total of 39813 reports associated with bladder cancer, of which 232 reports were associated with beta-blockers. The number of case reports for metoprolol, atenolol, carvedilol, bisoprolol, timolol, propranolol, sotalol and nebivolol associated bladder cancer were 93,37,36,33,10,7,6 and 6 respectively. Majority of the beta-blockers had significant inverse signal. Propranolol [ROR 0.064(95%CI= 0.031-.135)], metoprolol [ROR 0.17(0.139-0.208)], atenolol [ROR 0.164(0.119-0.227)], carvedilol [ROR 0.181(0.131-0.251)], bisoprolol[ROR 0.154(0.109-0.216)], nebivolol[ROR 0.113(0.051-0.253)], sotalol[ROR 0.199(0.09-0.444)] and timolol[ROR 0.128(0.069-0.238)] showed inverse association with bladder cancer. A reduction in signal strength was observed for pioglitazone from ROR 91.42(88.67-94.24) to ROR 3.86(2.91-5.12) when they were co-administered with beta-blockers hinting a protective effect of beta-blockers for bladder cancer.

Conclusion: Significant inverse association was found between beta-blocker use and bladder cancer. Scanning pharmacovigilance data for inverse signals can help to generate novel theories for drug repurposing, hypothetically for all indications. To validate these findings, in silico, in-vitro and in-vivo studies must be conducted and these findings translated to the clinic.

Keywords: Beta-blockers, Bladder cancer, FAERS, inverse-signalling

1023

Carvedilol and risk of cancer in patients with heart failure

Mr Chengsheng Ju[1], Dr Wallis Lau[1], Prof Li Wei[1]
[1]*UCL School of Pharmacy, London, United Kingdom*

Aim/Objective: Carvedilol is an evidence-based beta-blocker for heart failure (HF) management. Mechanistic studies suggest that carvedilol may reduce the cancer risks due to its pleiotropic pharmacological effects. We aimed to investigate the association between carvedilol versus other evidence-based beta-blockers for HF (bisoprolol and nebivolol) and cancer risks in patients with HF.

Methods: We conducted a population-based cohort study using the IQVIA Medical Research Data (IMRD)-UK data (formally known as THIN database). All patients with their first HF diagnosis between 2000 and 2019 were identified using the Read codes from diagnostic records. Beta-blocker exposure time was defined as the time since the first prescription record after the HF diagnosis. Patients were followed from the initiation of beta-blockers after the HF diagnosis until cancer occurrence, transfer out from practice, death, or end of study period. Confounding was adjusted by applying inverse probability of treatment weighting (IPTW) based on propensity scores. The risk of cancer was estimated using Cox proportional hazard regression models. Fine and Gray's subdistribution hazard model was used to account for competing risk from death.

Results: Preliminary results showed 42,383 patients with HF were included in the study, there were 4,262 carvedilol initiators and 38,121 other beta-blocker initiators. A total of 2,910 cases of incident cancer occurred during a median follow-up time of 3.1 years (interquartile range, 1.2-6.0 years). The crude incidence rate of cancer was 15.8 cases/1,000 patient-years for carvedilol and 16.9 cases/1,000 patient-years for other beta-blockers. Carvedilol use was not associated with a lower risk of cancer [hazard ratio (HR), 1.02; 95% confidence interval (CI), 0.92-1.13). Results from Fine and Gray's model were consistent (HR. 1.07; 95% CI, 0.96-1.18).

Conclusion: Carvedilol was not associated with a lower overall cancer risk in patients with HF as compared to other evidence-based beta-blockers.

Keywords: Heart failure, cancer, cardio-oncology, beta-blocker; cohort study.

1024

Inequalities in the availability of global core 14 essential drugs in health care facilities of 7 low- and middle-income countries

Mr Shariful Hakim[1], Mr. Abdul Baker Chowdhury[2], Dr. MD Jamal Uddin[1]
[1]Shahjalal University of Science & Technology, Sylhet-3114, Bangladesh, Bangladesh, [2]Department of Emergency Neurosurgery, College of Medicine, University of Florida, Gainesville, FL, USA

Objective: To explore potential inequalities in the availability of global core 14 essential drugs (EDs) in health care facilities (HCFs) of low-and middle-income countries.

Methods: In this study, we combined publicly available, nationally representative cross-sectional data about the availability of 14 EDs in 7,783 HCFs from Service Provision Assessment (SPA) surveys by the Demographic and Health Survey Program from Bangladesh, Democratic Republic of Congo (DR Congo), Haiti, Malawi, Nepal, Senegal, and Tanzania. A drug was only considered available if it was physically observed by the data collectors, the drug had not expired, and it was appropriate for use.

Results: The number of health facilities sampled in each country ranged from 341 in Senegal to 1524 in Bangladesh. Among the 14 EDs overall, most surveyed facilities had higher availabilities of "Amoxicillin tablets/capsules", which were representative of 78.2%, and “Simvastatin tablets/capsules” were least available during the survey (2.8%). Across the seven countries, hospitals have an average of 8.5 out of the 14 drugs, whereas lower-level facilities (non-hospitals) average just 4.6 drugs. The availability of drugs was generally higher in private health facilities compared to public facilities. Private facilities have an average of 6.7 drugs throughout the seven countries, but the public has just 4.2 drugs. There were fewer drugs in HCFs in rural areas than in urban areas. On average, there were 4.4 drugs in rural areas, but there were 6.8 drugs in urban areas.

Conclusions: The majority of HCFs in our study countries lacked the availability of EDs. We discovered important, previously undetected differences in drug availability. If countries want to strengthen their health care systems by improving the availability of EDs and achieving universal coverage, they need to pay more attention to within-country disparities.

Keywords: Availability, Essential drug, Health-care facility, Service Provision Assessment

1025

Nationwide Longitudinal Observational Study (2015-2019) for Long-Term Polypharmacy Reduction by National Database focusing on Policies and Guidelines in Japan

Mr. Takehiro Ishida[1]

[1]*Teikyo University Graduate School, Itabashi-ku, 日本*

Aim: Polypharmacy is a serious health issue mainly for older adults worldwide. However, there is no comprehensive evidence on the nationwide effectiveness of polypharmacy reduction policy. In Japan, polypharmacy reduction incentives were initiated for medical facilities by nationwide medication fee amendments in 2016 and 2018. Additionally, the “Proper Medication Guideline for Older Adults” was published to encourage polypharmacy reduction for healthcare providers in 2018. This study aimed to observe the long-term reduction in polypharmacy during the period including relevant policies and guidelines.

Methods: This nationwide longitudinal observational study was conducted using outpatient prescription reimbursement claims data available in openly disclosed summary of national database (NDB) over 4 years (April 2015 to March 2019), which covers almost all reimbursement claims in Japan. Older adults were defined as 75 years and above following a new academic definition published in 2017. The primary outcome was the polypharmacy reduction ratio in each prefecture calculated by the proportion of polypharmacy. Five independent variables such as number of clinics and pharmacies were evaluated by multiple linear regression analysis using prefecture-based NDB data.

Results: We observed 14.2% as nationwide long-term polypharmacy reduction ratio for four years. Moreover, the “75–89 years” subgroup and “90 years and above” subgroup showed 18.8% and 16.1% of polypharmacy reduction at the period. Multiple linear regression analysis revealed that number of clinics per 100,000 residents showed statistically significant association with polypharmacy reduction.

Conclusion: This study showed a successful nationwide reduction of polypharmacy prescriptions after the implementation of the polypharmacy management guidelines and incentive-based policies, and the reduction is bigger among older adults (75 years and above).

Keywords: Administrative claims; aged; health policy; polypharmacy; prescription fees

1026

Impact of the National Tuberculosis Control Program in South Korea using a Nationwide Database: An Interrupted Time Series Analysis

Dr In-Sun Oh[1,2], Dr. Ju Hwan Kim[1], Dr. Ju-Young Shin[1,2,3]
[1]School of Pharmacy, SungKyunKwan University, Suwon, South Korea, [2]Department of Biohealth Regulatory Science, SungKyunKwan University, Suwon, South Korea, [3]Samsung Advanced Institute for Health Sciences & Technology, Seoul, South Korea

Aim/Objective: In South Korea, tuberculosis (TB) control programs such as Public-Private Mix (PPM) and medical expense support (MES) have been implemented at national-level for the past decades, yet long-term evaluation of these programs has not been fully explored. We evaluated the effectiveness of these programs in South Korea.

Methods: We used the National Health Insurance System database between 2002 and 2020 to conduct an interrupted time series analysis with segmented regression. The effectiveness of two programs was evaluated by comparing the following measures before and after a point of intervention: TB prevalence and incidence, multidrug-resistant TB (MDR-TB) incidence, adherence to initial treatment regimen and proportion of treatment days covered (PDC). The PPM launched in 2011 and expanded in 2017, and MES in 2011 and expanded its budget in 2016. All analyses were adjusted for age and sex, Durbin-Watson statistic was used to assess autocorrelation, and seasonal dummy variables were included in the model for eliminating seasonal trends.

Results: TB incidence decreased from 11.8 (per 100,000 population) to 3.7, and the prevalence from 167.8 to 79.0 in 2004 and 2020, respectively. Treatment adherence improved throughout the study period: initial regimen adherence from 58.1% to 86.0%, PDC from 37.6% to 71.9% in 2004 and 2020, respectively. Following the PPM, there were monthly decline of -0.11% (95% confidence interval, -0.15 to -0.06) and -1.68% (-1.98 to -1.40) for TB incidence and prevalence, respectively, and monthly increase of 0.13% (0.03 to 0.23) and 0.12% (0.01 to 0.23) for initial regimen adherence and PDC, respectively. Following the MES, non-significant improvements were observed for TB incidence (-2.84%), MDR-TB incidence (-0.26%) and PDC (+4.36%).

Conclusion: We confirmed the long-term effectiveness, and advocate for sustained implementation of these programs to achieve the target goals of End TB strategy.

1027

Professionals' and patients' perspective on role of community pharmacists in pharmacovigilance and patient counseling

Dr Irina Kazaryan[1], Anahit Amirkhanyan[1], Dr. Anahit Sevikyan[1], Margarita Melikyan[2]
[1]Yerevan State Medical University, Yerevan, Armenia, [2]Manamey pharmacy, Yerevan, Armenia

Aim/Objective: In many countries community pharmacists are involved in pharmacovigilance and patient counseling. However, in some countries they are not active enough in reporting adverse drug reactions (ADR). Awareness of professionals and patients about engagement of community pharmacists in reporting ADR and other medicines use problems, as well as in counseling on medication safety is essential for improving effectiveness and safety of medicines use. The objective of this work was to study attitude of pharmacy professionals and patients to role of community pharmacy staff in providing patient medication safety in Armenia.

Methods: 297 pharmacy professionals, as well as 2066 patients were interviewed in Yerevan (capital of Armenia) according to designed and pretested questionnaire.

Results: 68.0% of pharmacists and technicians consider that community pharmacists in Armenia are engaged in ADR reporting; 66.6% of professionals indicated that they wish to be involved in this activity. 215 (72.4%) professionals supposed that community pharmacists are engaged in providing advices related to medicines safety and indicated that they are interested to be involved. More than a half of patients (56.7%) reported that they wish community pharmacy staff would be involved in ADR reporting; 54.0% indicated they would like pharmacists would provide advices related to medicines safety. The number of patients who think that pharmacists are already engaged in these activities was much less: 726 (35.1%) and 876 (42.4%), correspondingly ($p<0.001$).

Conclusion: Most of pharmacy professionals and patients are interested that community pharmacy staff would be involved in ADR reporting and advising on medicines safety issues. Some pharmacy professionals and most of patients are not aware about this role of pharmacy staff. Special educational strategies aimed to improve knowledge of pharmacists and awareness of patients could be beneficial. Lecture on Pharmacovigilance was included in continuing education course curricula for pharmacy professionals.

Keywords: pharmacovigilance, medicines safety, pharmacists.

1028

Incorporating telepharmacy into COVID-19 patient care could improve patients with their drug related problems: a preliminary study

Rujira Panya[1], Mrs. Adinat Umnuaypornlert[2]
[1]Dokkhamtai hospital, dokkhamtai, Thailand, [2]Division of Social and Administrative Pharmacy, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Muang, Thailand

Objective: Telepharmacy has been applied in the era of COVID-19 epidemic. However, the impact of telepharmacy in reducing drug-related problems (DRPs) in COVID-19 patients is still unknown. This study explored whether telepharmacy in home isolation COVID-19 patients could improve their DRPs.

Method: A survey was conducted in DokKhamtai district, Phayao Province, Thailand. From April 2022 to May 2022, 90 COVID-19 patients were interviewed by pharmacists using the validated questions. Telepharmacy processes raised from the cooperation of multidisciplinary. Primary care unit(PCU) sent a list of patients who had symptoms that compatible with COVID-19 to the hospital. The doctors diagnosed infection. Then pharmacists prepared and delivered medicines to PCUs. Patients got the medicines with leaflet from the community health workers. At day 2 after drug delivery, pharmacists followed up patients' symptoms and DRPs by telephone. If pharmacists found DRPs, they would solve the problems. The patients were followed up at day 5 after the first interview. Descriptive statistics was used to analyze data in this study.

Result: Ninety patients were followed up by telephone. Most of them were women (51.11%). 36.67% was <10 years. 28.89% were >61 years. 42.30% was at risk of developing severe symptoms. A drug waiting time was 1.55±0.99 days. 19 patients had drug related problems in the first follow up, which were 10 patients with adverse drug reactions and 4 need for additional drug therapy. One case had dosage too low and 1 case had dosage too high. Three patients had drug-herbal interactions. All DRPs were managed by pharmacist. All problems were resolved and followed up at the second interview. Most patients satisfied with this system.

Conclusion: From this preliminary study, Telepharmacy could improve DRPs in COVID-19 patients. We still need to monitor long term effectiveness and safety of using telepharmacy in patients even when COVID-19 epidemic is over.

1029

Interventions and Outcomes Related to Pharmacist Services for People Infected with COVID-19: A Systematic Review

Mr Ali Ahmed[1], Mr Sunil Shrestha[1], Dr Juman Dujaili[1], Dr Saval Khanal[2], Dr. Vibhu Paudyal[3]
[1]Monash University, Sunway, Malaysia, [2]University of Warwick, Coventry, United Kingdom, [3]University of Birmingham, Edgbaston, United Kingdom

Aim/Objective: Pharmacists are essential members of the healthcare team. The emergence of the coronavirus disease 2019 (COVID-19) pandemic has led to pharmacists undertaking additional clinical roles. This study systematically reviewed the pharmacist-services for those infected with COVID-19.

Methods: We searched PubMed, Embase, Scopus, CINAHL, International pharmaceutical abstracts and Web of Science from 1st December 2019 (first case of COVID-19 emerged) to 13th January 2022 to find the original research studies. Cochrane handbook of systematic reviews of interventions and PRISMA guidelines were followed for procedures and reporting of the review. pharmacist-led interventions were elaborated as reported by Descriptive Elements of Pharmacist Intervention Characterization Tool (DEPICT) version2. Newcastle Ottawa scale was used to assess study quality because all of the included studies were observational. The protocol of systematic review was registered on PROSPERO(CRD42021277128).

Results: Database searches yielded 10,838 citations; after the screening, seven original studies met the inclusion criteria, three of which were prospective cohorts and four were retrospective observational cohorts. Pharmacist interventions comprised of medication therapy management (n=7), therapeutic drug monitoring (n=7), adjusting doses (n=7) and informing physicians (n=3) about the change of therapy, and counseling of COVID-19 patients (n=7) regarding medicine and disease progression through face to face or electronic health records or tele pharmacy. Pharmacists were involved in the COVID-19 patient's regimen modifications 15.9%-20%, dosage adjustments 15.2%-36.7%, terminating the wrong medicines 34%-40%, and managing the common adverse drug reactions e.g., diarrhea, body rashes, and induced hepatitis caused by antibacterials, antivirals, anticoagulants. Suggesting the alternatives 39%-40% in case of missing drugs and the physician's acceptance rate of pharmacist suggestions was in the 88.5-95.5% range.

Conclusion: Findings show that pharmacists play important roles in COVID-19 treatment and have proven to be effective healthcare team members by detecting, resolving, and preventing medication errors and medication-related problems, ultimately saving healthcare and societal costs.

1030

Impact of the universal seasonal influenza vaccination policy in Manitoba, Canada: a population-based, province-wide record-linkage study

Mr George Okoli[1], Dr Christiaan Righolt, Mr Geng Zhang, Prof. Silvia Alessi-Severini, Dr. Paul Van Caeseele, Dr. I fan Kuo, Prof. Salaheddin Mahmud
[1]*University of Manitoba, Winnipeg, Canada*

Aim/Objective: Manitoba, Canada introduced universal seasonal influenza vaccination policy (USIVP) in 2010, providing seasonal influenza vaccine (SIV) free-of-charge to registered residents (Manitobans) at least, six months of age. We aimed to assess the impact of the USIVP on SIV uptake (vaccine receipt).

Methods: We conducted an ecological study utilizing the Manitoba immunization registry linked with other Manitoba administrative health databases. The study period was from 2000/01 to 2019/20 influenza seasons. The primary exposure was USIVP (five influenza seasons pre-policy [2005/06 to 2009/10] compared with post-policy [2010/1 to 2014/15]). The outcome was SIV uptake. We conducted pre-post logistic regression analysis stratified by age groups (<5, 5-17, 18-44, 45-64, ≥65 year-olds) and certain population socioeconomic and health-related characteristics. We presented results as adjusted odds ratios with 95% confidence intervals (CI).

Results: The adjusted odds of SIV uptake post-policy relative to pre-policy was significantly increased among all age groups except for ≥65 year-olds. The odds ratios ranged from 0.76 (95%CI 0.75-0.76) among ≥65 year-olds to 2.15 (95%CI 2.13-2.18) among 5-17 year-olds, but were largely homogeneous within age groups across sex, income quintile, and region of residence, and across categories of number of visits to primary care physician/hospitalization one year prior to an influenza season, except among <5 and 5-17 year-olds. Within age groups, the odds ratios were higher for not having a chronic disease compared with having, except for ≥65 year-olds among whom we observed homogeneity. These findings were mostly consistent irrespective of sex and region of residence although there was variability across income quintiles in Northern Manitoba.

Conclusion: USIVP possibly led to increased SIV uptake among age groups <65 years in Manitoba and may have had similar impact on SIV uptake across important population characteristics within age groups. The variation across income quintiles in predominantly indigenous Northern Manitoba requires attention.

Keywords: Influenza

1031

Risk of idiopathic thrombocytopenic purpura (ITP) and thrombocytopenia after influenza vaccination in elderly: a self-controlled case series (SCCS) study

Miss Hee-Jin Kim[1], Eunsun Lim[1], Haerin Cho[1], Na-Young Jung[1], Nam-Kyong Choi[1]
[1]*Department of Health Convergence, Ewha Womans University, South Korea*

Aim/Objective: To confirm the association between influenza vaccination and idiopathic thrombocytopenic purpura (ITP) among the elderly in Korea using a national database.

Methods: We identified the cases aged 65 years or older who had one or more ITP (ICD-10 code: D69.3) or thrombocytopenia (ICD-10 codes: D69.4, D69.5, D69.6) hospitalization episodes from September 2, 2017 to October 30, 2018 using a linked database of vaccination registration data from the Korea Disease Control and Prevention Agency and the National Health Insurance Service claims data. The cases were restricted to those who received the influenza vaccine once between September 1, 2017 and April 30, 2018 (17/18 season). We performed within-person comparisons using the self-controlled case series (SCCS) study design, the cases were followed up for 6 months from the dates of vaccination. The risk period was defined as 1 to 42 days, remaining periods were classified as control periods. We estimated the incidence rate ratio (IRR) between two periods. We also performed an additional subgroup analysis limited to ITP patients.

Results: In total, 1,693 cases with ITP or thrombocytopenia were identified, 365(21.6%) of whom were included in the risk period. Influenza vaccination showed a protective effect on ITP and thrombocytopenia during 42 days following vaccination compared to control period [IRR 0.65; 95% confidence interval (CI) 0.59-0.73]. Consistent results were also observed in sensitivity analyses, which set the risk period to 28 days and 84 days, respectively. When cases were limited to ITP, we found a tendency to increase the risk of ITP within 42 days after vaccination, but it was not significant [IRR: 1.14; 95% CI: 0.59-2.22].

Conclusion: The influenza vaccination was associated with a reduction in incidence of overall thrombocytopenic disorder. However, a subgroup analysis showed the possibility of an increased risk of ITP following influenza vaccination, thus further studies are needed.

1032

Pain assessment and prescription pattern of analgesics in the current practice of pain management in a tertiary care hospital; India

Jerin James[1], Mr Elstin Anbu Raj S[1], Dr Naveen S Salins[2], Dr Anuja Dwarkadas Damani[2], Dr Rajesh V[1,3]
[1]Department of Pharmacy Practice, Manipal college of Pharmaceutical Sciences, Manipal, India, [2]Department of Palliative Medicine and Supportive Care, Kasturba Medical College, Manipal, India, [3]Centre for Pharmaceutical Care, Manipal Academy of Higher Education, Manipal, India

Objective: Current study aimed to evaluate the pain assessment practice and prescribing pattern of analgesics in a tertiary care hospital.

Methods: It was a prospective observational study. Required data were collected from patient's medical notes and recorded in a pre-designed proforma. Ethical clearance was obtained from institutional ethics committee.

Results: The sample size was 317, in that 55.6% patients were male and remaining were female. Mean age of the patients was 51.04± 16.671. Most of the patients experienced mild to severe pain. Out of the 317, the pain was assessed in 89.6% of the patients. Wong-Baker face pain scale (WBFPS) was used for assess the pain in all the patients. Additionally, Numerical rating scale (NRS) (5.3%) was also used. Around 10.4% of the patients were administered analgesics without assessing the intensity of the pain. Even though, after initial assessment, proper follow-up and documentation were not performed in WBFPS and NRS, 33.5% and 26.7% respectively. Non-steroidal anti-inflammatory drugs, weak opioids and strong opioids were prescribed for controlling the pain in both pain assessed and non-assessed group, Paracetamol, Tramadol and Nalbuphine respectively. The commonly prescribed fixed drug combinations were Paracetamol + tramadol and Aceclofenac + paracetamol.

Conclusion: The pain assessment and documentation had some drawbacks in the study setting. An inevitable number of patients received opioids and non-opioids (strong and weak) without the pain assessment, which may result in adverse effects associated with the drugs. irrational usage of fixed drug combinations must be curtailed. Rather than the intensity of the pain, the interference due to pain in the patient's life also has to be evaluated for better pain management. So, a uniform pain assessment system must be developed in our hospital for providing better patient care, with consistent follow-up for adequate management in clinical practice.

Keywords: Pain assessment, Pain scale, Prescription pattern

1033

Human papillomavirus vaccine (HPV): India has a knowledge gap?

Dr Sheba Baby John[1], Dr. JUNY SEBASTIAN[1]
[1]*JSS College of pharmacy, Mysuru, India, Mysuru, India*

Background: Cervical cancer is the second most common cancer and due to this, more women in India die than in any other country. Human papilloma-virus (HPV) is the known cause of anogenital cancers. The HPV vaccine has proven its efficacy to reduce the incidents rate of these cancers worldwide. And also, HPV vaccines provide some cross-protection against the HPV types not included in vaccines. Unfortunately, the utilization rate of the HPV vaccine is very low compared to the other vaccines in the country.

Aim: To find out the root cause of low HPV Vaccine uptake in India.

Method: An observational study was conducted for a period from 2020 to 2022 in a tertiary care teaching hospital. Eligible study participants enrolled after taking informed consent exclusively designed as per the requirements of the Indian Council of Medical Research guidelines for biomedical research on human subjects. The study used Vaccine Hesitancy Open-Ended Survey Questions developed by WHO SAGE WG and data collection were done.

Results: Out of 315 individual participants, 44.76% (n=141) were accepting and 41.59%(n=131) study population is unaware of HPV Vaccine. Among this, 13.65% (n=43) were hesitant/refusers of HPV Vaccine. The general public including parents and future parents hesitated/ refused vaccination with the concerns of “Didn’t think it was needed”, “Didn’t know where to get reliable information” and “Didn’t think the vaccine was effective.”

Conclusion: The potential benefit of the HPV vaccine with cross-protection can help in the elimination of anogenital cancer caused by human papillomavirus. Recall-based interventions can be helpful to the parents, as the childhood vaccination in the country will be followed up till 10 years of age.

Keywords: Acceptance, Hesitancy, Refusal, Vaccine

1034

Impact of changing reimbursement criteria on Anti-VEGF treatment patterns among wAMD patients: An interrupted time series analysis

Miss Lin-Chieh Meng[1], Yu-Wen Huang[2], Professor Fei-Yuan Hsiao[1,2,3]

[1]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [2]School of Pharmacy, National Taiwan University, Taipei, Taiwan, [3]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan

Objectives: Under Taiwan's National Health Insurance, the reimbursement criteria for anti-VEGF used in wet Age-Related Macular Degeneration (wAMD) has been revised several times during the past decades. This study aims to evaluate the impact of reimbursement criteria change on the utilization pattern of anti-VEGF among wAMD patients in Taiwan.

Methods: An interrupted time series analysis (ITSA) was performed using Taiwan's National Health Insurance Research Database (NHIRD), and patients with wAMD diagnosis at first injection of anti-VEGF agents was identified from 2011 to 2019. Outcome of interest was time intervals between injections of anti-VEGF. The outcome of interest was retrieved quarterly, and the study period was divided according to the following regulations: (i) cancelled the annual three needles limitation and increased a maximum number of needles from six to seven, and (ii) prolonged the usage period for each application. Segmented regression models adjusted for autocorrelation were used to estimate the level change and the trend change of the time intervals between each anti-VEGF injections.

Results: The time intervals between each anti-VEGF injections decreased from 2011 to 2019. The cancellation of the annual three needles limitation was associated with a significantly shortened time intervals between the third and fourth needles (level change: -214.6 days [95%CI -259.5, -167.0], trend change: 1.2 [-6.4, 8.8]). However, prolongation of the usage period for each application revealed less effect on the time intervals (level change: 3.6 days [95%CI -39.0, 46.2], trend change: 1.3 [-6.4, 9.0]).

Conclusions: This is the first nationwide study using ITSA to demonstrate the impact of reimbursement policy on time intervals between each anti-VEGF injections. We found that after cancelling the annual three needles limitation, the time intervals was significantly decreased among wAMD patients. Future studies were warranted to explore whether such changes are associated with the benefits of visual effects.

1035

Real-World Treatment Patterns for Atopic Dermatitis in South Korea: A Nationwide Claims Database Analysis

Jihyun Lee[1], Ms Ahhyung Choi[2], Yunha Noh[2,3], In-Sun Oh[2,3], Ja-Young Jeon[4], Hyun-Jeong Yoo[4], Ju-Young Shin[2,3,5], Sang Wook Son[6]

[1]Department of Dermatology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [2]School of Pharmacy, Sungkyunkwan University, Suwon, South Korea, [3]Department of Biohealth Regulatory Science, Sungkyunkwan University, Suwon, South Korea, [4]Pfizer Pharmaceuticals Korea Ltd, Seoul, South Korea, [5]Department of Clinical Research Design & Evaluation, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, South Korea, [6]Department of Dermatology, Korea University College of Medicine, Seoul, South Korea

Aim/Objective: The phenotypes of atopic dermatitis (AD) are diverse, and ethnic differences have been suggested. To date, few studies have explored large-scale national data on the treatment patterns of AD in Asians. Therefore, we aimed to examine the real-world treatment patterns for AD, including the probability of discontinuation of AD treatment and restart after discontinuation.

Methods: A retrospective observational study was conducted using the Health Insurance Review and Assessment Service database in South Korea between January 1, 2016, to July 31, 2020. We identified patients who were newly diagnosed with AD and subsequently received at least one prescription for AD treatment. Prevalence of medication use at the treatment initiation and during the entire observational period were examined. Treatment discontinuation and restart were described.

Results: We identified 944,559 pediatric patients (<18 years) and 1,066,453 adults (≥18 years) with AD. Topical corticosteroids and antihistamines were the most commonly prescribed medications in all age groups. The frequency of topical corticosteroid prescription decreased as the age increased (0–1 year, 85.4%; 12–17 years, 71.7%, 18–39 years, 64.1%; ≥60 years, 58.9%). The median daily dose of systemic corticosteroids increased with age (5.0, 7.5, and 10.0 mg/day in the 0–5, 6–11, and ≥12-year groups, respectively). Although immunosuppressive drugs were not widely used in both children and adults, cyclosporine was the most frequently prescribed immunosuppressant, particularly among those aged ≥12 years or more (1–2%). Pediatric patients were more likely to discontinue treatment than adult patients. Treatment restart for moderate-to-severe AD was earlier than that for overall AD.

Conclusion: Differences were observed in the treatment patterns of AD between pediatric and adult patients. These findings will improve our understanding of the latest treatment patterns for AD, which may contribute to decision-making in clinical practice.

Keywords: Atopic dermatitis; claims database; treatment pattern

2000

Gabapentin misuse, abuse, suicide, dependence and behavior related adverse event reports: data mining within the FDA adverse events reporting system (FAERS)

Ms Hanya Aboulnaga[1]
[1]*Alsalam Port said General Hospital, Egypt*

Evaluation of Drug Dependence and International Product Misuse Related Adverse Event Reports Attributed to Gabapentinoid Use Within the FDA Adverse Events Reporting System (FAERS).
Gabapentin and pregabalin are widely prescribed in various clinical conditions. Although they are prescribed at therapeutic dosages that have low addictive liability levels, the prevalent to drug dependence and misuse are now increasing.

The aim is to evaluate cases of gabapentinoids misuse and drug dependence related adverse event reported to the FDA-Adverse Events-Reporting-System (FAERS)، compare pregabalin with gabapentin, the proportional reporting ratio (PRR)approach.
Data mining within the published FAERS database starting January2015to March2019 were queried for reports listing drug abuse, complete suicide or attempt suicide and behavior related to the adverse event due to theuse of Gabapentin or Pregabalin as the primary suspected drug was retrieved. The proportional reporting ratio (PRR)and the reporting odds ratio (ROR)were calculated.

Among2,420,910FAERSreports over the period of January 2015 to March 2019, 112 (0.33% of a total of 34,130) and1003(1.66% of a total of 60,255) adverse drug reaction reports of drug dependence and product-misuse related adverse events were, respectively, associated with gabapentin and pregabalin, an overall reporting increase over time.

We calculated the proportional reporting ratio(PRR)and the reporting odds ratio (ROR) for the Gabapentin were: Drug dependence (PRR:2.05,95%CI:1.24-3.41, ROR:2.06,95%CI:1.24-3.42).International-product-misuse (PRR:2.39,95%CI:1.96-2.92,ROR:2.41,95%CI:1.97-2.95).The PRR and ROR for the pregabalin were: Drug dependence(PRR:11.33,95%CI: 9.56-13.43,ROR:11.45,95%CI:9.64-13.59). International product misuse (PRR:12.74,95%CI:11.92-13.61,ROR:13.64,95%CI: 12.70-14.65).

Analysis of proportional reporting ratios for drug dependence and international produced misuse events values seem to indicate that these adverse drug reactions were more frequently reported for pregabalin (5.24,5.045 respectively) compared with gabapentin. As PRR greater than1,so the adverse event is commonly reported for individuals taking the drug of interest, relative to gabapentin.
Although FAERS is subjected to limitations, the present data seem to suggest that gabapentinoids may be a cause for concern, especially in patients with a history of substance misuse. Hence, healthcare professionals should be vigilant when prescribing those agents.

2001

The Suicide Risk of Augmentation Therapy in Patients with Treatment-resistant Depression – a population-based cohort study

Daniel Hsiang-Te Tsai[1,2], Mr. Avery Shuei-He Yang[1], Mr. Zi Xuan Wong[1], Dr. Edward Chia-Cheng Lai[1]
[1]School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [2]Centre for Newborns and Paediatric Infection, St George's University of London, London, UK

Aim/objective: To evaluate the suicide risk of augmentation therapy in patients with treatment-resistant depression (TRD).

Methods: We conducted a population-based cohort study using data from the National Health Insurance Database (NHID) to include patients diagnosed with depression who had previously received two antidepressants between January 1, 2002, and December 31, 2013. Patients with dementia, schizophrenia, bipolar disorder, alcoholism, and a history of antipsychotic usage within the past year are excluded to avoid misclassification. The outcome was suicide-related injuries and all-cause mortality. We used propensity score fine-stratification to conduct pairwise comparisons across patients who received antipsychotics and third-line antidepressants to estimate hazard ratios (HR) and 95% confidence intervals (95% CIs) for outcome events.

Results: We included a total of 14,051 patients with TRD (6295 patients had antipsychotics, and 7756 patients had third-line antidepressants). The mean age was 50.5 (SD 17.3) years and 35.2% were male. Compared to patients who received third-line antidepressants, patients receiving antipsychotics was not associated with increased suicide and self-inflicted injuries (adjusted HR 0.75, 95% CI 0.54-1.04). Interestingly, compared to patients who received third-line antidepressants, patients receiving antipsychotics marginally decreased their risk of all-cause mortality compared to those who received antidepressants (adjusted HR: 0.78; 95% CI: 0.68-0.90).

Conclusion: The study depicted that controlling the condition with antipsychotics may even benefit patients with TRD. The finding warrants further investigation into for the use of antipsychotics in patients with TRD to reduce unintended outcomes.

Keywords: treatment-resistant depression, antipsychotics

2002

The risk assessments of suicide attempts and commit suicide for asthma patients using Montelukast: a retrospective cohort study

Te-Jung Kung[1], Ming Neng Shiu[1]
[1]*Faculty of Pharmacy, National Yang Ming Chiao Tung University, Taiwan*

Objective: The study objective is to explore the effect of montelukast on suicide risk, including suicidal ideation, self-harm, suicide attempt and completed suicide, in asthma patients in Taiwan.

Methods: This is a retrospective cohort study through 2010-2019 National Health Insurance Research Database. Asthma patients with at least 60 days of montelukast exposure, classified as exposed group, would be 1:1 matched by age, sex and medication starting date to those with at least 60 days of ICS exposure but less than 60 days of montelukast exposure, classified as control group. Cox proportional hazard model is used to analyze the primary outcome, which is time to self-harm/suicide attempt or completed suicide events. Generalized estimating equation with negative binomial distribution is used to analyze the secondary outcome, which is the count of self-harm/suicide attempt or completed suicide events during the follow-up time.

Results: For primary outcome analyses, montelukast users had 1.51 times higher hazard rate of suicide than ICS users after the adjustment though the result is insignificant (95%CI 0.70-3.21). There're no significant results in any subgroups analyses either.
For secondary outcome analyses, montelukast users had 2.49 times higher risk of suicide than ICS users after the adjustment with statistical significance (95%CI 1.19-5.22). For the elderly with montelukast use, the adjusted rate ratio increased to 7.98 (95%CI 1.65-38.45). In those with follow-up period longer than 90 days, the adjusted rate ratio increased to 4.41 (95%CI 1.33-14.69).

Conclusion: There's significantly increased risk of suicide in the montelukast users compared to the ICS users, especially for the elderly and those using montelukast for more than 90 days. We suggest that for those who are considered to start the montelukast treatment, the suicide risk should be taken into account while making medical decisions, especially for the elderly.

Keywords: Montelukast; Asthma; Suicide; Retrospective cohort study

2003

Association of long-acting injectable and oral antipsychotics with hospitalizations for substance use in people with schizophrenia and comorbid substance use

Miss Yue Wei[1], Mr. Vincent KC Yan[1], Prof. Ian CK Wong[1,2,3], Prof. David J Castle[4,5], Dr. Wing Chung Chang[6,7], Dr. Esther W Chan[1,2,8]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, China, [2]Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, China, [3]Research Department of Practice and Policy, UCL School of Pharmacy, UK, [4]Centre for Addiction and Mental Health, University of Toronto, Toronto,, Canada, [5]Department of Psychiatry, University of Toronto, Toronto, Canada, [6]Department of Psychiatry, Queen Mary Hospital, The University of Hong Kong, China, [7]State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, China, [8]The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China

Objective: To compare the risk of hospitalizations for substance use between long-acting injectable antipsychotics (LAIAs) and oral antipsychotics (OAs) among people with schizophrenia and comorbid substance use in Hong Kong.

Methods: In this population-based self-controlled case series study, we used the electronic medical record database of the Hong Kong Clinical Data Analysis and Reporting System (CDARS) to identify people diagnosed with schizophrenia (International Classification of Diseases-9th Revision 295) and prescribed LAIAs and OAs during 2004-2019. Risk of hospitalizations for substance use between the full treatment periods of LAIAs alone and OAs alone was compared using Poisson regression by adjusting for age and season. The risk during the subsequent treatment periods (beyond the first 90 days in each treatment) of LAIAs alone and OAs alone was further evaluated.

Results: Of the 70,396 individuals with schizophrenia, 5336 (mean [SD] age, 37.5 [12.1] years; male, 61.2%) had at least one record of substance use in Hong Kong public health sectors and 2428 (mean [SD] age=35.4 [10.1] years; male, 65.7%) were prescribed LAIAs and OAs during the observation period. The absolute incidence of hospitalizations for substance use was 0.46/person-year for LAIAs treatment period and 0.53/person-year for OAs treatment period, and the adjusted incidence rate ratio (IRR) was 0.80 (95% CI 0.72-0.90). Similar associations (IRR=0.84 [0.72-0.99]) were observed between the subsequent treatment periods of LAIAs alone and OAs alone. After stratifying the patients by sex, the association was significant in males (IRR=0.79 [0.70-0.89]) but not in females (IRR=0.81 [0.62-1.06]).

Conclusion: The use of LAIAs was associated with a lower risk of hospitalization in patients with schizophrenia and comorbid substance use, especially in males. Clinicians should assess for broader use of LAIAs over OAs in appropriate clinical settings.

2004

Association between risk of neurodegenerative diseases and combined antiretroviral therapies in patients with HIV infection

Hye-Min Park[1], Ju-Young Shin[1]
[1]*School of Pharmacy, Sungkyunkwan University, Suwon-si, South Korea*

Background: For neurodegenerative diseases in human immunodeficiency virus (HIV) patients, the risk of neurodegenerative diseases has been lowered with the introduction of antiretroviral combination therapies(cART), combination of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTI). Although the neurotoxicity and increased life expectancy of cART are risk factors for neurodegenerative diseases, NNRTIs and NRTIs are related to the improvement of neurodegenerative diseases. The risk of neurodegenerative diseases is expected to be higher for those using combination of NNRTIs and NRTIs than those using other cARTs when the combination therapy improves neurodegenerative diseases. Herein, the risk of neurodegenerative diseases by cART was investigated using national based-claims data from the Health Insurance Review and Assessment Service in Korea.

Methods: In this study, HIV patients 30 years-old or older, and initiated cART between 2008 and 2012 were selected. The selected patients were divided into NNRTIs-, PIs-, or INSTIs-users. The incidence of neurodegenerative diseases was defined by prescriptions with diagnosis code and disease-related treatments. the inverse probability treatment weighting (IPTW) method using the propensity score estimated through gradient boosted modeling was applied to adjust covariates. The hazard ratios and 95% confidence interval (CI) for incidence of neurodegenerative diseases were estimated using a cause-specific proportional hazard model for considering competing risk.

Results: As a result, 2,788 cART users, consisting of 931 NNRTI users, 1,668 PI users, and 189 INSTI users were selected for this study. In multivariate analysis with IPTW, there was no significant increase in the risk of neurodegenerative diseases in the PIs users compared to the NNRTIs users. However, the risk of neurodegenerative disease was 3.05 times higher in the INSTIs users (95% CI 1.03-9.01: p-value=0.0439) compared to the NNRTIs users.

Conclusions: This study suggests that INSTI-related regimens had a higher risk of neurodegenerative diseases compared to NNRTI-related regimens.

2005

Effectiveness and safety of continuous use of low-molecular-weight heparin versus switching to Non-vitamin-K antagonists in patients with cancer-associated venous thromboembolism

Ms Wei KANG[1], Vincent K.C. Yan[1], Caige Huang[1], Silvia T.H. Li[1], Xuxiao Ye[1], Yue Wei[1], Shing Fung Lee[2,3,4], Victor H.F. Lee[5], Xue Li[1,6,7], Celine S.L. Chui[6,8,9], Francisco T.T. Lai[1,6], Eric Y.F. Wan[1,6,10], Carlos K.H. Wong[1,6,10], Ian C.K. Wong[1,6,11,12,13], Esther W. Chan[1,6,12,13]
[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, China, [2]Department of Clinical Oncology, Tuen Mun Hospital, Hospital Authority, China, [3]Department of Clinical Oncology, The University of Hong Kong, China, [4]Department of Radiation Oncology, National University Cancer Institute, Singapore, [5]Department of Clinical Oncology, Queen Mary Hospital, LKS Faculty of Medicine, The University of Hong Kong, China, [6]Laboratory of Data Discovery for Health (D24H), China, [7]Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong,China, [8]School of Nursing, LKS Faculty of Medicine, The University of Hong Kong, China, [9]School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, China, [10]Department of Family Medicine and Primary Care, LKS Faculty of Medicine, The University of Hong Kong, China, [11]Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom, [12]Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, China, [13]The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China

Aim/Objective: Subcutaneous injection of low-molecular-weight heparin (LWMH) for at least six months is the mainstay treatment for patients with cancer-associated venous thromboembolism (VTE) (CAT). We aimed to evaluate the effectiveness and safety of continuous use of LMWH versus switching to Non-vitamin-K antagonists (NOACs) in patients with CAT.

Methods: We conducted a territory-wide cohort study using electronic health records managed by the Hong Kong Hospital Authority. Patients with a CAT diagnosis between January 1, 2010 and December 31, 2021 were included. An inverse probability of treatment weighting (IPTW) approach was used to balance the baseline characteristics in the two treatment groups. Cox proportional hazards regression was used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for recurrent VTE, major bleeding, and all-cause mortality. Competing risk analysis using the Fine and Gray proportional sub-hazard model was also conducted with all-cause mortality as the competing event of interest.

Results: A total of 4,556 patients with CAT were included (Switching to NOAC users: 1,286 [28%]; Continuous LMWH users: 3,270 [72%]). The incidence of recurrent VTE, major bleeding, and all-cause mortality was 14.57, 4.61, and 24.65 per 10,000 person-days in the NOAC groups, 18.39, 5.55, and 37.81 per 10,000 person-days in the LMWH groups. Compared to continuous LMWH treatment, switching to NOACs was associated with a lower risk of recurrent VTE (HR 0.82, 95% CI 0.73-0.92) and all-cause mortality (HR 0.70, 95% CI 0.64-0.75), and no significant difference of major bleeding (HR 0.87, 95% CI 0.72-1.06) in patients with CAT.

Conclusion: In this territory-wide study of patients with CAT, we observed a lower risk of recurrent VTE and all-cause death, and non-inferior major bleeding risk in patients switching to NOAC treatment compared to continuous LMWH treatment.
Keywords: low-molecular-weight heparin (LWMH), Non-vitamin-K antagonists (NOACs), Venous thromboembolism (VTE), cancer-associated VTE (CAT)

2006

Evaluation of Statin Exposure and Influenza Vaccination on Risk of Rhabdomyolysis: A Case-Centered Analysis

Che-Yu Chen[1], Wan-Ting Huang[2], Miyuki Hsing-Chun Hsieh[1], Edward Chia-Cheng Lai[1]
[1]School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [2]National Taiwan University Children's Hospital, Taipei, Taiwan

Objective: To evaluate the risk of rhabdomyolysis in patients receiving statin and those with or without influenza vaccination concurrently.

Methods: We used a case-centered design and identified incident rhabdomyolysis cases during 2016 to 2018 from Taiwan's National Health Insurance Database. We included patients aged 50+ years receiving influenza vaccine within 1 year before rhabdomyolysis. We defined the rhabdomyolysis diagnosis date as the index date. We selected controls from the general population for each case and assigned the same index date. The matching criteria included sex, age (+/-2 years), other rhabdomyolysis risk factors (e.g., fibrates), and had influenza vaccination within a year before the index date. We used stratified logistic regression to estimate odds ratio (OR) by comparing observed odds to expected odds. The observed odds were binary variables based on exposure of statin during the 1 to 30 days risk interval before the index date. Expected odds were calculated as the proportion of matched controls who had exposed to statin during the same risk interval among all matched controls. We further stratified by whether patients had influenza vaccination within 0 to 7 days risk interval before the index date.

Results: We identified 2,527 cases with a mean age of 71.7 years (SD, 11.4) (67% male) and 5,632,174 matched control population. Compared to the controls, we found those with statin had higher risk of rhabdomyolysis (OR, 1.10; 95% CI, 1.00–1.21) regardless of influenza vaccination. Specifically, the risk profile was similar for those without influenza vaccination (1.09; 0.99-1.20), but the risk magnitude was increased for those had influenza vaccination (2.32; 1.06-5.20).

Conclusion: The findings suggested the exposure of statin was associated with risk of rhabdomyolysis. Moreover, the risk magnitude of rhabdomyolysis could be increased when patients received influenza vaccination and statin concurrently.

Keywords: influenza vaccine, statin, rhabdomyolysis, safety.

2007

PCSK9 Inhibitors and Infection-related Adverse Events: a pharmacovigilance study using the World Health Organization VigiBase

Ms DaHyun Park[1], Sungho Bea[2], Hyesung Lee[1], Ju-Young Shin[1,2,3]
[1]Department of Biohealth Regulatory Science, Sungkyunkwan University, Suwon, South Korea, [2]School of Pharmacy, Sungkyunkwan University, Suwon, South Korea, [3]Department of Clinical Research Design & Evaluation, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, South Korea

Aim/Objective: Protein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is a novel lipid-lowering agent for patients with cardiovascular disease. Although a substantial number of infection-related adverse events (AE) have been reported from landmark trials, increasing evidence has shown that PCSK9 induced viral infection. Thus, the association between PCSK9 inhibitors and infection remains controversial and needs to be addressed. This study aimed to identify the signals of infection-related AE associated with PCSK9 inhibitors.

Method: We performed an observational pharmacovigilance study using World Health Organization (WHO) VigiBase between Jan 1967 and Apr 2022. We included individual case safety reports (ICSRs) of PCSK9 inhibitors including alirocumab and evolocumab, compared with all other drugs. Infection-related ICSRs were retrieved using MedDRA System Organ Class “Infections and infestations”. Disproportionality analyses were conducted by calculating the reporting odds ratio (ROR) with 95% confidence intervals (CI).

Results: Among the total of 106,900 reports (122,706,481 drug-AE pairs) of PCSK9 inhibitors, 7797 reports (12,902 drug-AE pairs) were identified as infection-related AEs. The majority of ICSRs were female (54%), aged 65 and older (41%), and received evolocumab (81%). In addition to labeled AE noted by regulatory authorities, organ infections including gastrointestinal, urinary tract, and renal infections were identified. Specifically, signals for gastric infection (ROR 2.99, 95% CI 2.13-4.20), gastroenteritis viral (ROR 1.25, 95% CI 1.01-1.55), diverticulitis (ROR 1.93, 95% CI 1.68-2.23), urinary tract infection (ROR,1.38, 95% CI 1.29-1.47), cystitis (ROR 1.37, 95% CI 1.19-1.58), and kidney infection (ROR 1.43, 95% CI 1.16-1.75) were detected.

Conclusions: In this study, six infection-related symptoms on gastrointestinal, urinary, and renal organs were identified in addition to the respiratory infections, which are listed on the label. Our findings endorse the need for systematic surveillance for infection among PCSK9 inhibitors users.

Keywords: Signal detection; PCSK9 inhibitors; Infection; VigiBase;

2008

Trajectories of low-density lipoprotein cholesterol and incident cardiovascular disease risk in patients with chronic kidney disease

Miss Shih-Wei Wang[1,2], Dr. Lung-Chih Li[3,4], Dr. Chung-Ming Fu[3], Dr. Yueh-Ting Lee[3], Miss Hsiao-Ching Kuo[1], Dr. Chien-Ning Hsu[1,2]

[1]Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Taiwan, [2]School of Pharmacy, Kaohsiung Medical University, Taiwan, [3]Division of Nephrology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan, [4]Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan

Aim/Objective: Chronic kidney disease (CKD) and low-density lipoprotein cholesterol (LDL-C) are both predictors of cardiovascular disease (CVD). However, the relationship of longitudinal changes in LDL-C with CVD is not well understood in the CKD population. This study aimed to categorize patterns of dynamic changes in LDL-C values after CKD diagnosis and determine their associations with the risk of CVD.

Methods: The incident CKD cohort consisted of 137,127 adults with ≥ 3 LDL-C annual measurements during 2004-2018 from the largest healthcare system in Taiwan. Latent class growth mixed model in SAS Proc Traj procedure and multiple criteria for class enumeration were applied to decide the adequacy of LDL-C trajectory classes over 5 years of follow-up. Cox proportional hazard model was applied to estimate adjusted hazard ratio (aHR) with baseline characteristics and concomitant medications uses in the follow-up. Robustness of findings was examined based on sensitivity analysis by baseline kidney function and status of diabetes.

Results: Six distinct LDL-C trajectory groups were categorized. Comparing with the optimal group (LDL-C <100mg/dL over time), CVD risk was higher (aHR, 1.68[1.45–1.94] in the sustained high (>160 mg/dL) than declined high (from >160 to <100 mg/dL; aHR, 1.23[1.11–1.38]), and borderline (approximately 140 mg/dL over time; aHR, 1.16 [1.07–1.26]) groups. There were no such associations in patients with baseline eGFR <15 mL/min/1.73 m^2. Persistent diabetes strengthened the associations with 1.15–2.47-fold increased risk of CVD in patients with less optimal LDL-C (>120 mg/dL).

Conclusion: Among patients with CKD, certain longitudinal changes in LDL-C were associated with increased CVD risk. A stable level of LDL-C (near 120 mg/dL) over time was potentially beneficial for CVD prevention in CKD patients, while patients with CKD and diabetes required intensive lipid management and regular annual monitoring of LDL-C.

Keywords: low-density lipoprotein cholesterol, trajectory, CKD, CVD

2009

Prevalence and Prescription Trend of Metabolic syndrome in the United States: Analysis of National Health and Nutrition Examination Survey 2007-2018

Ning Wei Huang[1], Chung Hsuen Wu[1], Tsung Hua Shen[2]
[1]School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan, [2]Social and Administrative Pharmacy (SAPh) Department of Pharmaceutical Care & Health Systems, College of Pharmacy, University of Minnesota, Minneapolis, United States

Objective: In recent years, the prevalence of metabolic syndrome (MetS) including hypertension, hyperlipidemia, obesity, and hyperglycemia has increased but there is rarely drug analysis on the population with MetS. Thus, the objectives of this study were to (1) assess the trends in the prevalence of MetS (2) assess the trends in the associated risk factors of MetS, and (3) investigate the association between commonly used drugs and MetS among adults in the U.S.

Methods: We used data from the 2007-2018 National Health and Nutrition Examination Survey (NHANES) which is a nationally representative database. The diagnosed criterion of MetS was adopted from the American Heart Association to assess the MetS status among respondents aged 18 or above. Chi-square tests were used to compare the difference in characteristics between MetS and non-MetS patients. Multivariable logistic regression models were used to identify characteristics and medication use associated with MetS.

Results: The prevalence of MetS increased from 23.8% to 26.3% in 2007-2018 ($P<0.05$). Respondents with age ≥ 70y/o ($P<0.01$), Non-Hispanic White ($P<0.01$), the income-to-poverty ratio between 1.3 to 3.5 ($P<0.01$), widowed group ($P<0.01$), only government insurance group ($P<0.01$) were significantly associated with MetS. Medications including lipid-modifying agents, antihypertensive agents, and antidiabetics were significantly more likely to be used by respondents with MetS.

Conclusion: MetS was prevalent and increased from 2007 to 2018 among adults in the U.S. Polypharmacy among patients with MetS was common which raised the concern about medication safety among MetS patients. Future studies are needed to investigate the association between comorbidities, medication combinations, and MetS.

Keywords: metabolic syndrome (MetS), National Health and Nutrition Examination Survey (NHANES), trend, prescription medication

2010

Optimal timing of non-vitamin K antagonist oral anticoagulants after intracranial hemorrhage in atrial fibrillation patients: a sequential trial emulation study

Yu-Han Wu[1], Associate Professor Fang-Ju Lin[1,2,3], Clinical Assistant Professor Shin-Yi Lin[2,3], Attending Physician Sung-Chun Tang[4], Associate Professor Chi-Chuan Wang[1,2,3]

[1]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [2]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan, [3]School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [4]Stroke Center and Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan

Aim: To investigate whether and when to reinitiate non-vitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) patients with intracranial hemorrhage (ICH).

Methods: A retrospective study was conducted using national claims data from January 2011 to December 2019. We included AF patients receiving antithrombotic therapy who had later encountered ICH and survived to discharge. A sequence of target trials was emulated with 2 groups: NOACs and without antithrombotics, where patients' exposure to NOACs were assess at six consecutive 14-day intervals post-discharge. To explore when to reinitiate NOAC, we further stratified our analysis by stroke severity index: ≤16 (low ICH severity) and >16 (high ICH severity). Study outcomes were all-cause mortality, ICH, and ischemic stroke (IS). Adjusted hazard ratios (aHRs) were estimated using multivariable Cox models.

Results: We included 6,246 person-emulated-trials. NOAC reinitiation was associated with lower risks of all-cause mortality (aHR: 0.73; 95%CI: 0.61-0.88), but not ICH (aHR: 1.21; 95%CI: 0.81-1.80) and IS (aHR: 0.73; 95%CI: 0.47-1.14) compared to no antithrombotic therapy. Regarding timing of NOAC reinitiation, reinitiating within 14 days after discharge seemed to be associated with lower risks of ICH and IS in the low ICH severity group, while reinitiating within 28 days seemed to be associated with higher risks of ICH in the high ICH severity group.

Conclusion: Among ICH survivors with AF, NOAC reinitiation showed lower risks of all-cause mortality compared to no antithrombotic therapy, whereas risks of ICH and IS were similar between the NOAC and no antithrombotic groups. In patients with low ICH severity, reinitiating NOAC within 14 days after discharge is recommended when possible; in patients with high ICH severity, NOACs may be delayed until 1 month after discharge to reduce the risk of recurrent ICH caused by early NOAC reinitiation.

Keywords: non-vitamin K antagonist oral anticoagulants, intracranial hemorrhage, atrial fibrillation

2011

Association between Direct Oral Anticoagulants Discontinuation and Coding-Based Frailty after Minor Bleeding in Patients with Atrial Fibrillation: The Shizuoka Study

Shiori Nishimura[1,2], Dr Hiraku Kumamaru[1,2], Dr Satoshi Shoji[1,3], Dr Eiji Nakatani[1], Dr Hiroyuki Yamamoto[1,2,4], Dr Yoshiki Miyachi[1], Dr Hiroaki Miyata[1,2,4], Dr Shun Kohsaka[1,3]

[1]Shizuoka Graduate University of Public Health, Shizuoka, Japan, [2]Department of Healthcare Quality Assessment, The University of Tokyo Graduate School of Medicine, Bunkyo, Japan, [3]Department of Cardiology, Keio University School of Medicine, Shinjuku, Japan, [4]Department of Health Policy and Management, Keio University School of Medicine, Shinjuku, Japan

Aim/objective: Bleeding, even in its minor form, remains a concern for patients with atrial fibrillation (AF) who are on direct oral anticoagulants (DOACs). We aimed to evaluate the incidence of minor bleeding by the AF patients' frailty status, and how minor bleeding leads to discontinuation of DOAC.

Methods: We extracted all AF patients initiated on DOAC between 2013 and 2020 from an administrative claims database in Shizuoka, Japan. Patients were categorized into fit, mild, moderate and severe frailty groups using electronic frailty index (eFI) assessed via diagnostic records 12 months prior to the DOAC initiation. Minor bleeding was defined as a bleeding event that is not classified as major bleeding (i.e., hospitalization for intracranial bleeding, gastrointestinal bleeding or bleeding with shock) within 12 months after DOAC initiation. We then assessed the frequency of DOAC discontinuation among those experiencing minor bleeding events. DOAC discontinuation defined as >60-day non-prescription period after running out of supply.

Results: We identified 18, 887 patients with AF initiating DOAC (median age [25th–75th percentile] 79 [73–84] years). The 12-month cumulative incidences of minor bleeding were 16%, 18.9 %, 24.4%, and 32.8%, for fit, mildly frail, moderately frail, and severely frail patients, respectively. Among 3,962 patients who experienced minor bleeding within 12 months after DOAC initiation, 611 patients (15.4%) discontinued their DOAC treatment within 3 months of the event. The cumulative incidences of discontinuation were 14.3%, 14.6%, 15.7%, and 16.0% for fit, mildly frail, moderately frail, and severely frail patients, respectively.

Conclusion: Occurrence of minor bleeding was associated with coding-based frailty among AF patients initiated on DOAC, albeit the drug discontinuation rate was largely similar (~15%). Further study is needed to address its long-term consequences.

2012

Incidence of SARS-CoV-2 reinfection in Malaysia by vaccine types (BNT162b2, CoronaVac, and AZD1222) and risk exposure levels

Miss Hoon Shien Teh[1], Su Lan Yang[1], Wen Yea Hwong[1,2], Jing Lian Suah[1], Masliyana Husin[1], Sheamini Sivasampu[1], Kalaiarasu M. Peariasamy[1]

[1] Institute of Clinical Research, National Institute of Health, Malaysia, [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, the Netherlands

As SARS-CoV-2 continues to mutate and circulate, reinfection that was previously rare will become more common in newer strains. In this study, we aim to investigate the risks of reinfection by vaccine types and risk exposure levels.

We used consolidated national administrative data in Malaysia from April 1, 2021 to March 31, 2022 to characterize cumulative incidences of SARS-CoV-2 reinfection. Adults (aged ≥ 18) who had at least one infection throughout the study period were included for analysis. We defined reinfection as infection occurring 90 days after the primary infection. Reinfection cumulative incidences were stratified by a diverse portfolio of BNT162b2, CoronaVac, and AZD1222 vaccinations and an individual's risk exposure level. We categorized individual's risk exposure level based on the frequency that they were tagged as "casual contact" to a SARS-CoV-2 positive case by the Malaysia COVID-19 mobile application contact tracing system (MySejahtera).

Among 2,657,130 COVID-19 positive cases included, 55,956 (2.1%) had at least one episode of reinfection. Overall, incidence of reinfection was 9.9 times higher in the unvaccinated/partially vaccinated group compared to the booster group with either BNT162b2 or CoronaVac (3.59 per 100-population [95% CI 3.55-3.63] vs 0.36 per 100-population [95% CI 0.31-0.42]. Those with primary vaccination solely (2 doses of either BNT162b2, CoronaVac, or AZD1222) showed at least 3 times higher incidences of reinfection compared to homologous/heterologous booster combination. The reinfection incidence was also 4.6 times higher among the high-exposure adults than the low-exposure group (4.53 per 100-population [95% CI 4.47-4.59] vs 0.98 per 100-population [95% CI 0.96-1.00].

Booster dose confers protection against reinfection regardless of the vaccine types and risk exposure levels. While the full extent of waning immunity is still unknown, it is essential to continuously monitor the epidemiological signals of (re)infection cases to better inform pharmaceutical policy.

Keywords: reinfection, SARS-CoV-2, vaccine, risk exposure

2013

Myocarditis and Pericarditis After mRNA COVID-19 Vaccination in Taiwan from June 2021 to May 2022

Chih-Wan Lin[1], Yu-Ting Tseng[1], Chih-Ying Tsai[1], Wei-I Huang[1], Hsun-Yin Liang[1], Wei-Ju Su[2], K. Arnold Chan[3], Wen-Wen Chen[1]

[1]Taiwan Drug Relief Foundation, Taiwan, [2]Centers for Disease Control, Ministry of Health and Welfare, Taiwan, [3]Health Data Research Center, National Taiwan University, Taiwan

Objective: To describe characteristics and reporting rates of myocarditis/pericarditis reports following mRNA COVID-19 vaccination in Taiwan.

Methods: Spontaneous reports of myocarditis/pericarditis reported to Taiwan Vaccine Adverse Event Reporting System between June 2021 and May 2022 were collected and cases meeting Brighton Collaboration case definition level 1 to 3 were included. Reporting rates were estimated by age, sex, and dose number based on vaccination data obtained from Taiwan's National Immunization Information System. An observed-to-expected analysis was conducted by comparing the reporting rates with the background incidence rates, which were estimated during 2016-2019 using Taiwan's National Health Insurance Database; the primary analysis included hospitalized cases of myocarditis/pericarditis that occurred within 14 days after the vaccination, and sensitivity analyses varying the observation period were also performed.

Results: A total of 301 cases of myocarditis/pericarditis following mRNA COVID-19 vaccination were included. The majority of the cases occurred in males (72%), in the young population (aged 12-39 years: 84%), and within 14 days after vaccination (76%). Among 254 cases aged 12-39 years, 94% reported having chest pain, and 84% reported having elevated troponin levels; 226 cases were admitted to the hospital for further care, but most of them were recovered and discharged within one week. The highest reporting rates were observed after the second vaccination dose in males aged 12-17 years (144.5 per million doses of the BNT162b2 vaccines) and in males aged 18-24 years (113.7 per million doses of the mRNA-1273 vaccines). The observed-to-expected analysis showed that the observed number of cases were significantly higher than expected in young males and females, and sensitivity analyses revealed similar results.

Conclusion: The characteristics of myocarditis/pericarditis cases following mRNA COVID-19 vaccination in Taiwan were similar to those reported in other countries. However, limitations such as under-reporting and surveillance bias should be noted when interpreting the findings.

2014

The Association between COVID-19 Vaccine and Acute Myocardial Infarction in Korean Nationwide Study

Ms Na-Young Jeong[1], Cho Jae Yeong[2], Eunsun Lim[1], Jong-Chan Youn[3,4], Kye Hun Kim[2], Nam-Kyong Choi[1,5], CoVaSC committee[6]

[1]Department of Health Convergence, College of Science and Industry Convergence, Ewha Womans University, Seoul, South Korea, [2]Department of Cardiovascular Medicine, Chonnam National University Medical School/Hospital, Gwangju, South Korea, [3]Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [4]Catholic Research Institute for Intractable Cardiovascular Disease, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [5]Department of Industrial Pharmaceutical Science, College of Pharmacy, Ewha Womans University, Seoul, South Korea, [6]COVID-19 Vaccine Safety Committee, National Academy of Medicine of Korea, South Korea

Aim/Objective: To evaluate the risk of acute myocardial infarction (AMI) following COVID-19 vaccination in adults aged over 18

Methods: We used a large-linked database of Korea Disease Control and Prevention Agency vaccination data and the National Health Insurance Service claims data from January 1st, 2002 to July 31st, 2021. We included patients who were vaccinated before April 30th, 2021 and newly diagnosed with AMI within 90-days observation period. The AMI patients were defined who were diagnosed with AMI (ICD-10 code: I21) and received related procedures commenced during an inpatient episode. Those who had a history of AMI-related diseases or those confirmed with COVID-19 before vaccination were excluded. Using the self-controlled case series design, we estimated the incidence rate ratio (IRR) by fitting a conditional Poisson regression model. The risk window was defined as 1-28 days after each dose. Sensitivity analyses with different risk windows (7, 14, and 21 days) and subgroup analyses by gender, age group, and type of vaccines were performed.

Results: We included 3,422,281 adults who received at least 1 dose of COVID-19 vaccine. Among 919 cases for AMI, 480 and 439 events were observed in risk and control windows, respectively. Of these, 501 were men (54.6%) and a majority of patients were aged over 75 (N=764, 79.9%). The risk of AMI after COVID-19 vaccination was not significantly high compared with the risk in control window (IRR=1.02; 95% CI: 0.90-1.17). Similar results were observed in sensitivity and subgroup analyses.

Conclusion: There was no evidence of an increased risk of AMI following COVID-19 vaccination. However, considering that most of vaccinees were elderly and the types of vaccines were limited at the early phase of the introduction of vaccines, further evidence with an extended study period is needed.

Key words: COVID-19 vaccine, Self-controlled case series, Acute myocardial infarction

2015

The Risk of Acute Transverse Myelitis Following COVID-19 Vaccination in Korean Population-based Study

Ms Eunsun Lim[1], Yoo Hwan Kim[2], Na-Young Jeong[1], Jong Seok Bae[3], Nam-Kyong Choi[1,4], CoVaSC[5]
[1]Department of Health Convergence, College of Science and Industry Convergence, Ewha Womans University, South Korea, [2]Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, South Korea, [3]Department of Neurology, Kangdong Sacred Heart Hospital, South Korea, [4]Department of Industrial Pharmaceutical Science, College of pharmacy, Ewha Womans University, South Korea, [5]COVID-19 Vaccine Safety Committee, National Academy of Medicine of Korea, South Korea

Objective: To evaluate the risk of ATM following COVID-19 vaccination as concerns about the acute transverse myelitis (ATM) reported following COVID-19 vaccination.

Methods: We used a large-linked database of claims data from the National Health Insurance Service and COVID-19 vaccine registry from the Korea Disease Control and Prevention Agency from January 1, 2002, to October 31, 2021. We included ATM patients who were newly diagnosed with ATM (ICD-10 code: G37.3) and had ATM-related procedures code (e.g. CSF analysis or MRI) following first COVID-19 vaccination within 90 days on February 26, 2021(vaccine introduction) to July 31, 2022. We excluded history of ATM-related diseases or confirmed with COVID-19 before vaccination date. We performed a self-controlled case-series (SCCS) design within 90 days observation period (1-28 days risk period) after vaccination date and estimated incidence rate ratio (IRR). Subgroup analysis undertook by gender, age, vaccine types and Charlson comorbidity index (CCI).

Results: People received the first COVID-19 vaccination was 19,639,721. Among 52 ATM cases, risk and control intervals were 31 and 21cases, respectively. Of 21 were men (52.5%), and half of patients were over 65 (n=26, 50.0%). The risk of ATM increased following COVID-19 vaccination (IRR=2.16; 95% CI: 1.25-3.73). The ATM risk in subgroup analysis was increased for male (IRR=3.07, 95% CI: 1.35-7.00, 50-64 ages (IRR=3.54; 95% CI: 1.07-11.67), CCI score ≥ 5 (IRR=2.82; 95% CI: 1.53-5.21), and AstraZeneca vaccinees (IRR=3.17; 95% CI: 1.50-6.70).

Conclusion: Our analysis revealed an increase in ATM following COVID-19 vaccination. Nevertheless, several concerns should be considered for a causal link between ATM and COVID-19 vaccination: 1) validity of ATM diagnosis without detailed clinical information 2) relative rarity of ATM in general population 3) small number of ATMs in this analysis. Corroborative hospital-based case review and valid diagnosis can be planned as future work.

Keywords: COVID-19 vaccine, acute transverse myelitis

2016

Risk of arrhythmia after mRNA (BNT162b2) and inactivated (CoronaVac) covid-19 vaccination: a self-controlled case series study

Mr Min FAN[1], Dr Francisco Tsz Tsun Lai[1,2], Mr Franco Wing Tak Cheng[1], Prof Ian Chi Kei Wong[1,2,4], Dr Celine Sze Ling Chui[2,3,5]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, [2]Laboratory of Data Discovery for Health (D24H), Hong Kong Science Park, Hong Kong Science and Technology Park, Hong Kong, [3]School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, [4]School of Pharmacy, University College London, London, United Kingdom, [5]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Objective: Cardiac complications were found among people following the mRNA covid-19 vaccines by many publications. However, there are limited comparative studies on the relationship between arrhythmia and covid-19 vaccinations, especially after inactivated vaccines.

Methods: A self-controlled case series (SCCS) design was conducted to investigate the arrhythmia risk following three doses of covid-19 vaccines. The study period was from February 23rd, 2021 to March 31st, 2022. Patients with incident cardiac arrhythmia were included. Patients with a history of heart failure, coronary heart disease, myocarditis, heterologous vaccines, or a positive SARS-CoV-2 polymerase chain reaction test result were excluded. The day of each vaccination was defined as day 0. Risk periods of day 0, day 1-13, and day 14-28 days after each dose were defined to assess the risk of arrhythmia. Day 0 was considered as a separate risk to avoid event misclassification. Any other period was considered as baseline. An event-dependent modified SCCS was applied to avoid assumption violation since people with arrhythmia before vaccination may avoid the vaccination. Conditional Poisson regression was used to estimate the incidence rate ratio (IRR) and its corresponding 95% confidence interval (CI).

Results: During the study period, 15,557 patients were admitted to the hospital with a primary arrhythmia diagnosis. After applying the exclusion criteria, 6,445 patients with incident arrhythmia were included in the analysis: 1,801 with BNT162b2, 2,756 with CoronaVac, and 1,888 without any vaccination. Increased IRRs were found in day 1-14 (1.31, 95% CI: 1.02-1.68) and day 15-28 (1.38 95% CI: 1.04-1.82) following first dose after BNT162b2. No increasing risks were identified for other doses of BNT162b2 or all doses of CoronaVac.

Conclusion: We detected an increased risk of arrhythmia after the first doses of BNT162b2. Continuous monitoring of arrhythmia after mRNA covid-19 vaccines is needed.

2017

Risk of thyroid dysfunction associated with mRNA and inactivated COVID-19 vaccines: a population-based study of 2.3 million vaccine recipients

Miss Xi Xiong[1], Dr. Carlos King Ho Wong[1,2], Dr. David Tak Wai Lui[1], Dr. Celine Sze Ling Chui[1,2], Dr. Francisco Tsz Tsun Lai[1,2], Dr. Xue Li[1,2], Dr. Eric Yuk Fai Wan[1,2], Dr. Ching-Lung Cheung[1,2], Dr. Chi Ho Lee[1], Dr. Yu-Cho Woo[1], Mr. Ivan Chi Ho Au[1], Mr. Matthew Shing Hin Chung[1], Mr. Franco Wing Tak Cheng[1], Prof. Kathryn Choon Beng Tan[1], Prof. Ian Chi Kei Wong[1,2,3]

[1]The University of Hong Kong, Hong Kong, [2]Laboratory of Data Discovery for Health (D24H), Hong Kong, [3]University College London, United Kingdom

Objective: In view of accumulating case reports of thyroid dysfunction following COVID-19 vaccination, we evaluated the risks of incident thyroid dysfunction following inactivated (CoronaVac) and mRNA (BNT162b2) COVID-19 vaccines using a population-based dataset.

Methods: We identified people who received COVID-19 vaccination between 23rd February and 30th September 2021 from a population-based electronic health database in Hong Kong, linked to vaccination records. Thyroid dysfunction encompassed anti-thyroid drug (ATD)/levothyroxine (LT4) initiation, biochemical picture of hyperthyroidism/hypothyroidism, incident Graves' disease (GD), and thyroiditis. A self-controlled case series design was used to estimate the incidence rate ratio (IRR) of thyroid dysfunction in a 56-day post-vaccination period compared to the baseline period (non-exposure period) using conditional Poisson regression.

Results: A total of 2,288,239 people received at least one dose of COVID-19 vaccination (57.8% BNT162b2 recipients and 42.2% CoronaVac recipients). 94.3% of BNT162b2 recipients and 92.2% of CoronaVac recipients received the second dose. Following the first dose of COVID-19 vaccination, there was no increase in the risks of ATD initiation, LT4 initiation, biochemical picture of hyperthyroidism (BNT162b2: IRR 0.872, 95%CI 0.744–1.023; CoronaVac: IRR 0.830, 95%CI 0.713–0.967) or hypothyroidism (BNT162b2: IRR 1.002, 95%CI 0.838–1.199; CoronaVac: IRR 0.963, 95%CI 0.807–1.149), GD and thyroiditis. Similarly, following the second dose of COVID-19 vaccination, there was no increase in the risks of ATD initiation, LT4 initiation, hyperthyroidism (BNT162b2: IRR 1.039, 95%CI 0.899–1.201; CoronaVac: IRR 0.911, 95%CI 0.786–1.055), hypothyroidism (BNT162b2: IRR 0.935, 95%CI 0.794–1.102; CoronaVac: IRR 0.945, 95%CI 0.799–1.119), GD, and thyroiditis. Age- and sex-specific subgroup and sensitivity analyses showed consistent neutral associations between thyroid dysfunction and both types of COVID-19 vaccines.

Conclusion: Our population-based study showed no evidence of vaccine-related increase in incident hyperthyroidism or hypothyroidism with both BNT162b2 and CoronaVac.

Keywords: COVID-19 vaccines; BNT162b2 vaccine; Graves' disease; thyroiditis

2018

Long-Term Clinical Outcomes of Oral Antidiabetic Drugs as Fixed-Dose Combinations: A Nationwide Retrospective Cohort Study

Mr Sangjun Cho[1], PhD In-Sun Oh[1,7], MPH, PhD Han Eol Jeong[1,7], MD, PhD Young Min Cho[2], MD, PhD Yul Hwangbo[3], MD Oriana Hoi Yun Yu[4,5], PhD Ju-Young Shin[1,6,7]

[1]School of Pharmacy, Sungkyunkwan University, Suwon, South Korea, [2]Department of Internal Medicine, Seoul National University College of Medicine,South Korea, [3]Division of Endocrinology, Department of Internal Medicine, National Cancer Center, Goyang, South Korea, [4]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Montreal, Canada, [5]Division of Endocrinology and Metabolism, Jewish General Hospital, McGill University, Montreal, Canada, [6]Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Science & Technology, Sungkyunkwan University, South Korea, [7]Department of Biohealth Regulatory Science, Sungkyunkwan University, Suwon, South Korea

Aims: Patients with type 2 diabetes often require more than one medication for glycemic control. Although single pill fixed-dose combinations (FDC) might improve adherence, its impact on clinical outcomes remains unclear. We compared treatment patterns and clinical outcomes of FDC and two-pill combination (TPC) therapies using real-world data.

Methods: We conducted a nationwide retrospective cohort study using South Korea's healthcare database (2002–2015). We identified two cohorts of incident patients with type 2 diabetes who initiated FDC or TPC therapy within 4 months of their first prescription for metformin or sulfonylurea. We examined persistence and adherence patterns and the clinical outcome of a composite endpoint of death or hospitalization for acute myocardial infarction, heart failure, or stroke and compared the differences in treatment patterns and clinical outcomes using Cox models.

Results: Of 5,143 and 10,973 patients who initiated FDC and TPC therapy, respectively, we identified 5,143 patient pairs after propensity score matching. The FDC group exhibited greater median time to treatment discontinuation (163 versus 146 days), and proportion of days covered (PDC) at 12 months (mean 0.60 versus 0.57, $P < 0.0001$) and at 24 months (0.53 versus 0.51, $P=0.014$) than the TPC group. The FDC group, compared with the TPC group, had reduced risks of the composite clinical outcome (hazard ratio 0.86, 95% confidence intervals 0.77–0.97) and hospitalization for stroke (0.80, 0.67–0.96).

Conclusion: FDC therapy may provide favorable cardiovascular benefits, especially reducing the risk of hospitalization for stroke, and have better medication adherence among patients with type 2 diabetes.

2019

Clinical impacts of frailty on patients with diabetes mellitus considering the age of onset and drugs of choice

Shih-Tsung Huang[1], Professor Liang-Kung Chen[2,3,4], Professor Fei-Yuan Hsiao[1,5,6]

[1]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [2]Center for Healthy Longevity and Aging Sciences, National Yang Ming University, Taipei, Taiwan, [3]Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan, [4]Taipei Municipal Gan-Dau Hospital (Managed by Taipei Veterans General Hospital), Taipei, Taiwan, [5]School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [6]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan

Aim/Objective: Frailty substantially increased the risk of adverse clinical outcomes, which was also critical in diabetes management. This study investigated the complex interrelationships between the age of onset, frailty, anti-diabetic medications, and clinical outcomes in people with diabetes mellitus (DM).

Methods: A total of 123,172 patients aged 40 years and older who were newly diagnosed with DM were identified and categorized into four frailty subgroups (fit, mild, moderate, and severe) based on the multimorbidity frailty index (mFI). Cox proportional hazard models were used to examine associations between frailty and clinical outcomes at different ages of DM onsets (40-64, 65-74, 75-84, and 85+ years old). Outcomes of interest included generic outcomes (mortality and unplanned hospitalization) and DM-specific outcomes (cardiovascular disease related-mortality, major adverse cardiovascular events (MACE), diabetes-related hospitalization, and hypoglycaemia).

Results: The proportion of frailty increased with age at diagnosis among incident DM patients and the mFI scores increased significantly during the 10-years follow-up. Similar results were observed at 3-year, 5-year, and 10-years of follow-ups. Compared to non-frail DM patients, DM patients with mild, moderate, and severe frailty were associated with greater risks of all-cause mortality (e.g., mild frailty aHR 1.69 [95% CI 1.60-1.80], p<0.01; moderate frailty: aHR 2.46 [2.29-2.65], p<0.01; severe frailty: aHR 3.40 [3.16-3.65], p<0.01), unplanned hospitalizations, CV-related mortality, MACE, and hypoglycaemia.

Conclusions: Our study quantified the prevalence of frailty, captured its dynamic changes, and examined its impacts on various clinical outcomes among DM patients at different ages at onset. Frailty assessment and management should be implemented into routine diabetes care.

2020

Adaptation of risk equations for cardiovascular diseases in the Taiwanese type 2 diabetes population: adoption, validation, and recalibration

Kah-Suan Chong[1], Chun-Ting Yang[1], Huang-Tz Ou[1,3], Shihchen Kuo[1,2]

[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Taiwan, [2]Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, United States, [3]Department of Pharmacy, College of Medicine, National Cheng Kung University, Taiwan

Aim/Objective: Risk equations for predicting cardiovascular outcomes including myocardial infarction (MI), stroke, and heart failure (HF) in type 2 diabetes (T2D) are available; however, valid risk equations specific to the Taiwanese T2D population remain lacked. This study aimed to adopt, validate, and recalibrate existing risk equations for cardiovascular diseases which can be applicable for the Taiwanese T2D population.

Methods: Three existing risk prediction models, UKPDS Outcomes Model 2 (UKPDS-OM2), Risk Equations for Complications Of T2D (RECODe), and Chinese Hong Kong Integrated Modeling and Evaluation (CHIME), for cardiovascular outcomes were selected for adaptation. A total of 11,740 T2D patients during 2015-2018 were identified from National Cheng Kung University Hospital and followed until 2019/12/31. Half of study cohort was randomly selected as the derivation set for (1) identifying the risk equations with best model performances, and (2) recalibrating the risk equations by adjusting differences in observed and predicted event risks. The validation set comprising the other half of study cohort was used to determine the model performance of the recalibrated risk equations. Model performance was evaluated by discrimination (acceptable Harrell's C-statistic: ≥0.7) and calibration (perfect calibration slope: 1) indices.

Results: Some risk equations yielded satisfactory discrimination (C-statistic in CHIME equations for MI [0.77], stroke [0.72], and HF [0.78], and in RECODe equations for MI [0.77] and HF [0.80]). All CHIME equations showed better calibration (calibration slope for MI [0.47], stroke [0.72], and HF [0.78]) compared to those of the UKPDS-OM2 (0.04, 0.22, 0.48) and RECODe (0.23, 0.52, 0.59). After recalibration, the performances of CHIME equations were improved (calibration slope for MI [0.98], stroke [1.14], and HF [0.94]).

Conclusions: CHIME cardiovascular disease risk equations which were adapted to the Taiwanese T2D population could facilitate clinical and policy decision-making in Taiwan and may be adapted to other Asian countries.

Keywords: risk equations, validation, recalibration

2021

Association of non-alcoholic fatty liver disease risk with GLP-1RAs and SGLT2is in type 2 diabetes: A nested case-control study

KAICHENG CHANG[1,2], Fan-Chi Kuo[2], Chen-Yi Yang[2], Chun-Ting Yang[2], Huang-Tz Ou[2,3,4], Shihchen Kuo[5]
[1]Department of Pharmacy, Chang Gung Memorial Hospital,Taiwan, [2]School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Science, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [3]Department of Pharmacy, National Cheng Kung University Hospital, Tainan, Taiwan, [4]School of Pharmacy, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [5]Division of Metabolism, Endocrinology & Diabetes, Department of Internal Medicine, University of Michigan Medical School, United States

Aim/Objective: Non-alcoholic fatty liver diseases (NAFLDs) is the most common liver disorder among type 2 diabetes (T2D) patients. Newer classes of glucose-lowering agents (GLAs), glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2is), have been shown to improve liver-related biomarkers, while their effects on the development of NASH remain inconclusive.

Methods: A nested case-control study was conducting using Taiwan's National Health Insurance Research Database. T2D patients initiated with non-insulin GLAs in 2007-2018 were included and the date of receiving the first GLA was defined as the cohort entry date. Patients with a NAFLD history, aged less than 40 years, or without stable GLA use were excluded. Patients with incident NAFLDs were matched up to 10 randomly sampled controls based on patient age, gender, cohort entry date, T2D diagnosis date, and disease risk score. Conditional logistic regression analyses were employed to estimate the association of NASH with GLP-1RA and SGLT2i treatment. Subgroup and sensitivity analyses were performed to examine the robustness of primary analysis results.

Results: A total of 621,438 T2D patients with stable GLA use were included. During a median 1.4-year follow-up, the incidence of NAFLDs was 2.7 per 1000 person-years. After matching, 5,730 incident NAFLD cases (mean age: 57.6 years, male: 53.2%) and 45,070 controls (mean age: 57.7 years, male: 52.7%) were identified. Use of GLP-1RAs or SGLT2is was associated with an insignificantly lower risk of NAFLDs (odd ratios [95% CIs]: 0.84 [0.46-1.52], 0.85 [0.63-1.14]). Higher cumulative doses of SGLT2i therapy were associated with a lower NAFLD risk (0.53 [0.27-1.05]). The results were robust across sensitivity and subgroup analyses.

Conclusion: Use of GLP-1RAs and SGLT2is may be associated with potential benefit on NAFLDs in T2D patients, while larger research is warranted to confirm our findings.

Keywords: T2D, NAFLDs, SGLT2is, GLP-1RAs

2022

Cardiovascular Events of Incretin Mimetics and SGLT-2 Inhibitors as an add-on to Metformin Monotherapy: A Systematic Review and Network Meta-Analysis

Dr Krishna Undela[1], Gifty Lawrance[1], Christy Thomas[1]
[1]*NIPER Guwahati, Kamrup, India*

Objective: To systematically synthesize the evidence on the comparative major adverse cardiovascular events (MACE) of incretin mimetics and sodium-glucose co-transporter-2 (SGLT-2Is) as an add-on to metformin monotherapy in patients with type 2 diabetes mellitus (T2DM).

Methods: A thorough literature search was performed in PubMed, Cochrane CENTRAL and Google Scholar from inception to 30th April 2022. A combination of keywords, MeSH terms and entry terms on diabetes mellitus, metformin, glucagon-like peptide-1 receptor agonists (GLP-1-RAs), dipeptidyl peptidase-4 inhibitors (DPP-4Is) and SGLT-2Is were used in combination with Boolean operators. All randomized controlled trials (RCTs) investigating the MACE of GLP-1-RAs, DPP-4Is and SGLT-2Is as an add-on to metformin monotherapy in patients with T2DM were included in the study. The fixed or random-effects model was used based on the heterogeneity identified using the I^2 statistic and Cochran's Q test. Traditional meta-analysis was performed using RevMan 5.4.1 and network meta-analysis using R 4.2.0.

Results: Out of 4357 non-duplicate RCTs identified through database searching, a total of 16 studies with 16,843 patients were included in this study. The pooled analysis revealed a significant reduction in cardiovascular death (OR=0.78, 95% CI 0.63-0.98, P=0.03) and all-cause mortality (OR=0.82, 95% CI 0.69-0.97, P=0.02) with GLP1-RAs add-on to metformin compared to control group. Incretin mimetic and SGLT-2Is were not associated with other MACE outcomes such as non-fatal myocardial infarction, unstable angina requiring hospitalization and hospitalization for heart failure as an add-on to metformin monotherapy. Network meta-analysis revealed lixisenatide ranked best for reducing the risk of non-fatal myocardial infarction, while placebo was the worst.

Conclusion: The use of GLP-1-RAs was associated with reducing MACE than DPP-4Is and SGLT-2Is when added to metformin monotherapy. Patients should be involved in collaborative decision-making and discussions regarding potential benefits and side effects, regardless of which class is more appropriate for therapy.

2023

Newer class of antidiabetic drugs and bladder cancer: a pharmacovigilance-based drug-repurposing in faers database

Dr Subeesh Viswam[1], Mr Lipin Lukose[1], Ms Gursimran Kaur[1], Ms Rifa shareen[1], Ms Amulya Bhatkal[1], Ms Roopa Acharya B[1], Ms Gouri Nair[2]

[1]Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Udupi, India, [2]Department of Pharmacology, M. S. Ramaiah University of Applied Sciences, Bengaluru, India

Aim/Objective: To identify potential drug-repositioning of Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors and Inhibitors of dipeptidyl peptidase 4 (DPP-4) by inverse associations revealed through disproportionality analysis in FDA Adverse Event Reporting System (FAERS) database

Methods: The case/non-case retrospective disproportionality analysis was performed in the publicly available FAERS database using OpenVigil 2.1(2004Q1-2022Q1). The preferred term used for the study was “bladder cancer” and the drugs included were SGLT2 and DPP-4 inhibitors. The effect of SGLT2 and DPP4 inhibitors on co-administration with pioglitazone, a drug known to cause bladder cancer, was also measured. Reporting odds ratio (ROR) was used as a measure for disproportionality. A value of ROR+1.96SE<1 and ≥5 cases was considered as a threshold for inverse signal.

Results: The FAERS database had a total of 39813 reports associated with bladder cancer, of which 136 were associated with SGLT2 inhibitors, and 116 were associated with DPP-4 inhibitors. The number of cases for empagliflozin, canagliflozin, sitagliptin and linagliptin associated bladder cancer were 35,30,72 and 14, respectively. Significant inverse signals were obtained for empagliflozin [ROR 0.437(95%CI:0.314-0.609)] and canagliflozin [ROR 0.398(0.278-0.569)] among SGLT2 inhibitors, and for sitagliptin [ROR 0.784(0.622-0.988)] and linagliptin [ROR 0.372(0.22-0.628)] among DPP-4 inhibitors. A reduction in signal strength was observed for pioglitazone from ROR 91.42(88.67-94.24) to ROR 1.9(0.79-4.59) when they were co-administered with SGLT2 inhibitors, and a reduction to ROR 16.23(12.38-21.28) with DPP-4 inhibitors thus hinting at the protective action of SGLT2 and DPP-4 inhibitors for bladder cancer.

Conclusion: The discovery of an inverse relationship between bladder cancer and SGLT2 inhibitors empagliflozin and canagliflozin, and DPP-4 inhibitors sitagliptin and linagliptin. A possible combination of newer antidiabetic drugs with pioglitazone may reduce the risk of pioglitazone-induced bladder cancer. However, in-silico, in-vitro, and in-vivo studies followed by a superior epidemiological study are required to validate these findings.

Keywords: Bladder Cancer; SGLT2-inhibitors; DPP4-inhibitors; Pioglitazone.

2024

A New System for Drug Safety Signal Detection and Triage Integrating Prescription Sequence Symmetry Analysis and Tree-Based Scan Statistics

Ms. Miyuki Hsing-Chun Hsieh[1,2], Hsun-Yin Liang[2], Wei-I Huang[2], Chih-Ying Tsai[2], Yu-Chun Chiu[2], Pi-Hui Chao[2], Wen-Wen Chen[2], Swu-Jane Lin[3], Edward Chia-Cheng Lai[1]

[1]Institute of Clinical Pharmacy & Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [2]Taiwan Drug Relief Foundation (TDRF), Taipei, Taiwan, [3]Department of Pharmacy Systems, Outcomes & Policy, College of Pharmacy, University of Illinois at Chicago, Chicago, USA

Objective: To delineate a new triage system integrating prescription sequence symmetry analysis (PSSA) and tree-based scan statistics (TreeScan) for drug safety signal generation and prioritization. We conducted an exploratory study in non-fluorinated quinolones (NFQ) and sodium-glucose co-transporter-2 inhibitors (SGLT2i) to test feasibility of this system.

Methods: Based on international guidance and the current pharmacovigilance framework in Taiwan, we proposed a triage system for drug safety signal active surveillance integrating PSSA and TreeScan as data mining tools. Population-wide National Health Insurance Research Database was used as longitudinal data source. For the exploratory analysis, we applied new user, active comparator design to minimize selection bias. Active comparators for NFQ and SGLT2i were fluoroquinolones and DPP4 inhibitors, respectively. We defined index date as the first prescription date of NFQ (or SGLT2i). For PSSA, we compared the frequency of any other medications that had been used before versus after the index date to detect imbalanced prescription sequences. For TreeScan, we followed patients from the index date until any incident event defined by ICD codes.

Results: The proposed system first determined an appropriate comparator for the drug to be screened, followed by implementing data-mining using PSSA and TreeScan. All alerts detected from both tools were further classified as known adverse drug reactions (ADRs), events related to other causes (e.g., indication, etc.), or potential signals according to the triage algorithm. The detected alerts from NFQ study showed that there were relatively low proportion of known ADRs, most events were related to indication, patients' characteristics, or bias. No safety signals were found. In contrast, we found few signals from SGLT2i, amongst 4 suggesting potential association with chemotherapy and anti-Parkinson agents that required further investigation.

Conclusion: The new system can facilitate standardized screening, aid in detecting and categorizing potential safety signals, therefore improve the efficiency of signal detection.

2025

Identifying predictors of adverse drug reactions: Where machine learning fails

Stephanie Long[1], Dr. Tibor Schuster[1]
[1]*McGill University, Montreal, Canada*

Aim/Objective: Causal inference helped explain the birthweight and obesity paradoxes: selection bias due to conditioning on a common cause of the exposure and outcome (collider) i.e., collider-stratification bias (CSB). This has important implications for the interpretation of machine learning (ML), which is increasingly being applied to pharmacoepidemiological data due to its ability to achieve better or comparable covariate balance than logistic regression. Tree-based ML approaches e.g., classification & regression trees and random forests (RF) which implicitly condition on input variables may be particularly susceptible to CSB. RFs are a popular approach for identifying important predictors from large datasets through variable importance measures (VIMs). CSB's effect in estimating exposure-outcome effects is recognized, its impact on ML's VIMs is less understood. Using causal inference, we assessed the accuracy of RF's VIMs in the presence of CSB.

Methods: A Plasmode simulation was conducted using a high-dimensional dataset on adverse drug events (ADE) previously described in the literature. We generated binary outcome and collider variables from logistic models. Exposure variables stochastically determined the outcome and a collider variable, independent of the outcome. RF's VIMs were compared to the known causal relevance of the input variables on the outcome.

Results: Variable importance of true exposure variables was not systematically affected by CSB, though the validity of VIMs were affected, leading to erroneous selection of collider variables, causally independent of the outcome, as important outcome predictors.

Conclusion: Using ML for ADE prediction is more efficient than traditional compound testing, though not without flaws. In the presence of CSB, VIMs may not be valid measures of the causal relevance of variables and may mislead the selection of truly important ADE predictors. ML must consider causal data-generating mechanisms otherwise it may lead to erroneous assessment of variable importance regarding outcome prediction.

Keywords: adverse event prediction, bias, machine learning

2026

Analysis and signal mining on 1177 reports of adverse drug reactions related to antibacterial-induced coagulopathy

An Fu[1]

[1]*Medical school of Chinese PLA, 中国*

Objective: This research aimed at exploring the regularity and characteristics of antibacterial-induced coagulopathy, to provide a reference for safe use of antibacterial in clinics.

Methods: We examined antibacterial-induced coagulopathy reports submitted to the adverse drug reactions(ADR) surveillance system of Chinese PLA, and reviewed demographic and clinical characteristics of the study group, primary suspect drug, therapies and outcomes of reports. Meanwhile, we detected signals on ADR with the method using the 95% confidence interval (CI) for the reporting odds ratio (RORCI) and the Bayesian Confidence Propagation Neural Network (BCPNN). All cases were divided into three subgroups, including coagulation dysfunction, thrombocytopenia, and coagulation dysfunction accompanied with thrombocytopenia, according to different mechanisms of coagulopathy.

Results: Most of patients were male (69.84%) and over 60 years old (76.98%). The majority (95.52%) of ADR occurred within 15 days after medication, and lasted for no more than 14 days (95.48%). Patients with coagulation dysfunction alongside thrombocytopenia got a higher risk of bleeding($P<0.001$). We confirmed association of coagulopathy and 13 antibacterial types. Cefoperazone, tigecycline, and linezolid showed the strongest signals, and related to both coagulation dysfuction and thrombocytopenia. Moreover, We found several signals unlisted in the instructions, such as cefoperazone-induced hypofibrinogenemia, tigecycline-induced thrombin time prolongation, and linezolid-induced prothrombin time prolongation. Among the study population, 85% was cured or got better after drug withdrawal or (and) supportive care.

Conclusions: There are many types of antibacterial drugs being related to coagulopathy, but surveillance and evaluation of bleeding risk should be focused on those associated with both coagulation dysfunction and thrombocytopenia. Coagulation indicators should be monitored on time in clinics, and once they getting abnormal, dosage regimen of antibacterial should be changed in time and supportive care was needed, to prevent the occurrence of serious bleeding events.

2027

Predicting antibiotic-resistance in hospitalised patients using machine learning models with epidemiological data

Mr Ha Nguyen[1], Mr Tien-Hoang Tran[2], Ms Thi-Lan-Nhi Vu[2], Mr Chung-Ping Chiu[3], Mr Shi-Jie Jian[3], Dr Hoa-Quoc Nguyen[1,4], Dr Dun-Wei Cheng[3], Associate Professor Doan-Trang Dang-Nguyen[1,2], Associate Professor Ngoc-Khoi Nguyen[1], Associate Professor Sun-Yuan Hsieh[3]

[1]University of Medicine and Pharmacy at Ho Chi Minh city, Viet Nam, [2]University Medical Center Ho Chi Minh City, Viet Nam, [3]Department of Computer Science and Information Engineering, National Cheng Kung University, Taiwan, [4]Queen's University of Belfast, United Kingdom

Introduction: According to a 2022 article by nature, there was at least 1.27 million deaths/year caused by antimicrobial resistance (AMR), higher than that of HIV/AIDS and malaria. This figure is prominently relevant for low-income areas, which account for the majority of Asia. Antibiotic stewardship has proven to be an effective strategy against AMR. Nevertheless, its viability in low-income areas remains low due to insufficient equipment and delay in laboratory testing.
This study aims to develop a low-cost machine learning algorithm that can be implemented in clinical settings to improve the precision of empirical prescribing.

Method: We performed a retrospective study to analyse data from 17,021 electronic health records (EHC) with 39,451 sample cultures from UMP-HMC. Five machine learning models were built based on 80% of the EHC data and further tested in the remaining 20% in order to assess the predictability of antibiotic susceptibility from 7 antibiotics against 5 different organisms. (the data was split randomly)
We used epidemiological variables that are easily obtained. The following metrics are used to assess predictability: accuracy from training sets and test sets, and the area under the receiver operating characteristics (ROC) from the test sets. Finally, models are cross-validated to avoid overfitting.

Result & Discussion: The average accuracy of all the models is above 68%, in which 3 models achieved > 99% accuracy. These preliminary results demonstrate that machine learning can be implemented to enhance antibiotic stewardship, as speculated and suggested widely in the literature. Nonetheless, the models that have high accuracy are narrowed in scope, specific antibiotics against specific organisms.

Conclusion: This analysis has demonstrated that low-cost EHR-derived variables were associated with improved accuracy in predicting AMR. Our group is continually experimenting with advanced machine learning algorithms to produce more generalized models while keeping their accuracy to practical standards.

2028

Validity of Claims-Based Algorithm to Identify Venous Thromboembolism in Japan

Haoqian Chen[1], Yuichi Tamura[2], Nobuhiro Tanabe[3], Kenichi Hiasa[4], Kouta Funakoshi[4], Tasuku Okui[4], Naoki Nakashima[4], Toshitaka Hirano[5], Naonobu Sugiyama[5], Melanie Rua[1], Soko Setoguchi[1,6]
[1]Rutgers, State University of New Jersey, New Brunswick, United States, [2]International University of Health and Welfare Mita Hospital, Japan, [3]Chibaken Saiseikai Narashino Hospital, Japan, [4]Kyushu University Hospital, Japan, [5]Pfizer Japan Inc., Japan, [6]Rutgers Robert Wood Johnson Medical School, New Brunswick, United States

Background: Regulatory agencies in Japan encourage the use of real world data for post-marketing surveillance. However, algorithms to define medical conditions, including venous thromboembolism (VTE), are not validated.

Purpose: To determine positive predictive values (PPV) of claims-based algorithms to identify VTE.

Methods: We analyzed claims and electronic medical record (EMR) data from a large tertiary healthcare system. A committee of clinical/epidemiology experts developed claims-based algorithms for pulmonary embolism (PE)/deep vein thrombosis (DVT). We randomly sampled 56 algorithm-defined cases - 31 DVT (without PE); 25 PE (with DVT)-, reviewed EMR to identify gold standards (GSs), conducted descriptive analyses, and calculated PPV of algorithms with 95% confidence interval (CI) for: 1) physician diagnosis of VTE in medical records and 2) adjudication by experts, considering Japanese VTE guidelines.

Results: Among 686 claims-defined VTE cases, 429 were DVT (mean age 64 and 66% female) and 257 were PE (mean age 59 and 55% female). With 56 cases randomly sampled for pilots, all received ≥1 treatments: 48% warfarin, 63% direct oral anticoagulants, 54% other anticoagulants, 5% relevant procedures, and 20% oxygen administration. Supporting symptoms were observed in 46% of cases with 20% dyspnea, 7% chest pain, 5% syncope, 25% leg swelling, and 4% palpitation. Thrombosis was observed in 54%, 48%, and 4% on computerized tomography angiography, Doppler ultrasound, and ventilation perfusion, respectively. PPV using GS of physician diagnosis were 81% (CI: 69-92), 80% (CI: 68-93), and 80% (CI: 72-89); while using expert adjudication, were 84% (CI: 73-95), 84% (CI: 72-96), and 84% (CI: 76-92) for DVT, PE and VTE, respectively.

Conclusion: Our pilot validation study for VTE in Japan showed PPVs of 80-85%, similarly to PPVs from US, Canada, and Europe. The full validation study is underway to confirm validity of algorithms and to develop better algorithms.

Keywords: PE/DVT Validation; Claims-based definition; Positive Predictive Value;

2029

Overcoming Real-World Data Limitations in Creating External Control Arms for Randomized Clinical Trials

MS Mengfei Wu, PhD Katherine Tsai, Abhishek Padhi, Hashmath Ulla T A Syed, Shradhit Subudhi, Shubhankar Thakar, Abhinav Bansal, MD Qin Ye
[1]*ZS Associates, United States*

Aim/Objective: Adoption of real-world data (RWD) in randomized clinical trials (RCTs) offers great promise to reduce timeline and cost of drug development. We conducted a study to simulate an external control arm (ECA) using a US-based electronic medical record (EMR) database for a phase III RCT. The goal was to identify key data challenges and corresponding solutions when replacing RCT controls with ECAs.

Methods: A historical, placebo-controlled, phase III RCT (NCT00119613) was selected for creating a retrospective ECA. The trial investigated the efficacy of Darbepoetin Alfa in treating anemia due to concomitant chemotherapy in patients with small cell lung cancer (SCLC). A large-scale EMR database was used to construct ECA by matching to RCT treated patients. RWD index date was defined as the start date of chemotherapy, and trial inclusion/exclusion (I/E) criteria were assessed during the one-year baseline period prior to index date. Machine learning model XGBoost was considered to impute key I/E criteria with missing values. Eligible ECA patients met I/E criteria, didn't receive anemia treatment, and were 1:1 optimally matched to RCT treated patients using propensity score matching (PSM).

Results: 51K SCLC patients were sourced from EMR. The application of I/E criteria was validated by medical experts, especially for ambiguous descriptions such as unstable cardiac condition. Over 70% of patients were missing ECOG and ferritin at baseline. After filtering through I/E criteria, only 41 patients were eligible for PSM. The patient size increased to 421 by imputing ferritin and 1219 by imputing both ferritin and ECOG.

Conclusion: Retrospective RWD incompleteness and a lack of fit-for-purpose curation were identified as key data limitations. We recommend applying data feasibility assessment, prospective data collection and curation as well as leveraging machine learning for imputation to improve the quality of future ECA-enabled studies.

Keywords: External control arm, real-world data, randomized clinical trial

2030

Risk of acute kidney injury associated with dapagliflozin compared with DPP-4 inhibitors: a propensity-matched cohort study

Hui-Eon Lee[1], Haerin Cho[2], Na-Young Jeong[2], Hee-Jin Kim[2], Nam-Kyong Choi[1,2]
[1]Department of Industrial Pharmaceutical Science, College of Pharmacy, Ewha Womans University, Seoul, South Korea,
[2]Department of Health Convergence, College of Science and Industry Convergence, Ewha Womans University, Seoul, South Korea

Aim/objective: To examine whether initiation to dapagliflozin use is associated with increased incidence of acute kidney injury (AKI) in patients with type 2 diabetes mellitus

Methods: We used the Korea National Health Insurance Service-National Sample Cohort database from 2013 to 2019. This retrospective cohort study included patients with the initial use of dapagliflozin during the index period from September 1, 2014 to December 31, 2018 as an exposure group. Control group consisted of patients used dipeptidyl peptidase-4 inhibitors (DPP-4i) during the index period. The first prescription date of each drug was defined as the individual index date. Patients who have been prescribed all SGLT-2 inhibitors and DPP-4i within 1 year before the index date were excluded from the analysis. We matched each dapagliflozin users to DPP-4i users in a 1:1 ratio by using a propensity score which was quantified by multivariate logistic regression analysis. In the model, we included age, sex, insurance type, and comorbidities as covariates. We defined the first incident AKI in follow-up period within 180 days after the index date as an outcome. We estimated hazard ratios (HR) using a Cox regression model and subgroup analyses were conducted to evaluate the impact of covariates.

Results: Our study contained 3,114 dapagliflozin users and 48,893 DPP-4i users. After propensity score matching 3,113 patients were included in each group. Dapagliflozin group had 16 cases and DPP-4i group had 6 cases of AKI during follow-up period. Compared to DPP-4i users, the adjusted HR of AKI in dapagliflozin users was 0.80 (95% CI: 0.22-2.98). In subgroup analyses, risk differed by gender: men, HR=2.00 (95% CI: 0.18-22.05); women, HR=0.33 (95% CI: 0.04-3.21).

Conclusions: The results showed that dapagliflozin is not associated with the risk of AKI in patients with type 2 diabetes.

Key words: dapagliflozin, DPP-4 inhibitors, acute kidney injury, propensity score

2031

Association Between Use of Non-Steroidal Anti-Inflammatory Drugs and the Risk of End-Stage Renal Disease: A Nested Case-Control study

Miss Yu-Huan Shih[1], Ju-Ling Chen[2], Chien-Huei Huang[3], Yu-Ching Chang[4], Ming-Cheng Wang[5], Ching-Lan Cheng[2,3]

[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [2]School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [3]Departments of Pharmacy, National Cheng Kung University Hospital, Tainan, Taiwan, [4]Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan, [5]Division of Nephrology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University; Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Aim/Objective: We aimed to examine the risk of progression to end-stage renal disease (ESRD) among non-steroidal anti-inflammatory drugs (NSAIDs) users who enrolled in Taiwan pre-ESRD pay-for-performance program (pre-ESRD P4P).

Methods: We conducted a nested case-control study using Taiwan National Health Insurance Database (NHID). The study cohort consisted of pre-ESRD patients (CKD stage 3b-5) who had at least one prescription record of NSAIDs between 2012 and 2017. Among them, we identified patients with ESRD (cases) and their matched controls (matched by age, sex, cohort entry month and the follow-up duration in the pre-ESRD P4P at a ratio of 1:1 up to 1:4). Exposure status was classified as current, recent, past or non- use. Multivariable conditional logistic regression models were applied to estimate odds ratios (ORs) of study outcome and 95% confidence intervals (CIs).

Results: We identified 9,835 cases of ESRD and 28,484 matched controls. The results of multivariable analysis demonstrated that compared with NSAID non-use, current use, recent use, and past use was associated with a no significantly increased risk of ESRD with an adjusted OR (95% CI) of 0.97 (0.83–1.13), 0.884 (0.75–1.03), and 0.918 (0.81–1.03), respectively. The striking differences between the case and control groups were the proportion of EPO (96.5% of case-patients use, compared with 13.7% of controls), SGLT2 inhibitor (0.1% vs. 0.6%) and GLP-1 receptor agonist (0.2% vs. 0.4%).

Conclusion: Considering the imbalanced distribution of covariates between cases and controls, further study is needed to adjust unmeasured confounding factors to validate the association between NSAIDs and progression to ESRD.

2032

Exit-Site Infection and Subsequent Risk of Peritoneal Dialysis-Related Peritonitis: Self-Controlled Case Series Analysis

Mr Surapon Nochaiwong[1,2], Chidchanok Ruengorn[1], Kajohnsak Noppakun[3], Apichat Tantraworasin[2]
[1]Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand, [2]Center for Clinical Epidemiology and Clinical Statistics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, [3]Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Aim/Objective: To investigate the association between exit-site infection (ESI) and subsequent risk of peritoneal dialysis (PD)-related peritonitis.

Methods: A multicenter retrospective cohort study using self-controlled case series analysis among end-stage kidney disease who newly received PD treatment based on three large PD centers in northern Thailand was conducted, from January 1, 2006, to December 31, 2019. Based on the cohort at risk of ESI, all cases of peritonitis were selected. The observational period was started after the PD initiation, and follow-up was censored at the study end date (December 31, 2020) or death. The risk periods after ESI were divided into risk windows for each person: 1-15 days; 16-30 days; 1-3 months; 3-6 months; 6-9 months; and 9-12 months. All other periods were classified as the control period. The incidence rate ratios (IRRs) with corresponding confidence intervals (CIs) were estimated using the fixed-effects conditional Poisson regression.

Results: Of 2213 patients with incident peritonitis (median episode of peritonitis 1.0 [range 1.0-10.0]), 1177 were male (53.2%), and mainly based on continuous ambulatory PD (93.4%), with a mean age of 58.1 ± 13.7 years. The IRR of subsequent PD-related peritonitis was 8.24 (95% CI, 4.89-12.13) for 1-15 days after ESI; 5.34 (95% CI, 3.77-6.18) for 16-30 days after ESI; 4.74 (95% CI, 3.55-6.79) for 1-3 months after ESI; 2.25 (95% CI, 1.17-3.23) for 3-6 months after ESI; 2.01 (95% CI, 1.18-2.86) for 6-9 months after ESI; and 1.85 (95% CI, 1.24-2.54) for 9-12 months after ESI.

Conclusions: The incidence of PD-related peritonitis was higher across the one-year risk periods, particularly in the period immediately after the episode of ESI. These findings can be seen as a prognostic potential safety signal. Proactive monitoring and interventions that mitigate the risk of PD-related peritonitis following ESI is recommended.

Keywords: infection, peritoneal dialysis, peritonitis, self-controlled case series

2033

Polymorphisms of the CYP3A5 gene and their impact on tacrolimus dosage and trough concentration among kidney transplant patients.

Yen-Lin Chang[1,5], Tzu-Hung Hsiao[2], Yi-Ming Chen[2,4], Ching-Heng Lin[2], Yi-Ju Liao[1], Ming-Fen Wu[1], Cheng-Hsu Chen[3]

[1]Department of Pharmacy, Taichung Veterans General Hospital, Taichung, Taiwan, [2]Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan, [3]Division of Nephrology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan, [4]Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung, Taiwan, [5]Department of Public Health and Institute of Public Health, Chung Shan Medical University, Taichung, Taiwan

Background: Genetic variation in CYP3A5 genes, which encode key enzymes in tacrolimus metabolism, is associated with tacrolimus (TAC) clearance and dose requirements. Due to the wide interindividual pharmacokinetic variability, optimizing TAC dosing based on genetic factors is not well established in Asian populations.

Objectives: To evaluate the association between CYP3A5 polymorphisms and tacrolimus pharmacokinetic/ pharmacodynamic endpoints that can better guide to achieve the target tacrolimus dosage.

Methods: CYP3A5 genetic polymorphisms in 431 renal transplant recipients were determined using the Axiom Genome-Wide TWB 2.0 array plate from the Taiwan Precision Medicine Initiative (TPMI) project. Statistical analysis was applied to examine the effect of genetic variation on TAC C0/D and pharmacodynamic endpoint at initial, discharge, 90, 180, 270, 360 days after transplantation.

Results: We found that approximately 52% of the Taiwanese population as the CYP3A5 non-expresser may appear less to express the CYP3A5 protein.
Recipients carrying the non-expresser genotype CYP3A5 showed a significantly higher TAC C0/D than those with the expresser genotype ($p < 0.05$). The difference was statistically significant at different time points. We also found that CYP3A5 non-expresser had a higher percentage (32.14%) than the CYP3A5 expresser (14.49%) who exceeded the TAC trough concentration of 12 ng/mL to 20 ng/mL (TAC overexposure) within three months after post-transplantation ($p < 0.05$).

Conclusions: The CYP3A5 non-expresser is 52% in the Taiwanese population, may need adjustment of tacrolimus dosage to avoid the drug-related toxicity. Our finding suggests that the initial dosage of Tac determined by CYP3A5 genotype is a way to reduce Tac overexpose and enhances the clinical effect of kidney transplantation.

Key word: Tacrolimus, gene polymorphisms, pharmacokinetic, pharmacodynamic

2034

Risk of vascular events under the treatments with Janus kinase inhibitors in rheumatoid arthritis patients using Japanese health insurance database

Ryoko Sakai[1,2], Dr. Eiichi Tanaka[2,3], Dr. Eisuke Inoue[4], Ms Azumi Isobe[1], Dr. Masayoshi Harigai[2,3]
[1]Department of Public Health and Epidemiology, Meiji Pharmaceutical University, Kiyose, Japan, [2]Division of Rheumatology, Department of Internal Medicine, Tokyo Women's Medical University School of Medicine, Shinjuku-ku, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University Hospital, Shinjuku-ku, Japan, [4]Showa university Research Administration Center, Showa University, Shinagawa-ku, Japan

Aim/Objective: To compare the risk of vascular events among Janus kinase inhibitors (JAKIs) users, biological disease-modifying antirheumatic drugs (bDMARDs) users, and methotrexate (MTX) users in patients with rheumatoid arthritis (RA) using a large health insurance claims data in Japan.

Methods: This retrospective longitudinal population-based study was conducted using claims data provided by Medical Data Vision Co., Ltd (Tokyo, Japan). We defined patients as RA cases if they had at least one ICD10 code of RA, were new users of JAKIs, bDMARDs or MTX between July 2013 and July 2020, and were ≥16 years old. Patients were followed from the first month in which cases met the above criteria until the earliest of the month of the first vascular event, of the loss of follow-up, or of the last exposure to above agents, or July 2021. Vascular events included thromboembolism, arterial thrombosis, acute myocardial infarction, and stroke, and were defined when patients had at least one ICD code and medications for each disease. We calculated incidence rate (IR), IR ratio (IRR, JAKIs vs. bDMARDs, JAKIs vs. MTX), and adjusted hazard ratio (HR [95% CI]) of the vascular event using a time-dependent Cox regression model after adjusting for age, sex, and comorbidities at baseline.

Results: In the study population (n=53,448), incidence rate (IR [95%CI]/1,000 PY) of vascular events was 10.1 [7.9-12.9] for JAKIs, 6.8 [6.2-7.5] for bDMARDs, and 11.3 [10.6-12.0] for MTX. IR ratio (IRR) of JAKIs was 1.5 [1.1-1.9] (vs. bDMARDs) and 0.9 [0.7-1.2] (vs. MTX). Adjusted hazard ratio (HR) of JAKIs using a time-dependent COX model was significantly elevated (1.5 [1.1-2.0]) vs. bDMARDs, but was not elevated (1.2 [0.9-1.6]) vs MTX.

Conclusion: JAKIs user had a significant higher risk of the overall vascular events than bDMARDs, and a similar risk to MTX user in patients with RA.

2035

The Risk of Fracture after Denosumab Discontinuation in Osteoporosis Patients: A Nationwide Cohort Study

MSc Yu-Hsuan Kuo[1], M.D. Hsien-Tsung Lu[2,3], Ph.D. Chung-Hsuen Wu[1]

[1]Department of Clinical Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan, [2]Department of Orthopedics, College of Medicine, School of Medicine, Taipei Medical University, Taipei, Taiwan, [3]Department of Orthopedics, Taipei Medical University Hospital, Taipei, Taiwan

Objectives: Denosumab discontinuation (disDmab) leads to a decline of the bone mineral density and a higher risk of rebound-associated fractures. However, the incidence rates of fractures after discontinuation among Asian population remained unclear. This study aimed to 1) assess the incidence rates of the major osteoporotic fracture (MOF), the vertebral fracture (VF), and multiple vertebral fractures (MVFs) after disDmab; 2) assess the effect of the duration of denosumab treatment on fracture risks after disDmab; and 3) examine the effect of the delayed subsequent treatment on fracture risks after disDmab.

Methods: A retrospective cohort study was conducted using the Health and Welfare Database in Taiwan. Osteoporosis patients aged ≥ 50 years with ≥ 2 doses of denosumab from 2012 to 2015 were included. The incidence rates of MOF, VF, and MVFs after disDmab were reported. The propensity score matching and the Cox proportional hazard regression models were conducted to estimate the risk of MOF, VF, and MVFs, respectively.

Results: The incidence rates after disDmab were 4.79, 2.33, 0.60 per 100 person-year for MOF, VF, and MVFs, respectively. Patients with ≥ 2.5 years of denosumab use were significantly associated with a higher risk of MVFs (HR: 3.26, 95% CI: 1.68-6.35) compared to patients with < 2.5 years of denosumab use. The delayed subsequent treatment for > 60 days was significantly associated with the higher risk of MOF (HR:1.42, 95% CI:1.08-1.87) and VF (HR:1.43, 95% CI:1.01-2.01) compared with the delayed subsequent treatment within 1-30 days.

Conclusion: The incidence rates of fractures after denosumab discontinuation were low in Taiwan. Patients with ≥ 2.5 years of denosumab use were recommended to continue denosumab therapy and frequently monitored the adherence. Prescribing the subsequent treatment in less than 60 days after denosumab discontinuation to prevent fracture was recommended.

Key Words: denosumab, discontinuation, fracture, incidence