CARDIOVASCULAR RISK AND ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS AND OBSERVATIONAL STUDIES (METADTCR)

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Introduction: Androgen deprivation therapy (ADT) is the cornerstone therapy in advanced prostate cancer management. Currently, to study cardiovascular risk, many studies pooled ADT modalities, sometimes with orchiectomy. Our objective was to compare the coronary and cerebrovascular risk (myocardial infarction, ischemic stroke) and the cardiovascular and overall mortality across the different ADT modalities.

PROSPERO Registration: CRD42014010598.

Methods: We performed a literature search of randomized controlled trials (RCTs) and observational studies using MEDLINE and Embase since 1950 to July 28, 2014, without language restriction provided that they gave data on prostate cancer patients comparing one ADT modality to another or radiotherapy or total prostatectomy or placebo. ADT modalities were GnRH agonists, GnRH antagonists, antiandrogens (steroidal or nonsteroidal), and newer drugs (abiraterone, enzalutamide). Orchiectomy was the relevant alternative. For observational studies pooling several ADT modalities, details on each ADT group were requested to the author. We will also perform a network meta-analysis including RCTs.

Results: Among 3614 abstracts, 47 cohorts fulfilled inclusion criteria and 8 provided sufficient data to be analysed. One study gave details on cardiovascular death and 2 on only coronary and cerebrovascular risk, but cardiovascular events definition were too heterogeneous to be pooled (one study added arrhythmia and heart failure to ischemic heart disease). For the 6 other studies, as they did not compare the same modalities of ADT, they were not meta-analysed for overall survival. A total of 153 abstracts mentioning RCT fulfilled inclusion criteria, and data analysis is ongoing.

Conclusions: Data from observational studies did not support consistent evidence that any particular ADT modality may increase cardiovascular risk or overall survival. We are conducting a nationwide population-based prospective cohort of 4 years thanks to the French Health Reimbursement Agency database, which allowed us to investigate more in depth the association between different ADT modalities and cardiovascular risk.

CARBOXYLESTERASE 1 C.428G>A SINGLE NUCLEOTIDE VARIATION REDUCES HYDROLYSIS OF CLOPIDOGREL AND ENALAPRIL, BUT NOT THAT OF QUINAPRIL

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Background: Carboxylesterase 1 (CES1) hydrolyzes about 90% of the prodrug clopidogrel to inactive carboxylic acid metabolite and about 40% to 60% of the prodrugs quinapril and enalapril to their active metabolites. In vitro studies have shown that the *CES1* c.428G>A (p.G143E, rs71647871) single-nucleotide variation (SNV) can markedly affect metabolism of clopidogrel and ACE inhibitors.

Materials and Methods: We studied pharmacokinetics and pharmacodynamics of 600-mg oral clopidogrel, 10-mg oral quinapril, and 10-mg oral enalapril in 10 carriers and 12 noncarriers of the *CES1* c.428G>A SNV. Clopidogrel, its carboxylic acid acyl-β-D-glucuronide, and active *cis* 5-thiol metabolite plasma concentrations and platelet aggregation were measured for up to 12 hours. Quinapril and quinaprilat plasma concentrations were measured for up to 24 hours and those of enalapril and enalaprilat for up to 48 hours.

Results: Clopidogrel carboxylic acid to clopidogrel area under the plasma concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$) ratio was 53% smaller in *CES1* c.428G/A carriers than in noncarriers ($P = 0.009$), indicating impaired hydrolysis of clopidogrel. Consequently, $AUC_{0-\infty}$ of clopidogrel and its active *cis* 5-thiol metabolite were 123% ($P = 0.004$) and 67% ($P = 0.009$) larger in c.428G/A carriers than in noncarriers. Consistent with pharmacokinetics, average inhibition of $P2Y_{12}$-mediated platelet aggregation 0-12 h after clopidogrel intake and maximum observed platelet inhibition were 19 percentage points higher in c.428G/A carriers than in noncarriers ($P = 0.036$ and $P = 0.041$, respectively). $AUC_{0-\infty}$ of enalaprilat was 20% lower in *CES1* c.428G/A carriers than in noncarriers ($P = 0.049$). The *CES1* c.428G>A genotype had no significant effect on quinapril pharmacokinetics.

Conclusions: The *CES1* c.428G>A SNV increased clopidogrel active metabolite concentrations and antiplatelet effects by reducing hydrolysis of parent clopidogrel to inactive metabolites. Therefore, the *CES1* c.428A allele may increase clopidogrel efficacy and bleeding risk. The *CES1* c.428G>A SNV decreased active enalaprilat concentrations by reducing the hydrolysis of enalapril, but had no observable effect on quinapril pharmacokinetics.

POPULATION PHARMACOKINETIC MODELING AND SIMULATIONS OF LONG-ACTING INTRAMUSCULAR RISPERIDONE ISM®

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Background/Introduction: The aim of the project was to develop a population PK model for a novel and long-acting intramuscular (i.m.) formulation (ISM®) of the atypical antipsychotic risperidone, including a relatively complex absorption profile combined with a previously published population PK disposition model of risperidone and its metabolite 9-OH-risperidone after oral risperidone in schizophrenic patients.

Material and Methods: A population PK analysis for risperidone ISM® using Monolix software was conducted based on 1520 plasma samples from two single-dose studies, ROV-RISP-2009-01(17 healthy subjects) and PRISMA-1(48 schizophrenic subjects). Simulations were subsequently undertaken predicting the steady-state PK exposure of active moiety after risperidone ISM®.

Results: The PK disposition models of risperidone and 9-OH-risperidone consisted of two compartments for each compound. Four flexible depot compartments were included to describe the relatively complex absorption profile. Exponential models described IIV for the structural model parameters, and an additive error model in the log domain described residual variability. The influence of the CYP2D6 genotype on the formation rate of 9-OH-risperidone was included in form of a mixture model fixing parameters based on the previously published population PK model. Goodness of fit plots indicated that the model described the data well. The residual error was relatively low with 18% to 19% CV. Simulations were subsequently undertaken, predicting steady-state PK exposure of active moiety after multiple doses of 37.5 to 150 mg risperidone ISM® administered every 28 days for 12 weeks. In addition, different possible dose de-escalation schemes with a starting dose of 100 mg risperidone ISM® were simulated.

Conclusions: Plasma concentrations of risperidone and 9-OH-risperidone after single i.m. injections of risperidone ISM® were well described by a population PK model. The predictive performance was successfully qualified so that this model can be further used for simulations aiding to provide a dosing rationale for risperidone ISM®.

INFECTIOUS RISK OF BIOLOGICAL DRUGS VERSUS CONVENTIONAL SYSTEMIC TREATMENTS IN MODERATE TO SEVERE PSORIASIS

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Introduction: Moderate to severe psoriasis affects about 0.5% of the population. Its management is based on conventional systemic treatments (TSC: phototherapy, acitretin, methotrexate, and cyclosporine) and biological second-line drugs (etanercept, infliximab, ustekinumab, adalimumab, golimumab). Results of studies comparing the infectious risk of TSC and biological drugs are divergent.

Objective: To compare the infectious risk associated with biological drugs versus TSC for moderate to severe psoriasis.

Material and Methods: We conducted a retrospective cohort in the French Health Insurance Database for the Midi-Pyrenees region from 01/01/2010 to 31/12/2013, with patients treated incidentally for moderate to severe psoriasis. After a 6-month observation period with all patients exposed to TSC, we compared patients exposed to biological drugs ("exposed") versus TSC ("unexposed"). We performed a Cox model on the first infectious event, for up to 6 months after the last dispensation of psoriasis drug. An infectious event was defined as delivery of any anti-infectious systemic drug or a hospital diagnosis of infection.

Results: The 101 "exposed: patients and 788 "unexposed" patients were comparable in terms of socio-demographic data and comorbidities. Considering the first infectious event over a period of 2 years, no significant difference was found between "exposed" and "unexposed" (HR = 0.94; 95% CI, 0.71–1.22; $P = 0.62$). Being a woman (HR = 1.23), benefit from the Universal Health Coverage (HR = 1.44), suffering from chronic hepatitis B or C (HR = 2.74), history of neoplasia (HR = 1.70), a previous infectious event during the observation period (HR = 1.74), and the number of drugs consumed during the observation period (HR = 1.03) significantly increased the risk of infection.

Conclusions: We did not reveal any difference in infection risk between the TSC and biological drugs in the management of moderate to severe psoriasis. This risk appears constant the first 2 years of use.

TRENDS IN OPIOID ANALGESICS USE IN EUROPE: A TEN-YEAR PERSPECTIVE

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Background: The aim of this study was to investigate the trends in opioid analgesics consumption in Europe between 2002 and 2012.

Material and Methods: Data were collected for all European Countries. Statistics on opioids consumption were researched and extracted from the consumption databases of the respective national authorities (sales data from health medicines agency or reimbursement data for national healthcare system). Data were expressed in Defined Daily Doses-DDDs/1,000 inhabitants/day (DID). Total opioid consumption (ATC code N02A) and use of selected substances (morphine, oxycodone, fentanyl, codeine, dextropropoxyphene, and tramadol) were investigated.

Results: Data collected were mainly represented by sales data collected by the national authorities from wholesalers. During the observed period, total consumption of opioids increased steadily, then decreased suddenly after 2009 (–43% in France from 2009 to 2012: 44 to 20 DID). France was the largest consumer of opioids in 2002- 2009 (about 50 DID). Up to 2009, the quantity used were mainly represented by dextropropoxyphene combinations (54% of total consumption in 2009 [25/45 DID] and up to 73% [43/58 DID] in 2005). In 2012, France, Belgium, and Denmark were the main opioids users. While morphine use remained constant or tended to decrease (except in UK: 1 to 2 DID from 2005 to 2012), use of fentanyl is increasing in all countries, in particular in the Netherlands (+65% between 2005–2012: 2.3 to 3.8 DID).

Conclusions: This study highlights the substantial changes in opioids consumption patterns that occurred as a consequence of definite withdrawal of dextropropoxyphene in March 2011. Opioids consumption patterns in Europe are now characterized by an increasing use of fentanyl and tramadol.

A NOVEL APPROACH TO TEACHING PHARMACOTHERAPEUTICS LEARNING BY DOING IN A STUDENT-RUN CLINIC

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Background: Medical students should be better prepared for their future role as prescribers. A new educational concept to achieve this is learning by doing. This encompasses legitimate, context-based training and gives students responsibility as early as possible in their medical education. Student-run clinics (SRCs) are an example of this concept. We describe the development of a new SRC primarily focused on medical pharmacotherapy education, the learner-centered student-run clinic (LC-SRC), and its feasibility.

Method: A feasibility study was performed in which a team of (1st-, 3rd-, and 5th-year) students treated patients under the supervision of an internist. Patients were selected from the internal medicine outpatient clinic for follow-up in the LC-SRC. Feasibility was evaluated using a set of questionnaires for patients, supervisors, and students.

Results: In total 31 consultations were conducted; 31 students and 4 clinical specialists participated. A pharmacotherapeutic treatment plan was drawn up in 33% of the consultations. Patients were content with the care provided and rated the consultation with a 7.9 (SD 1.21) (range, 1–10). Supervisors regarded LC-SRC safe for patients with guaranteed quality of care. They found the LC-SRC a valuable tool in medical education, although it was time-consuming. Students appreciated their (new) responsibility for patient care and considered the LC-SRC a very valuable extracurricular activity.

Conclusion: The LC-SRC is feasible and could be a valuable addition to the medical curriculum. The benefits and learner effects need to be investigated in a larger study with a longer follow-up.