SAFEGUARD*: MECHANISTIC STUDIES ADDRESSING PANCREAS EFFECTS OF INCRETIN DRUGS IN HUMAN TYPE 2 DIABETES

Mark M Smits MD, Linde M Morsink MD, Michaela Diamant MD PhD, on behalf of the SAFEGUARD consortium*

Diabetes Center, VU University Medical Center, Amsterdam, 1081 HV The Netherlands. m.diamant@vumc.nl

Background: Off-target effects of several previously approved antihyperglycemic agents have increased the awareness that post marketing studies are desperately needed to monitor the risk/benefit-profile throughout the lifecycle of drugs for the treatment of type 2 diabetes (T2D). In 2008, the FDA has issued a guidance for industry providing recommendations for evaluation of cardiovascular safety of newly developed T2D drugs. These recommendations, among others, include the requirements for establishing independent cardiovascular safety committees, perform meta-analyses of cardiovascular events across phase-2 and -3 trials and providing protocols describing sound statistical methodology for these meta-analyses. Ever since, many novel T2D drugs have come to the market, giving rise to new safety issues. Accordingly, the incretin-based agents, glucagon-like-peptide-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 inhibitors (DPP-4I), have been associated with renal side-effects and pancreatic safety, while the GLP-1RA have additionally shown consistent heart rate acceleration. Based on the increased awareness, the European Medicines Agency has endorsed funding by the European Union (EU-FP7) of the SAFEGUARD-project, a consortium with the overarching aim to assess the cardio- and cerebrovascular, renal and pancreatic safety of currently marketed non-insulin anti-hyperglycemic agents. For the sake of this workshop, we will focus on the multifaceted approach adopted within the SAFEGUARD-project to evaluate for pancreatic safety.
Methods: The SAFEGUARD-project, consisting of 15 international (EU and US), mostly academic partners and 8 work packages (WP), will utilize different strategies to assess pancreatic safety of blood glucose lowering agents. Within the consortium, multidisciplinary expertise is present consisting of pharmacoepidemiologists, pharmacovigilance experts, statisticians, pharmacologists, diabetes experts and clinicians. WP3, having access to large-sized international databases of spontaneous adverse reactions (i.e. WHO, FDA and EMA), will assess associations between T2Ddrugs and pancreatic events using disproportionality analyses. Using a.o. pre-specified ICD-9/10, READ and ICPC codes, WP4 will extract and combine data from nine population-based health care databases in 6 countries (EU and US) capturing longitudinal drug exposure (1999-2012) and event data on more than 35 million subjects (over 1.7 million T2D patients), compatible with >240 million patient-years. Constructing a pooled database at this scale, pancreatic safety can be assessed for all anti-hyperglycemic agents, allowing correction for other known risk factors. Within WP5, a systematic review and meta-analysis of reported pancreatic side-effects from clinical trials and observational studies will be performed, in order to provide overall effect-size estimates for the risk of pancreatitis and pancreatic carcinoma. Additionally, published pharmacoepidemiological studies will be reviewed to synthesize evidence and provide summary effect-size estimates.
Finally, in WP6, we will conduct mechanistic intervention studies, using state-of-the-art smart-phenotyping methodology in T2D individuals in order to detail the effects of incretin-based therapies on the gastrointestinal system and pancreas. In a randomized clinical trial setting, 120 patients with T2D will be exposed to a GLP-1RA, or DPP-4I or placebo treatment for 12 weeks. Baseline and follow-up assessments of pancreatic and biliary system structure, using magnetic resonance (MR) imaging, secretin-enhanced MR cholangiopancreatography and gallbladder ultrasound, and digestive function, using ^{13}C-Mixed Triglyceride Breath test will be performed. Also, fecal and serum samples will be collected to measure pancreatic enzymes (Elastase-1/chymotrypsin; lipase/amylase) and other biomarkers.
Conclusion: The EU-FP7 SAFEGUARD-project offers a unique approach to expand our knowledge regarding pancreatic safety of current anti-hyperglycemic agents for the treatment of T2D, by combining data from RCT, observational studies, large-sized databases and pharmacovigilance with mechanistic studies in humans. This consortium will create a solid back-bone for future initiatives addressing pharmacovigilance.

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