Evidence-based methodology for identifying drugs with potential toxicities to the liver using WHO Vigibase data

A comparative analysis for Liver related Adverse Events for Rosiglitazone and Troglitazone

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Background

Developing a new drug from a research idea to the launch of a finished product is a complex multidisciplinary process which takes on average 12 to 15 years and cost in excess of $1 billion (Dimasi et al., 2003). In the US, FDA's Center for Drug Evaluation and Research (CDER) is in charge of regulations and approvals, and has put in place a number of requirements and processes to ensure that the new medicines are efficacious and safe before they are tested in human patients and get to market. The nature of the tests depends on the therapeutic area, intended patient population, drug class and other factors, but the basic regulatory battery that has been put together over 60 years ago relies on animal testing in a rodent (normally rat) and non-rodent species (usually Beagle dogs, non-human primate models, or, more recently, more exotic species like mini-pig). In spite of this exhaustive testing, some new medicines still cause unexpected side effects (Leone et al., 2AD) in patients either in late stage clinical trials or even on the market (FDA 2009, n.d.; Anon, 2006), which causes their withdrawal from commercial markets because of risks to larger population, with big costs to the pharmaceutical company that developed it (Gwathmey et al., 2009). Where risks or harms is the reason for withdrawal, this will usually have been prompted by unexpected adverse effects that were not detected during Phase III clinical trials, i.e. they were only made apparent from post marketing surveillance data collected from the larger population over longer periods of time. Of 462 medicinal products that were withdrawn from the market between 1953 and 2013, the most common reasons were cardio- and hepatotoxicity (Björnsson et al., 2AD; Graham et al., 2AD).

Closing the knowledge gap between the various stages of drug discovery and development may help companies develop drugs with safer profiles, improve the pharmaceutical industry's bottom line and protect the population from serious harms due to adverse drug reactions. The investigational toxicology approach (Atienzar et al., 2016), where research scientists work alongside chemists, toxicologists and clinicians to discover the mechanisms of serious adverse drug reactions (ADRs) of medicinal products in their early stages and develop early discovery

testing strategies that help de-risk the drug discovery pipelines, has been employed over the last decade by a number of large pharmaceutical companies. The search for most predictive and cost-effective tests that could help improve predictive abilities of the testing process is an active area of investigation in industry and academia . Moreover, the problem of prediction of adverse reactions in industrial chemicals, cosmetics and pesticides is even more daunting, and caused US Environmental Protection Agency (US EPA) to start the Toxicity Forecaster program (ToxCast™). ToxCast™ is a multi-year effort launched in 2007 that uses automated chemical screening technologies (called "high-throughput screening assays") to expose living cells or isolated proteins to chemicals. The cells or proteins are then screened for changes in biological activity that may suggest potential toxic effects. These methods are thought to have a potential to predict human adverse events more accurately and cost-effectively, compared to the legacy animal tests. EPA contributes the results of ToxCast to a federal agency collaboration called Toxicity Testing in the 21st Century (Tox21). Tox21 pools chemical research, data and screening tools from multiple federal agencies including the National Toxicology Program/ National Institute of Environmental Health Science, National Center for Advancing Translational Sciences and the Food and Drug Administration. Together, Tox21 has compiled high-throughput screening data on nearly ten thousand chemicals. As part of EPA's commitment to gather and share its chemical data in open and transparent ways, all ToxCast chemical data is publicly available for anyone to access and use through a user-friendly web application. Currently, the ToxCast dashboard provides an accessible portal for users to search and query the ToxCast chemical screening data. EBTC working group has set out to explore ToxCast data on selected chemicals (drugs) and explore its connection with the human adverse events .

Objective

The main question of the EBTC Tox 21 project is: How well do the a) standard preclinical tests mandated by regulatory agencies and b) US EPA ToxCast™ *in vitro* tests predict the liver outcomes in humans as described by c) Frequencies of liver-related ADRs in WHO Vigibase? The working group is conducting a systematic review of the published preclinical animal data and human controlled trials according to the published protocol https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=112353

For this investigation, we will evaluate drug pairs, wherein a drug withdrawn from the US market (with or without a documented liver toxicity) will be compared to a drug that was still on the US market as of 1/1/2017, when the study was initiated.

Drug Class	**US FDA Status**	
	Withdrawn	**Still in the Market**
Statins	Cerevastatin *(Rhabdomylysis)*	Pitavastatin
Thiazolidinediones	Troglitazone *(DILI)*	Rosiglitazone
Anti-histamines	Astemizole *(QT prolongation)*	Mizolastine
NSAID/ Fluoroquinolone	Rofecoxib *(Heart attack)*	Ciprofloxacin (concern for DILI)
Anti-coagulants (thrombin inhibitors)	Ximelagatran *(DILI)*	Argatroban

At the first step of the project a comparative analysis will be done for in vivo, in vitro and adverse event data of two anti-diabetic drugs (Rosiglitazone Maleate and Troglitazone) with distinct liver toxic profiles. Three evidence streams will provide their independent findings which subsequently will be analyzed:

Evidence Stream 1: Systematic literature review of animal and human published studies described in the protocol (Katya Tsaioun, Hubert Dirven, Kirsten Beck Færden, Daniele Wikoff, Rebecca Ram, Nicole Kleinstreuer, Amanda McCormack, Rob Wright, Gunn Elisabeth Vist, n.d.). Evidence stream 1 will provide the data that regulators usually have at their disposal when they make a decision about safety of the drugs. This evidence stream constitutes the preclinical and clinical legacy tests.

Evidence Stream 2: Tox 21/ Tox Cast in vitro mechanistic data described in the protocol (Tsaioun et al., 2018). This evidence stream constitutes the new in vitro tests that are included in ToxCast.

Evidence Stream 3: Human Adverse event data from WHO Vigibase database, described herein. Vigibase data will constitute the "gold standard" for human safety.

Methodology

Liver related *Adverse Events safety Data* will be analyzed f*rom* the given *Data Set*[1] for Rosiglitazone and Troglitazone separately. Rosiglitazone was approved in US in May 1999 and is still on the US market. Troglitazone was approved in January 1997 and was withdrawn from US in March 2000. The duration of Troglitazone presence in the US (the approval and the withdrawal) was considered as reference for analysis. Troglitazone was legally approved in the USA for 3 years. Hence, the first 3 years of safety data available in Vigibase for Troglitazone was taken into consideration for the present analysis. In order to compare the Liver toxicity risk for Troglitazone with Rosiglitazone, the safety data for Rosiglitazone was kept limited to the first 3 years of Vigibase data. Due to the limitation of reporting date in Vigibase and time lag, a sensitivity analysis by including an additional year of data for both Troglitazone and Rosiglitazone will be performed. In summary, 4 years of ADRs Vigibase data will be used in this analysis.

Step 1

Number of Unique Cases will be counted.

Total Liver related adverse events count will be compared with other non-liver related adverse events for outcomes for the first 4 years after approval in the US, and plotted against the dose and demographic characteristics.

Step 2

[1]*Data Set* : Individual Cases having Liver toxicity as reported adverse event (events) are retrieved separately for Rosiglitazone and Troglitazone from Pharmacovigilance database (WHO Vigibase) as of 2 Jan 2018..

The Liver related adverse events will be classified in 6 prime categories[2] comprised of a list of important liver events.

The occurrence of the respective list of important liver related adverse events will be presented in various plots and chart using open-source visualization software.

Step 3

The proportional *Reporting Ratio* and *Probability of occurrence* will be calculated for 4 years each for Rosiglitazone and Troglitazone separately.

List of Important Liver related adverse events that will be considered for presentation purpose:

General: Liver disorder, Hepatotoxicity, Liver injury, Hepatotoxic effect, Hepatic pain

Liver Function Biomarkers: Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Bilirubinaemia, Bilirubin increased, Blood bilirubin abnormal, Blood bilirubin increased, Hepatic enzyme increased, Hepatic enzymes increased, Hyperbilirubinemia, Liver function test abnormal, Liver function tests abnormal nos

Medical Diagnosis: Hepatic failure , Hepatitis granulomatous, Acute hepatic failure, Hepatitis fulminant, Hepatic disease, Hepatitis nos, Autoimmune hepatitis, Hepatitis acute , Hepatomegaly, Hepatitis chronic active, Hepatosplenomegaly, Hepatitis cholestatic , Jaundice, Hepatitis cholestatic, Jaundice cholestatic, Hepatitis, Jaundice NOS, Ocular icterus, Yellow skin, Hepatic encephalopathy, Hepatic infarction, Hepatitis A, Hepatitis A antibody positive, Hepatitis B antibody positive

Biliary tract disorder: Biliary cirrhosis, Bile duct stone , Bile duct stricture , Bile duct carcinoma , Portal hypertension , Hepatorenal syndrome , Hypertension portal , Gallbladder disorder , Cholecystitis , Cholecystitis chronic , Cholelithiasis , Cholestasis intrahepatic, Cholestasis , Cholangitis , Portal vein thrombosis , Hepatic cirrhosis , Cryptogenic cirrhosis

Histological Changes: Biopsy liver abnormal, Hepatic necrosis , Hepatic steatosis , Hepatocellular damage, Liver fatty

Liver Malignancies: Hepatic neoplasm , Hepatic neoplasm malignant , Hepatic metastases

[2]All the reported liver related adverse events were classified in to the following 6 prime categories.

General, Liver Function Biomarkers, Medical Diagnosis, Biliary tract disorder, Histological Changes and Liver Malignancies

References

Anon. (2006). Melagatran/ximelagatran: market withdrawal. *Prescrire Int*.

Atienzar, F.A., E.A. Blomme, M. Chen, et al. (2016). Key Challenges and Opportunities Associated with the Use of In Vitro Models to Detect Human DILI: Integrated Risk Assessment and Mitigation Plans. *BioMed Research International 2016*, 1–20. Available at: http://www.hindawi.com/journals/bmri/2016/9737920/ [Accessed October 20, 2016].

Björnsson, E., P. Jerlstad, A. Bergqvist, et al. (2AD). Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. *Scandinavian Journal of Gastroenterology 40*, 1095–1101. Available at: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L41291360 http://dx.doi.org/10.1080/00365520510023846 http://findit.library.jhu.edu/resolve?sid=EMBASE&issn=00365521&id=doi:10.1080%2F00365520510023846&atitle=Fulminant+drug-induced+.

Dimasi, J.A., R.W. Hansen, and H.G. Grabowski. (2003). The price of innovation: new estimates of drug development costs. *Journal of Health Economics 22*, 151–185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12606142.

FDA 2009. FDA terfenadine withdrawal. *2009*. Available at: http://www.fda.gov/safety/safetyofspecificproducts/ucm180605.htm.

FDA, C. Public Health Advisories (Drugs) - Trovan Information. Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/drugsafetyinformationforheathcareprofessionals/publichealthadvisories/ucm052276.htm [Accessed June 25, 2014].

Graham, D.J., L. Green, J.R. Senior, et al. (2AD). Troglitazone-induced liver failure: a case study. *Am J Med 114*, 299–306.

Gwathmey, J.K., K. Tsaioun, and R.J. Hajjar. (2009). Cardionomics: a new integrative approach for screening cardiotoxicity of drug candidates. *Expert Opin Drug Metab Toxicol 5*, 647–660. Available at: http://informahealthcare.com/doi/abs/10.1517/17425250902932915.

Katya Tsaioun, Hubert Dirven, Kirsten Beck Færden, Daniele Wikoff, Rebecca Ram, Nicole Kleinstreuer, Amanda McCormack, Rob Wright, Gunn Elisabeth Vist, S.F. Systematic reviews of the hepatotoxic effects of specified compounds/drugs as observed in humans and experimental animals (rats, mice, dogs and non-human primates). Available at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=112353 [Accessed December 29, 2018].

Leone, R., M. Venegoni, D. Motola, et al. (2AD). Adverse drug reactions related to the use of fluoroquinolone antimicrobials: An analysis of spontaneous reports and fluoroquinolone consumption data from three Italian regions. *Drug Safety 26*, 109–120. Available at: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L36188561 http://dx.doi.org/10.2165/00002018-200326020-00004 http://findit.library.jhu.edu/resolve?sid=EMBASE&issn=01145916&id=doi:10.2165%2F00002018-200326020-00004&atitle=Adverse+d.

Tsaioun, K., S. Bandhakavi, and H. Dirven. (2018). Evidence-based methodology for identifying drugs

with potential human liver toxicities using US EPA ToxCast data set. Available at: https://zenodo.org/record/2463115#.XCgNy89Kh-V [Accessed December 29, 2018].