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Visualizing and Cleaning unsolicited Safety data (ICSRs) using R in aiding Causality Assessment

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ABSTRACT

Unsolicited Individual Case Safety Reports (ICSRs) are one of the main sources of safety data used to perform analytics/causality assessment for signal detection and aggregate reports. It has been a rule rather than an exception, that this data is large and "dirty". Wrangling of such data by Safety Physicians and Scientists often consumes 60-70% of their time. Using data visualization in signal detection and aggregate reports has not been given its due importance.

R is free and is highly conducive to perform exploratory data analysis as compared to SAS. Hence, using R programing language, we will attempt to clean and visualize unsolicited ICSRs. To achieve the goal of optimizing the process of analysis/causal assessment the following is desired - Assigning weightage/ranking of ICSRs based on information content for focused analysis & visualization of data in aggregate analysis. We will index (assign weightage to or rank the ICSRs based on information content) the correct information by defining criteria and logic to identify "Noteworthy cases".

INTRODUCTION

Unsolicited Individual Case Safety Reports (ICSRs) is one of the main sources of safety data to perform analytics/ causality assessment for Signal detection and Aggregate reports. This kind of data is large and "dirty", this being the rule rather than an exception. Wrangling of such data by Safety Physicians and Scientists often consumes 60-70% of their time. Often, the safety resource is hard-pressed for time for doing the actual analysis/causality assessment. The veracity of unsolicited data from the safety database is often done at the analysis stage. Subsequently, there are no efforts put in to present the data as visuals. Hence, using data visualization in signal detection and aggregates reports has not been given its due importance.

In pharmacovigilance causality assessment is the process which attempts to determine the cause/s of adverse events reported. It is the assessment of a relationship between a drug treatment and the occurrence of an adverse event. By reporting events spontaneously, the reporter has some basis of suspicion that the event has been caused by consuming pharmaceutical products. However, such spontaneously reported cases usually do not have enough information for a robust causal assessment. The usual parameters for a causal assessment are described in subsequent sections. R programing language will help rank or give weightage to cases which have sufficient information and weed out cases with limited information in turn saving time and effort.

CAUSALITY ASSESSMENT IN PHARMACOVIGILANCE

The popular method of causality assessment in pharmacovigilance is loosely based on the Bradford-Hill criteria. The Hill criteria, otherwise known as Hill's criteria for causation, are a group of minimal conditions necessary to provide adequate evidence of a causal relationship between incidence and a consequence, established by the English epidemiologist, Sir Austin Bradford Hill (1897-1991) in 1965. Criteria assesses causality from multiple information sources using the following parameters-strength of association, temporality, consistency, theoretical plausibility, coherence, specificity in the causes, dose response relationship, experimental evidence, analogy.

There are many structured and algorithmic methods described for a causality assessment in pharmacovigilance. However, they have their own limitations as such assessments are very subjective and bank heavily on expert judgments. For practical purposes we have chosen some of the Hill criteria (described below) to be considered while assessing relationship between drug and the event.

COMMON CRITERIA CONSIDERED FOR CAUSAL ASSESSMENT

The common criteria present in ICSRs, which are considered for assessments are the following:

1. Time to Onset (TTO): This determines the time taken for the event to occur after the drug is consumed. Such temporal relationships along with pharmaceutical knowledge about the drug and adverse event will help determine the relationship. A close temporal relationship is a positive indicator of cause.

2. Concomitant Medication (ConMed): Medication consumed by patients along with suspect product are called concomitant medication. Identifying such medication which are known to cause the reported event provides an alternative explanation for the event.

3. Medical History/Co-morbidities (CoM/Med History): Medical history and co-morbidities are used to assess an alternate explanation for the adverse events reported.

4. Dechallenge/Rechallenge (De/Rechll): The act of stopping the suspect medication of the adverse event is called dechallenge. If the adverse event resolves after stopping medication is called positive dechallenge. If the medication is again introduces as therapy and the adverse event appears again is called a positive rechallenge. Positive Dechallenge/rechallenge is an important indicator of causality.

5. Evolution of the event (Narr): The narrative in an ICSR describes the evolution of the event which would help establish the causal relationship. Hence, for practical purposes, the length of the narrative is an important aspect of establishing a causal assessment.

HY'S LAW

The law is based on observations by Hy Zimmerman, a major scholar of drug-induced liver injury. Hy's Law cases have three components:

- The drug causes hepatocellular injury, generally defined as an elevated aminotransferase by 3-fold or greater above the upper limit of normal. Often with aminotransferases much greater (5-10x) the upper limit of normal.
- Among subjects showing such aminotransferase elevations, they also have elevation of their serum total bilirubin of greater than 2× the upper limit of normal, without findings of cholestasis (defined as serum alkaline phosphatase activity less than 2× the upper limit of normal).
- No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, pre-existing liver disease, or another drug capable of causing the observed injury.

METHODS

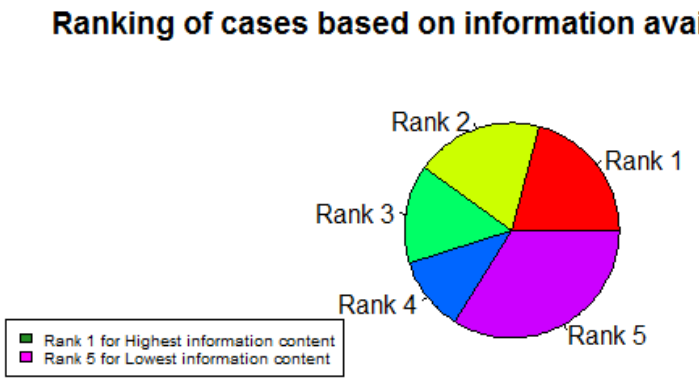
The unsolicited ICSRs were sourced in the form of excel spreadsheets from the FDA Adverse Event Reporting System (FAERS). For the purpose of a focused analysis, we chose the drug zoledronic acid and the event of interest for this paper was "Hepatic failure". We downloaded 44,644 cases of zoledronic acid as suspect drug from the time period of 2013-2017. Using the programing language R, we used the Standardized MedDRA Query (SMQ) "Hepatic failure" to isolate and search pertinent cases (126) of hepatic failure. We then proceeded to clean the dataset using the information content in each case based on the causal criteria described above.

RANKING BASED ON INFORMATION IN EACH CASE USING THE CAUSATION CRITERIA

Using R, the ranking of cases was assigned based on the information content. The highest ranking case was designated with most number of causal criteria information. The ranking of cases is as described in the below table.

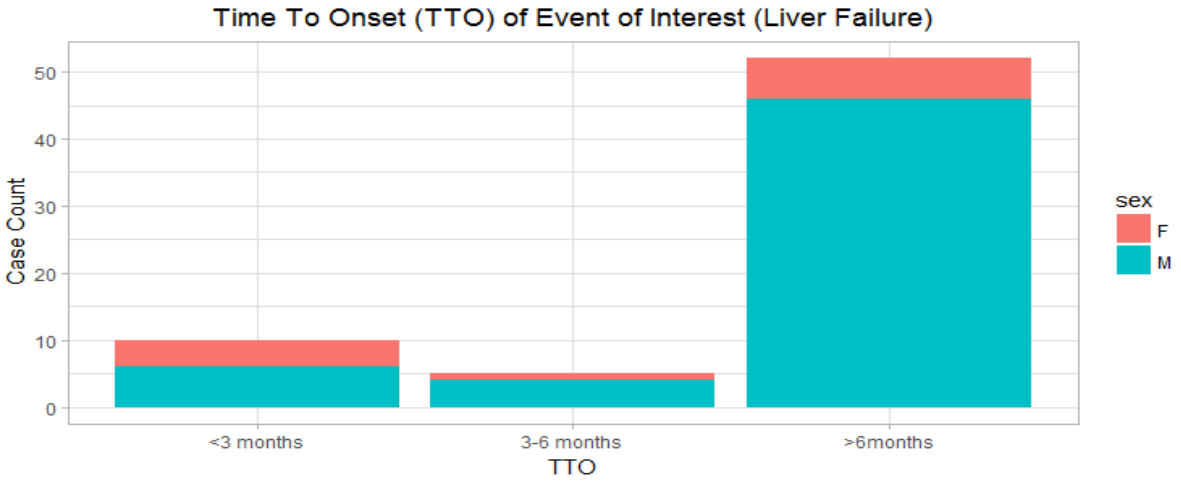
Ranking	Information Content based on causation criteria
R1	TTO + ConMeds + CoM/Med History + De/Rechl + Narr
R2	TTO + ConMeds + CoM/Med History + De/Rechl
R3	TTO + ConMeds + De/Rechl + Narr
R4	TTO + ConMeds + CoM/Med History + Narr
R5	Absence of all 5 criteria

Further causality assessment of cases was done only for cases ranked R1, R2, R3 and R4. The following diagram illustrates the number of cases with the various ranking assigned using R.



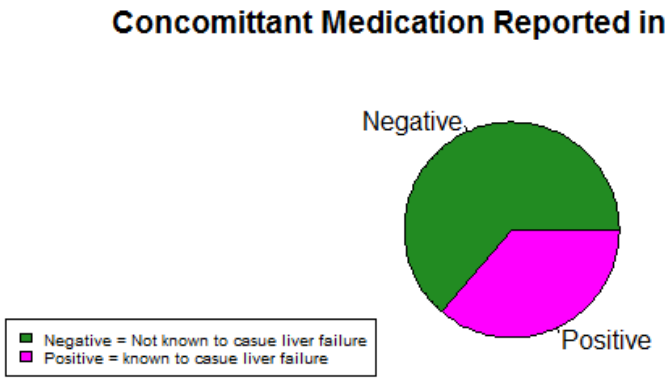
TIME TO ONSET ANALYSIS

The following diagram illustrates the time to onset of cases. This diagram indicates the time frame by which the event occurred after initiating therapy. It also takes into consideration the gender of the patients.



CONCOMITANT MEDICATION

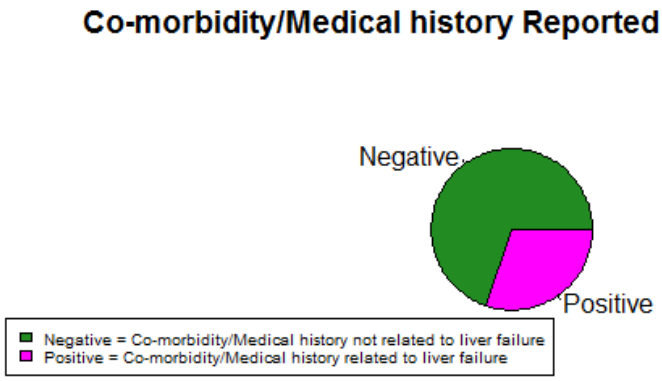
A list of all medication causing liver dysfunction was prepared and compared with the reported concomitant medication using R. Only those cases were considered for further causality assessment, which were concomitant "negative", as concomitant "positive" cases, provided an alternate explanation to the event and would not fit into Hy's law criteria for DILI. The diagram below illustrates the same.



THI

CO-MORBIDITIES/MEDICAL HISTORY

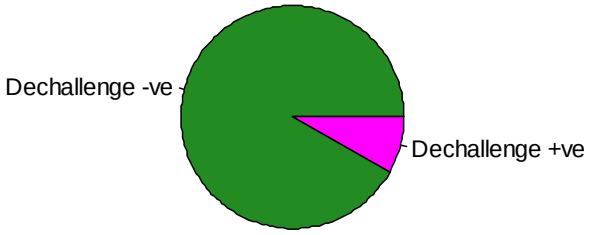
A list of all medical conditions causing liver dysfunction was prepared and compared with medical condition reported for each patient using R. Only those cases were considered for further causality assessment which were "negative", as "positive" cases provided an alternate explanation to the event and would not fit into Hy's law criteria for DILI. The diagram below illustrates the same



DE-CHALLENGE/RE-CHALLENGE INFORMATION

Using R, all cases with de-challenge and re-challenge were isolated and identified. There were no cases with re-challenge information. Among the de-challenge reported cases, a positive de-challenge is a potent indicator for a causal association. The diagram below shows the cases with a positive and negative de-challenge.

Dechallenge and Rechallenge Reported in 47 of 126 Cases



CONCLUSION

The cleaning up of the unsolicited ICSRs from the publicly available FAERS system was achieved by ranking the cases based on information content. The ranking of cases was further achieved by using R. This cleansing or ranking of cases achieved the desired result of focusing only on those cases which had information pertinent to make a causality assessment. None of cases met the Hy's law criteria of a "noteworthy" case. A lot of time and effort was thus saved by avoiding to read and assess cases with limited pertinent information.

The visualizations attempted using R can further be used in regulatory aggregate documents like the Periodic Safety Update Reports. This would shorten the time to report to a great extent thus increasing readability and coherence. Visualizations are encouraged by health authorities. As demonstrated in the above, the visualizations, granularity of the dataset can be represented for easier analysis.

Pharmacovigilance scientists and physicians would gain more insights from datasets, if they encouraged to use the programing languages such as R, to aid in their causality assessment.

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