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ORIGINAL RESEARCH ARTICLE

Profiling Cumulative Proportional Reporting Ratios of Drug-Induced Liver Injury in the FDA Adverse Event Reporting System (FAERS) Database

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Abstract

Background Early prediction and accurate characterization of risk for serious liver injury associated with newly marketed drugs remains an important challenge for clinicians, the pharmaceutical industry, and regulators. To date, a biomarker that specifically indicates exposure to a drug as the etiologic cause of liver injury has not been identified.

Objectives Using cumulative proportional reporting ratios (PRRs), we investigated 'real-time' profiles of a set of pharmaceuticals, over the first 3 years of US marketing, for the signaling of clinically serious drug-induced liver injury (DILI) in a large spontaneous-reporting database.

Methods Using report counts of hepatic failure or clinically serious liver injury obtained from the FDA Adverse Events Reporting System (FAERS) database, PRRs of adverse drug event terms were calculated by division of counts of domestic reports of these events by counts of all serious adverse events for each of 13 selected drugs associated with a broad range of hepatotoxic risk (including three linked to only rare instances of clinically apparent liver injury) with reference to all other drugs in the database. Drug-specific cumulative PRRs were measured at successive intervals (calendar quarters) using cumulative tallies of FAERS reports to generate time-based profiles over the initial 3 years of US marketing.

Results In the set of drugs analyzed, those with no known hepatotoxic risk demonstrated time-based cumulative PRR profiles that approximate the background rates of hepatic failure and serious liver injury reported in the entire FAERS database. In contrast, those that were removed from marketing or subjected to marketing restrictions due to their potential to cause liver injury were associated with profiles of rapidly rising cumulative PRRs that were greater than 5 within the first 10 million domestic prescriptions or the first four quarters of US marketing. The systematic tracking and identification of rising PRRs for DILI associated with newly marketed pharmaceutical and biological agents is a valuable tool for identification of safety signals within the FAERS database.

Limitations Disproportionality profiling of spontaneous reports in FAERS (e.g., cumulative PRR measurements), which signals an association between a recently marketed drug and liver injury, is not a method to quantitatively measure drug-related risk. Regulatory actions in response to emerging drug safety concerns often depend on an accurate assessment of risks using multiple sources of data and the consideration of overall benefits and risks of the agent. Causality must be determined through analysis of individual cases to exclude other etiologies of liver injury.

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Conclusion The FAERS database can be used to advance empiric hepatotoxicity time-trending reporting levels for newly marketed agents in order to rapidly identify recently launched potential hepatotoxic agents and initiate further evaluation.

1 Introduction

Reliable early prediction and accurate characterization of hepatotoxic risk associated with newly marketed drugs remains an important challenge for clinicians, the pharmaceutical industry, and regulators [1]. From a diagnostic perspective there is no single set of biomarkers that unequivocally identifies exposure to a drug as the etiologic cause of liver injury [2, 3]. For this reason, drug-induced liver injury (DILI) is a diagnosis of exclusion and depends on a probabilistic assessment of causal association in individual cases [4]. Although not fully understood, exposure to different drugs may initiate liver injury through a number of distinct immunologic and non-immunological mechanisms, which in some circumstances may be overlapping [5–7]. Because of such differences, DILI cases are marked by different drug exposure times until the onset of hepatotoxic changes, variable rates of injury progression, and diverse clinical signatures. DILI may be the culmination of a complex set of biochemical and pathophysiologic perturbations that reflect synergy between the toxic effects of the parent drug and/or its metabolite(s) and an individual's susceptibility due to genetic, environmental, and/or other host-derived factors. It has been postulated that susceptibility to DILI may be linked to faulty cellular protective or regenerative mechanisms, host immunological responses, or mitochondrial function [8–10]. Differences in these susceptibility factors are likely to influence an ability of the liver to adapt and recover from an injury caused by a therapeutic xenobiotic [11, 12].

Since serious episodes of DILI are rare, the identification and quantitative assessment of risk for these events during clinical trials marked by the exposure of only a few thousand test subjects is generally limited. Moreover, because there often can be a delay in the recognition of idiosyncratic DILI in clinical practice and, even when recognized, such events are typically under-reported to regulatory bodies (e.g., the US FDA's MedWatch program), precise measurements of the incidence of DILI are elusive [13–15]. Despite such limitations, with expanding use of a new drug within the population, treatment of some individuals with higher susceptibility to liver injury induced by the drug is inevitable and over time spontaneous case reports are likely to be reported to regulatory bodies [15, 16]. In the USA, spontaneous adverse event reports that are submitted to the FDA are entered into the FDA Adverse Event Reporting System (FAERS) database [17]. FAERS serves as the FDA's repository of spontaneous reports submitted by manufacturers, healthcare providers, and patients of adverse events linked to suspect drugs and biological agents. To date, this database has accumulated more than 7 million reports and receives more than 2,000 new reports each day. As the largest domestic surveillance catchment for spontaneous reports, FAERS plays an important role in the detection and characterization of rare drug-related adverse events.

With an objective to expeditiously screen newly marketed pharmaceutical or biological agents for emerging signals of drug-related acute liver failure (ALF) and serious DILI in the FAERS database, in real-time, without depending on other data input, we have piloted a method to profile agents with cumulative proportional reporting ratios (PRRs), one of several data-mining algorithms under study for the surveillance of adverse drug reactions (ADRs). To determine whether this method discriminates between agents that are likely to be associated with increased risk from those with low risk, we have analyzed and graphically compared time-trending cumulative PRR profiles from the beginning of marketing for a number of selected drugs that are associated with different known levels of risk for serious idiosyncratic hepatotoxicity. Importantly, such signal profiling alone is hypothesis-generating and must be followed by an in-depth analysis of individual cases of acute liver injury as well as a thorough investigation of other pertinent data-streams to reliably characterize the risk for DILI in patients exposed to a newly marketed suspect hepatotoxic drug.

2 Methods

To investigate a method for the prompt detection of emerging signals of drug-related ALF and serious DILI for newly approved drugs in the FAERS database, the time-trending levels of spontaneous reporting of cases associated with 13 domestically marketed drugs were determined from the beginning of marketing by successive measurements of cumulative PRRs. Based on both published literature and their regulatory history, the drugs that were selected for this study are associated with a broad spectrum of risk for idiosyncratic DILI. They include some agents that have previously been withdrawn or subjected to marketing restrictions in the USA due to hepatotoxicity (bromfenac, troglitazone, trovofloxacin), are marked by descriptions of serious DILI in the Warnings and/or Precautions sections of product labeling (telithromycin, diclofenac, pioglitazone, rosiglitazone, atorvastatin, levofloxacin, and moxifloxacin), or have not been found to be associated with significant DILI risk (clopidogrel,

amlodipine, and celecoxib). FAERS reports that were analyzed were limited to DILI outcomes of death, hospitalization or disability, or characterized as life-threatening or requiring an intervention(s) to preclude harm.

FAERS reports suggestive of serious DILI were those coded with the MedDRA® (Medical Dictionary for Regulatory Activities)[1] preferred terms of "hepatic necrosis," "hepatitis fulminant," "liver transplant," or contained within the MedDRA® higher level term "hepatic failure and associated disorders". Cumulative PRRs were measured at progressive intervals of time (calendar quarters) from market launch through the first full 12 calendar quarters or approximately 3 years of US marketing. For the purpose of these analyses, the first full marketing quarter includes the period of time 4–6 months following market launch. This approach was utilized to address differences in drug launch for different drug products within calendar quarters.

To measure PRRs, tallies of categorically serious domestic (US) DILI reports (crude numbers of reports not individually reviewed) associated with a specified drug were divided by contemporaneously reported total counts of all serious domestic (US) FAERS reports linked to that drug and then divided by a fraction of the same measures made with respect to all drugs in the database. Within any specified timeframe, by definition a PRR higher than 1.0 for any drug indicates the receipt of more reports for the outcome of interest (e.g., serious liver injury) than background, with reference to all other agents in the database [18]. To test positive findings of time-trending profiles of cumulative PRR measures for DILI among those drugs in our study set that underwent marketing withdrawal or changes in approved labeling in the USA and/or other countries due to hepatotoxicity (bromfenac, troglitazone, trovafloxacin, diclofenac, and telithromycin), we determined how many US marketing quarters elapsed before three minimal criteria previously shown to reduce false-positive signaling findings in a similar large drug-related adverse event spontaneous reporting database were all met. These include the appearance of a minimum of three reports of serious DILI, a cumulative PRR >2, and the crossing of a common boundary of statistical significance by Chi-squared (χ^2) testing (χ^2 >3.86 indicates a 95 % confidence interval, assuming 1 degree of freedom with the Yates correction) [18].

In order to assess DILI signaling with reference to utilization, nationally projected drug prescription data over time were obtained through IMS Health's "Vector One: National". This data resource provides nationally projected counts of prescriptions dispensed through US retail pharmacies that reflect the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. The pharmacies in the database account for nearly all retail pharmacies and represent approximately half of retail prescriptions dispensed nationwide. IMS Health receives all prescriptions from approximately one third of the stores and a significant sample of prescriptions from the remaining stores.

3 Results

Cumulative PRR profiles of clopidogrel and amlodipine over the first 3 years of US marketing are shown in Fig. 1, together with the profiles of atorvastatin, troglitazone, trovofloxacin, and bromfenac. Although associated with only a scant number of reports as suspect drugs for clinically serious liver injury, both clopidogrel and amlodipine had relatively large exposure in the USA, as summarized in Table 1. Shown in the table, small DILI report counts relative to all reports for each agent coincide with cumulative PRRs that reach a plateau at levels substantially below 1.0, at the end of 12 full quarters of US marketing.

As shown in Table 1, a modest number of FAERS reports consistent with serious DILI ($n = 15$) associated with atorvastatin as a suspect drug were received through the first 12 quarters of US marketing. Nonetheless, the cumulative PRR that became stable over successive marketing quarters is 1.6.

Bromfenac, troglitazone, and trovafloxacin exemplify agents with robust signals of clinically serious DILI that have been withdrawn from US marketing or heavily restricted. Within a short period after the launch of each of these agents the cumulative PRR profiles in FAERS demonstrate highly disproportionate reporting of life-threatening hepatotoxicity. Shown in Fig. 1, before the first 3 million US prescriptions were dispensed, and within the first year of marketing, remarkable elevations in cumulative PRRs occurred, both for bromfenac (PRR ~12) and trovafloxacin (PRR ~7). In the context of relatively low utilization of each of these agents, a disproportionate number of reports of serious DILI were cumulatively submitted to FAERS. A slightly more gradual peak relative to cumulative utilization was observed with troglitazone. Nonetheless, after ten quarters of US marketing and the first 10 million domestic prescriptions of this thiazolidinedione, the cumulative PRR for serious DILI was approximately 10, coinciding with the receipt of approximately 100 domestic reports of serious DILI in FAERS.

The cumulative PRR profiles of clinically serious liver injury of the NSAIDs celecoxib, diclofenac, and bromfenac

[1] MedDRA® is an internationally recognized adverse event coding system used by regulatory authorities and the biopharmaceutical industry. MedDRA® was developed by the International Conference on Harmonisation (ICH) and is managed by the Maintenance and Support Services Organization (MSSO)/International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

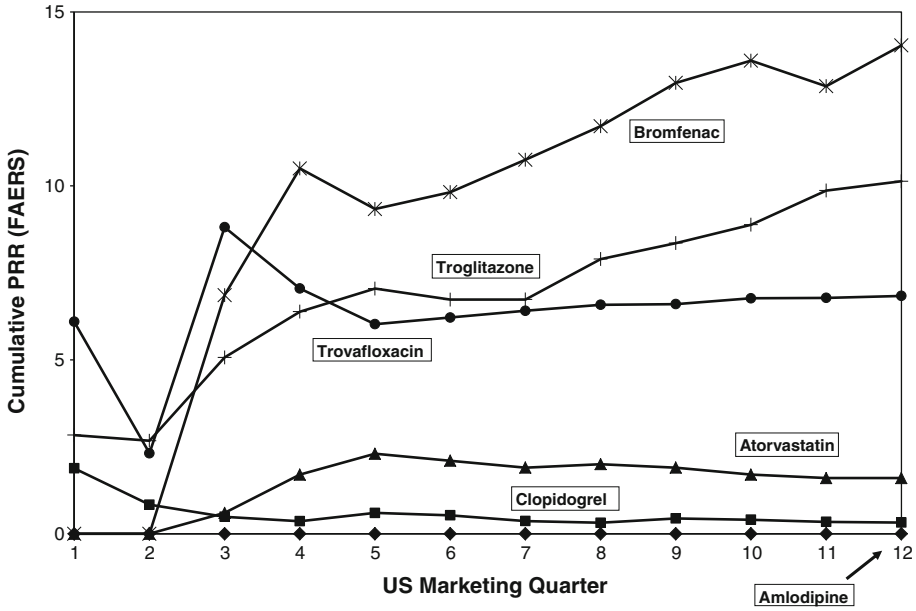

Fig. 1 FAERS proportional reporting rate profiles of the selected drugs bromfenac, troglitazone, trovofloxacin, atorvastatin, clopidogrel, and amlodipine for serious idiosyncratic drug-induced liver injury, during the first 3 years of US marketing. *FAERS* FDA Adverse Event Reporting System, *PRR* proportional reporting rate

Table 1 3-year cumulative US FAERS reports of serious drug-induced liver injury, proportional reporting rate values, and domestic retail prescriptions for selected drugs, from beginning of US marketing

Drug	DILI reports in FAERS[a]	PRR (FAERS)	Number of prescriptions (in millions)[b]
Troglitazone[c]	117	10.1	11.8
Trovafloxacin[c]	93	6.8	2.4
Bromfenac[c]	53	14	2.6
Atorvastatin	15	1.6	64.1
Clopidogrel	3	0.3	11.0
Amlodipine	0	0	13.4

DILI drug-induced liver injury, *FAERS* FDA Adverse Event Reporting System, *PRR* proportional reporting rate

[a] Crude counts, not individually reviewed or de-duplicated

[b] Obtained from IMS Health, Vector One: National (VONA)

[c] Drug withdrawn from US marketing. Bromfenac was approved in July 1997 and withdrawn in June 1998. Troglitazone was approved in January 1997 and withdrawn in March 2000. Trovafloxacin was approved in December 1997 and withdrawn in June 2006

are compared in Fig. 2. As observed with the other high-risk idiosyncratic hepatotoxins in this study that were ultimately withdrawn or subjected to restrictions in marketing, a signal for serious liver injury associated with bromfenac rose shortly after the initiation of US marketing. Following the identification by comprehensive case review of ALF deaths and liver transplants that occurred within the first four quarters of domestic marketing and 2.6 million domestic prescriptions, bromfenac was withdrawn from the US market. Ultimately, at least four ALF deaths and eight liver transplants related to bromfenac exposure were documented to have occurred during this timeframe [19]. As shown in Fig. 2, when it was withdrawn from the US market, bromfenac was associated with a real-time cumulative PRR signal for serious DILI of >10. Reporting of hepatotoxicity associated with bromfenac continued well after market withdrawal, possibly stimulated by articles appearing in the medical literature [20–23].

In contrast to bromfenac and other agents included in this analysis, the PRR for diclofenac was elevated from the outset of US marketing, remaining flat throughout the 3-year observation period. It is likely that such heightened recognition by practitioners of a link between diclofenac and hepatotoxicity from use outside of the USA was responsible for increased spontaneous reporting to FAERS, even at the initial phases of domestic marketing [24, 25]. In contrast to both bromfenac and diclofenac, no serious liver injury signal is appreciated for celecoxib, a cyclo-oxygenase (COX)-2 selective NSAID, with a cumulative PRR for serious DILI of ~1 through 12 quarters of marketing. This finding is consistent with very low or negligible levels of reporting for serious liver injury.

Figure 3 compares 3-year time-trending cumulative PRR profiles of troglitazone, rosiglitazone, and pioglitazone for serious DILI. During its marketing in the USA, numerous reports of troglitazone-associated ALF were reported to FAERS. After an exhaustive retrospective analysis of domestic drug utilization and individual liver injury cases was completed, it was determined that within the first 12 months of marketing 3.6 million domestic prescriptions had been dispensed. In the same period there were 24 unique FAERS cases assessed by FDA reviewers as 'possibly or probably' related to troglitazone [26]. At the end of the first 12-month period of marketing, the real-time

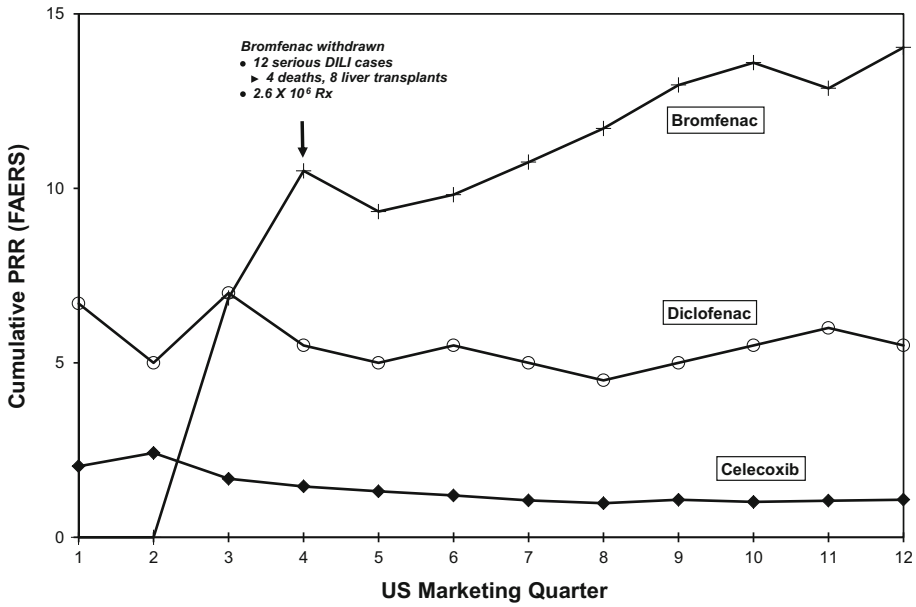

Fig. 2 FAERS proportional reporting rate profiles of the NSAIDs celecoxib, diclofenac, and bromfenac for serious drug-induced liver injury. The numbers of bromfenac drug-induced liver injury cases in FAERS with serious outcomes and projected numbers of US prescriptions dispensed through retail pharmacies are shown at the time of product withdrawal after four quarters of marketing (*solid arrow*). *DILI* drug-induced liver injury, *FAERS* FDA Adverse Event Reporting System, *PRR* proportional reporting rate, *Rx* prescriptions

cumulative PRR for serious DILI associated with troglitazone was approximately 7.0. With this early trend suggesting a substantial risk of hepatotoxicity, it is not surprising that after 3 years of marketing and 11.8 million cumulative prescriptions, troglitazone was finally withdrawn. A retrospective analysis of individual cases that was completed after the withdrawal of this agent documented 94 cases of drug-associated ALF, including 63 deaths and ten liver transplantations [27, 28].

With substantial US drug utilization and accrual of domestic FAERS reports, the cumulative PRRs associated with pioglitazone and rosiglitazone stabilized at approximately 4, consistent with comparatively lower reporting for hepatotoxicity than for troglitazone [29].

In Fig. 4, the 3-year PRR profiles of levofloxacin and moxifloxacin for serious DILI are compared with the profiles of telithromycin and trovofloxacin. After the fifth quarter of US marketing, the approved indication of trovafloxacin was narrowed to serious and life-threatening infections. During the first three full quarters of trovofloxacin marketing the cumulative PRR was volatile, reflecting effects of a few sporadic reports of serious DILI that were submitted to FAERS. However, after the first five quarters of marketing, with continued receipt of more reports, the cumulative real time profile stabilized at levels ranging between 6.7 and 7.0. Consistent with this early trend, by the end of 14 months of US marketing, FAERS had received more than 100 unique cases of clinically symptomatic trovafloxacin-associated liver injury, which after careful analysis included 14 cases of ALF, with six deaths and four liver transplants [30].

Data for telithromycin, a ketolide antibiotic associated with cases of clinically serious idiosyncratic DILI, are also shown in Fig. 4. With this antimicrobial agent, the observed cumulative PRR after 3 years of US marketing increased well above expectations to approximately 12. In contrast with rapidly rising levels associated with troglitazone, bromfenac, and trovofloxacin (see below), the cumulative PRR of clinically serious DILI linked to telithromycin remained below 2.5 over the first five quarters of marketing but then peaked after ten quarters of marketing. The delayed rise of this PRR signal coincided with widespread publicity surrounding published post-marketing reports of hepatotoxicity associated with the antibiotic [31]. Concern about these cases in conjunction with other considerations led to narrowing of the approved indications of telithromycin use in the modified product label [32, 33]. The cumulative PRR profile for telithromycin is described further in Sect. 4.

In contrast to trovofloxacin and telithromycin, both levofloxacin and moxifloxacin are associated with PRR levels that have reached a plateau at levels below 2. Although cases of clinically serious DILI have been associated with both of these agents [34], when drug utilization is taken into account these have been reported substantially less frequently than with trovofloxacin or telithromycin [35].

PRR measures of FAERS reports as a test of strength of association of a drug with an adverse event are hypothesis-generating exercises. As such, there is an intrinsic trade-off between sensitivity and specificity when establishing a statistical threshold for drug safety signals with no a priori absolute standards [36, 37]. To determine when in successive marketing quarters the cumulative PRRs of clinically serious DILI for trovafloxacin, troglitazone, bromfenac, diclofenac, and telithromycin (drugs that were withdrawn or subjected to changes in labeling in the USA

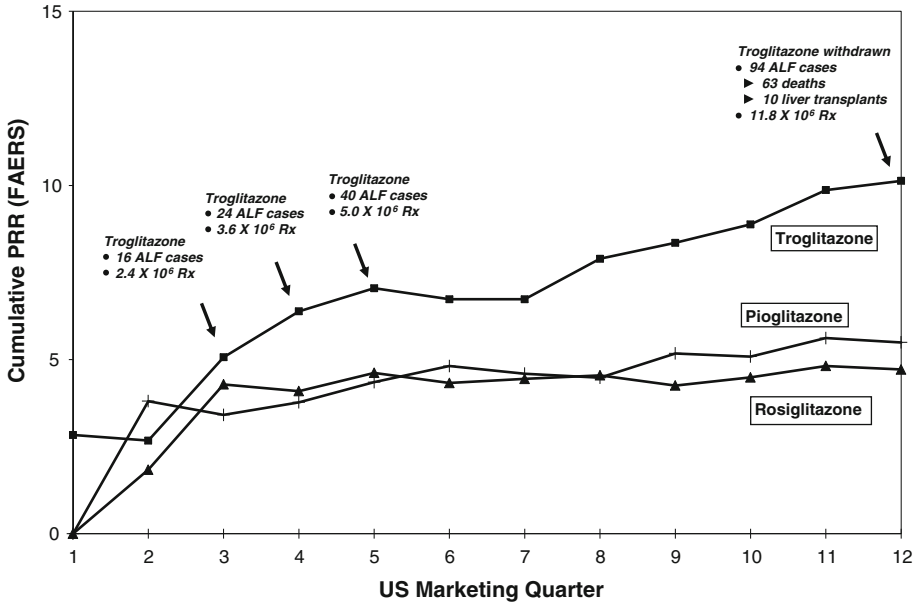

Fig. 3 FAERS proportional reporting rate profiles of the thiazolidinediones troglitazone, pioglitazone, and rosiglitazone for serious drug-induced liver injury. The cumulative numbers of cases of acute liver injury in FAERS associated with troglitazone with increasing US prescriptions dispensed through retail pharmacies are shown at different time points after marketing initiation, until product withdrawal after 12 quarters of marketing (*solid arrows*). *ALF* acute liver failure, *DILI* drug-induced liver injury, *FAERS* FDA Adverse Event Reporting System, *PRR* proportional reporting rate, *Rx* prescriptions

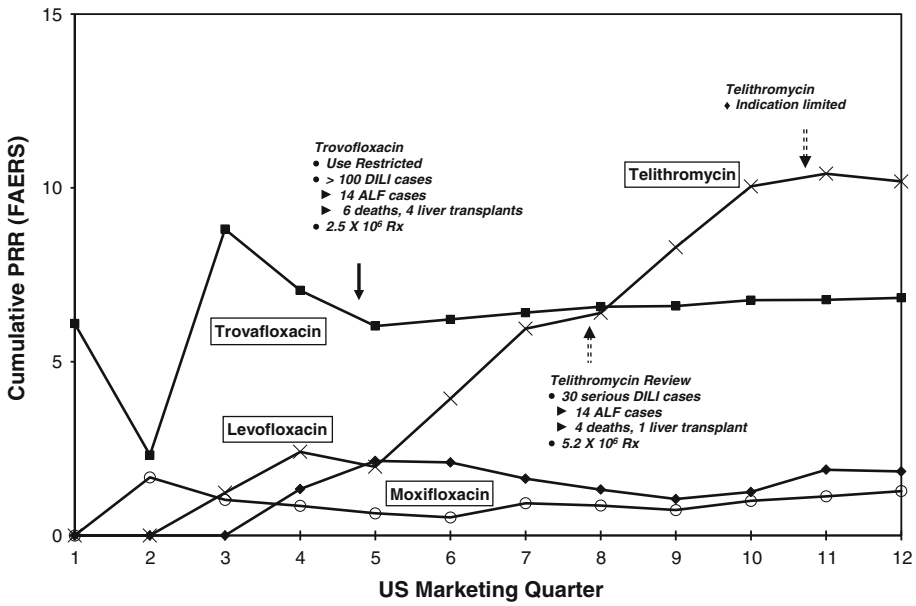

Fig. 4 FAERS proportional reporting rate profiles of the fluoroquinolones trovafloxacin, levofloxacin, and moxifloxacin and the ketolide telithromycin for serious drug-induced liver injury. The numbers of drug-induced liver injury cases in FAERS linked to trovofloxacin with serious outcomes and US prescriptions are shown at the time of marketing restriction after five quarters of marketing (*solid arrow*). Accompanying the telithromycin proportional reporting rate profile, time points coinciding with a review of cumulative serious drug-induced liver injury case counts in FAERS and a product label change to reduce approved indications of use of the antibiotic are shown. *ALF* acute liver failure, *DILI* drug-induced liver injury, *FAERS* FDA Adverse Event Reporting System, *PRR* proportional reporting rate, *Rx* prescriptions

and/or other countries because of hepatotoxicity) met minimal criteria for significant signaling, the corresponding FAERS data was analyzed for the appearance of (a) a minimum of three reports of serious DILI; (b) a cumulative PRR >2; and (c) the crossing of a common boundary of statistical significance by χ^2 testing with reference to all

other drugs in the database (χ^2 >3.86 indicating a 95 % confidence interval, assuming 1 degree of freedom with the Yates correction) [18]. In keeping with their overall hepatotoxic profiles, each of these agents passed this threshold within the first four full quarters of marketing.

With an interest in other signaling techniques, cumulative PRR profiles of bromfenac, troglitazone, trovafloxacin, and atorvastatin were graphically compared with their corresponding time-linked standard crude reporting rate profiles over the first 3 years of US marketing. Among the four drugs that were compared, DILI signaling reflected by rising PRR levels from initiation of marketing coincided with or preceded the reporting rate increases that occurred (these data are included as Electronic Supplementary Material that is available online).

4 Discussion

We have utilized a method for measuring proportional reporting levels in a large spontaneous ADR report database to analyze, in real time, trends for reporting of clinically serious idiosyncratic DILI associated with a set of drugs connected to different levels of risk. The set of drugs that we selected for this analysis are marked by a broad range of idiosyncratic hepatotoxic risk and consequent regulatory actions. They include agents that have been removed from the US market since 1997 or subjected to significant marketing restrictions due to serious hepatotoxic risk that became increasingly apparent in a post-marketing setting, as well as others with virtually no risk. As shown in this study, cumulative PRR analysis provides a convenient method to systematically track and graphically compare emerging signal strengths for DILI of contemporaneously marketed members of a pharmacological class used to treat the same or similar patient populations, from the time of their initial marketing. Importantly, computations of disproportionate reporting measures such as cumulative PRRs only depend on the enumeration of reports submitted to FAERS in real time. As such, they represent estimates of disproportionality that do not require other data sources (e.g., utilization data) which typically engender a delay. Although cumulative time-trending PRR profiles for DILI in FAERS tend to stabilize over increasing periods of time after the initial launch of a product, they are not quantitative measures of risk. Nonetheless, when taken together with available relevant clinical trial and epidemiological data, they are indicators of reporting levels for drug-specific associated hepatotoxic events with reference to the reporting for all drugs in the database.

It is important to note a number of important limitations inherent in spontaneous reports. In conjunction with a commonly observed phenomenon referred to as the 'Weber effect,' in which the reporting of adverse events to FAERS associated with a product is highest following initial marketing and declines over time, a number of other secular variations also cause changes in levels of reporting [38]. Thus, it is not possible to reliably derive quantitative measures of DILI risk from levels of spontaneous reporting of individual agents or accurately infer quantitative differences of risk from comparisons of PRR profiles between products. Discrepancies in the time of their initial US marketing can also be linked to substantial differences in levels of reporting among similar products. However, when large differences appear in reporting levels of DILI associated with drugs in the same treatment class launched into the US market within several years of each other, further review of all available data will often reveal differences of risk between products [39].

In the set of drugs profiled in this study, those that were removed from marketing or subjected to marketing restrictions due to a potential to cause liver injury were associated with rapidly rising cumulative PRRs in FAERS that were greater than 5 within the first 10 million domestic prescriptions or first four quarters of US marketing. Within these parameters, with differences in uptake of individual drugs in the US market as well as perceived risk for serious hepatotoxicity among healthcare providers, it is not surprising that we found some variability in timeframes between the initiation of marketing and the PRR rises among hepatotoxic drugs that we analyzed. This is likely due to secular effects in levels of spontaneous reporting due to differences in clinical identification, publicity, or publications surrounding the individual drugs. As an example, in the case of telithromycin, the PRR for serious DILI may have substantially increased only after the first 16 months of US marketing because of low drug utilization as well as a delayed recognition of the antibiotic's association with hepatotoxicity among practitioners due to the unusual form of clinical cases marked by short latency, systemic symptoms, and ascites.

It is self-evident that recognition of a suspected causal association between newly marketed drugs and hepatotoxicity in the healthcare community would be influenced by signals gathered from a number of data streams. For example, in the case of troglitazone, among 2,510 study subjects treated with the glitazone in pre-approval controlled studies, 0.2 % developed ALT rises >30 × upper limit of normal and two subjects developed concomitant hyperbilirubinemia, a harbinger for the post-marketing cases of serious DILI that later emerged in the post-market phase. Moreover, among 585 study subjects in the National Institutes of Health (NIH) Diabetes Prevention Program treated with troglitazone, one developed fatal hepatotoxicity [26].

Findings of disproportionate reporting for serious DILI as a signaling step would ordinarily trigger the investigation and characterization of individual cases of serious liver injury for clinical phenotype and severity, as well as causal association with the suspect drug [13]. It needs to be emphasized that DILI signaling from other information domains such as publications, clinical trial findings, and epidemiological study reports would also independently trigger a comprehensive evaluation of individual cases of drug-associated hepatic injury. In the absence of highly specific biomarkers, causality assessments in cases of suspected DILI require rigorous exclusion of confounding effects and alternative causes of liver injury.

From the findings in our study, the systematic tracking and identification of rapidly rising PRRs for DILI in FAERS associated with a newly marketed product can play an important role in drug safety signal identification. However, actions taken by regulatory authorities depend on the accurate assessment of risk using multiple sources of data and a consideration of overall benefits and risks. For this reason, the application of uniform quantitative thresholds for PRR profiles and drug utilization that must be met to automatically trigger a pre-specified set of actions for all newly marketed potentially hepatotoxic agents would be inappropriate. Rather than applying rigid quantitative criteria for PRR boundaries and drug utilization levels that must be met to automatically trigger a pre-specified set of investigational actions including individual case follow-up and characterization, a contextual approach to determine signal thresholds is warranted. Further studies are necessary to establish criteria for such an approach.

It should be noted that the absence of disproportionate reporting in FAERS of clinically serious acute liver injury during the first few years of US marketing associated with clopidogrel, amlodipine, and celecoxib is mirrored by similar findings for 40 other drugs considered to have low or no hepatotoxic potential that have been separately analyzed by our group. These drugs are contained in a NIH-sponsored comprehensive compilation of critical evaluations of scientific and clinical information surrounding the association of hepatotoxicity with specific pharmaceuticals, biological agents, and herbal products [40].

Over the first 3 years of their US marketing, each of these agents has been associated with relatively very few numbers of FAERS reports of serious acute liver injury and cumulative PRRs of ~ 1 in almost all cases.

The evaluation of DILI risk with any therapeutic drug or biological product should be periodically updated, since it may be substantially affected by the assimilation of new important information. Without precise methodological measures to accurately predict the frequency of rare events in a population of treated patients, residual uncertainty surrounding agent-specific DILI risk is inevitable. With accrual of more safety information, it is expected that a clearer picture of DILI risk will develop over the product's life-cycle. Therefore, the accurate evaluation of drug-related risk depends on an iterative process by which important safety information accrues over time. During clinical development, registrational trials may enroll only a few thousand study subjects treated with the drug. Thus, detection of rare idiosyncratic severe DILI cases may be absent because of insufficient study power. Of specific interest, the registrational study database for a drug may not contain any cases of severe DILI or 'Hy's Law' cases marked by a diagnosis of drug-induced clinical jaundice or hyperbilirubinemia (serum bilirubin >2.5 mg/dL) that accompanies an elevation of serum aminotransferases. 'Hy's Law' postulates that approximately 10 % of DILI cases that manifest concurrent elevations in serum aminotransferases and bilirubin due to drug-induced hepatocellular injury will result in an outcome of orthotopic liver transplantation or death [41]. Thus, the presence of even a few such cases in which non-DILI causes have been excluded in clinical trials is highly predictive that the study drug is likely to cause life-threatening DILI in a larger treatment population [42]. Because the greatest level of uncertainty regarding the level of DILI risk associated with a new drug will occur during the early marketing period, it is critical to have monitoring systems in place at the time of drug launch into the marketplace. An important public health goal related to post-market DILI risk assessment is to compress the time and cumulative level of utilization that is required to accurately characterize drug-related risk. To gauge DILI risk, results from different post-market data streams obtained over time must be proactively collated and reviewed [12, 43, 44]. These include spontaneous adverse event reports, peer-reviewed literature, DILI registries, and epidemiological studies.

In addition to PRR profiling, other measures of disproportionate reporting of ADRs have been used for surveillance purposes. These include the Reporting Odds Ratio (ROR), the Multi-item Gamma Poisson Shrinker (MGPS), and the Bayesian Confidence Propagation Neural Network (BCPNN). The MGPS and the BCPNN methods, respectively, measure the Empiric Bayes Geometric Mean (EBGM) and the Information Component (IC) as measures of disproportionality. The European Medicines Agency (EMA) has utilized the PRR in their pharmacovigilance practices. To address the statistical problem of multiplicity and minimize over-signaling with small report counts for some drug events when screening for signals across a very large numbers of drug adverse event combinations in their spontaneous drug adverse event report databases, the FDA and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) have been utilizing MGPS, whereas the Uppsala Monitoring Centre of the World Health Organization (WHO) has employed the BCPNN method.

For the purpose of pharmacovigilance screening, each of these data-mining methods may set somewhat different boundaries that offset sensitivity and specificity for the signaling of a drug's causal association with risk of hepatotoxicity. Since they generate rather than test hypotheses of ADR causal association, no single computational approach is inherently superior to the others [36, 37]. After screening the FAERS database for data-mining signals of drug-associated liver injury cases by one or more of these methods, a thorough individual case review for clinical phenotyping and causality assessments remains an essential second step to evaluate DILI risk. Since idiosyncratic serious DILI is typically rare, to maximize sensitivity for emerging DILI signaling of newly marketed products in screening the FAERS database in this initial study we used simple cumulative PRR testing, rather than incorporate an additional statistical stringency employed by MGPS that sets a Bayesian lower 5 % confidence interval boundary (e.g., EB05) to define ADR signals.

Despite the utilization of a variety of statistical methods to refine measures of spontaneous reporting disproportionality, there is no gold-standard technique to absolutely separate true and false drug-associated adverse event signals. With this caveat, the cumulative PRRs for five agents with hepatotoxic profiles (trovofloxacin, troglitazone, bromfenac, diclofenac, and telithromycin) were subjected to serial statistical assessments over the course of marketing quarters. As advanced by Evans et al. a χ^2 value greater than 3.86 was taken to represent a critical statistical limit of reporting disproportionality [18]. All five agents met this bar upon receipt of three or fewer serious DILI reports. Further, these agents reached this threshold of measured proportionate reporting significance within four quarters of marketing. The finding supports a previous assertion based on Poisson modeling that receipt of even a small number of spontaneous reports of a serious and rare adverse event should prompt further investigation [45].

Previously, Suzuki et al. [46] highlighted inspection of multiple data streams in the identification of new drugs that are hepatotoxic. The authors included a review of DILI cases from DILI registries in three countries (Spain, Sweden, and the USA), a disproportionality analysis of the WHO spontaneous Adverse Drug Event (ADE) database ("Vigibase™"), and an active review of the literature. That analysis provided a snapshot of disproportionality measurements without reference to trending cumulative profiles as a function of time of marketing or drug utilization.

5 Conclusions

The FAERS database with or without the addition of utilization data can be used to advance empiric hepatotoxicity reporting levels for new agents. Since they are derived exclusively from the FAERS database, cumulative PRR profiles are especially useful as 'real-time' DILI signal measures. Such signaling tools may facilitate the rapid identification of recently launched potential hepatotoxic agents in order to initiate further case evaluation.

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Conflict of Interest Allen Brinker, Joseph Tonning, Jenna Lyndly, David Moeny, Jonathan Levine, and Mark Avigan are currently employed at the US Food and Drug Administration and have no conflicts of interest to declare that are directly relevant to the content of this study.

Disclaimer The views expressed are those of the authors and do not necessarily represent the position of, nor imply endorsement from, the US Food and Drug Administration or the US Government.

Reference

1. Temple RJ, Himmel MH. Safety of newly approved drugs: implications for prescribing. JAMA. 2002;287(17):2273–5.
2. Lucena MI, García-Cortés M, Cueto R, et al. Assessment of drug-induced liver injury in clinical practice. Fundam Clin Pharmacol. 2008;22(2):141–58.
3. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol. 1990;11:272–6.
4. Andrade RJ, Camargo R, Lucena MI, González-Grande R. Causality assessment in drug-induced hepatotoxicity. Expert Opin Drug Saf. 2004;3(4):329–44.
5. Uetrecht JP. New concepts in immunology relevant to idiosyncratic drug reactions: the "danger hypothesis" and innate immune system. Chem Res Toxicol. 1999;12:387–95.
6. Gupta NK, Lewis JH. Review article: the use of potentially hepatotoxic drugs in patients with liver disease. Aliment Pharmacol Ther. 2008;28:1021–41.
7. Gunawan BK, Kaplowitz N. Mechanisms of drug-induced liver disease. Clin Liver Dis. 2007;11(3):459–75.
8. Wallace KB, Starkov AA. Mitochondrial targets of drug toxicity. Annu Rev Pharmacol Toxicol. 2000;40:353–88.
9. Boelsterli UA, Lim PL. Mitochondrial abnormalities—a link to idiosyncratic drug hepatotoxicity? Toxicol Appl Pharmacol. 2007;220:92–107.
10. Jones DP, Lemasters JJ, Han D, Boelsterli UA, Kaplowitz N. Mechanisms of pathogenesis in drug hepatotoxicity putting the stress on mitochondria. Mol Interv. 2010;10(2):98–111.
11. Senior JR, Avigan M. Detection of hepatotoxicity during drug development: practical problems and regulatory measures. In: Arroyo V, Andrade R, editors. International hepatology updates. Barcelona: Permanyer Publications; 2007. p. 147–66.
12. Watkins PB, Seligman PJ, Pears JS, Avigan MI, Senior JR. Using controlled clinical trials to learn more about acute drug-induced liver injury. Hepatology. 2008;48(5):1680–9.
13. Fontana RJ, Seeff LB, Andrade RJ, Björnsson E, Day CP, Serrano J, Hoofnagle JH. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology. 2010;52(2):730–42.

14. Begaud B, Martin K, Haramburu F, Moore N. Rates of spontaneous reporting of adverse drug reactions in France [letter]. JAMA. 2002;288(13):1588.
15. Goldman SA. Limitations and strengths of spontaneous reports data. Clin Ther. 1998;20 Suppl C:C40–4.
16. Sachs RM, Bortnichak EA. An evaluation of spontaneous adverse drug reaction monitoring systems. Am J Med. 1986; 81(5B):49–55.
17. Brinker A, Beitz J. Use of a spontaneous adverse drug events database for identification of unanticipated drug benefits. Clin Pharmacol Ther. 2002;71(1):99–102.
18. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10(6):483–6.
19. Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass AE, Thompson LJ. The safety of newly approved medicines: do recent market removals mean there is a problem? JAMA. 1999;281(18):1728–34.
20. Moses PL, Schroeder B, Alkhatib O, Ferrentino N, Suppan T, Lidofsky SD. Severe hepatotoxicity associated with bromfenac. Am J Gastroenterol. 1999;94(5):1393–6.
21. Hunter EB, Johnston PE, Tanner G, Pinson CW, Awad JA. Bromfenac (Duract)-associated hepatic failure requiring liver transplantation. Am J Gastroenterol. 1999;94(8):2299–301.
22. Rabkin JM, Smith MJ, Orloff SL, Corless CL, Stenzel P, Olyaei AJ. Fatal fulminant hepatitis associated with bromfenac use. Ann Pharmacother. 1999;33(9):945–7.
23. Fontana RJ, McCashland TM, Benner KG, for the Acute Liver Failure Study Group, et al. Acute liver failure associated with prolonged use of bromfenac leading to liver transplantation. Liver Transpl Surg. 1999;5(6):480–4.
24. McAdams M, Staffa J, Dal Pan G. Estimating the extent of reporting to FDA: a case study of statin-associated rhabdomyolysis. Pharmacoepidemiol Drug Saf. 2008;17(3):229–39.
25. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf. 2007;30(10):891–8.
26. Lumpkin MM. Troglitazone: presentation to advisory committee. Presentation before the Metabolic and Endocrine Advisory Committee; 2000. Slide presentation http://www.fda.gov/ohrms/dockets/ac/00/slides/3615s1a.ppt. Accessed 10 Oct 2012.
27. Murphy EJ, Davern TJ, Shakil AO, for the Acute Liver Failure Study Group, et al. Troglitazone-induced fulminant hepatic failure. Dig Dis Sci. 2000;45(3):549–53.
28. Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. Am J Med. 2003;114(4): 299–306.
29. Floyd JS, Barbehenn E, Lurie P, Wolfe SM. Case series of liver failure associated with rosiglitazone and pioglitazone. Pharmacoepidemiol Drug Saf. 2009;18(12):1238–43.
30. FDA Public Health Advisory. Postmarketing Drug Safety Information: trovafloxacin. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053104.htm. Accessed 10 Oct 2012.
31. Clay KD, Hanson JS, Pope SD, Rissmiller RW, Purdum PP 3rd, Banks PM. Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review. Ann Intern Med. 2006;144(6):415–20.
32. Brinker AD, Wassel RT, Lyndly J, Serrano J, Avigan M, Lee WM, Seeff LB. Telithromycin-associated hepatotoxicity: clinical spectrum and causality assessment of 42 cases. Hepatology. 2009;49(1):250–7.
33. FDA post-marketing safety information on telithromycin [posted February 12, 2007]. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107824.htm. Accessed 8 Oct 2012.
34. Orman ES, Conjeevaram HS, Vuppalanchi R, for the DILIN Research Group, et al. Clinical and histopathologic features of fluoroquinolone-induced liver injury. Clin Gastroenterol Hepatol. 2011;9(6):517–23.
35. Brinker A. Telithromycin-associated hepatotoxicity. Presentation before the Anti-Infective Drugs Advisory Committee in Joint Session with the Drug Safety and Risk Management Advisory Committee, December 14, 2006. Slide presentation: http://www.fda.gov/ohrms/dockets/AC/06/slides/2006-4266s1-01-07-FDA-Brinker.ppt. Accessed 8 Oct 2012.
36. Deshpande G, Gogolak V, Smith SW. Data mining in drug safety: review of published threshold criteria for defining signals of disproportionate reporting. Pharm Med. 2010;24(1):37–43.
37. Hauben M, Madigan D, Gerrits CM, Walsh L, Van Puijenbroek EP. The role of data mining in pharmacovigilance. Expert Opin Drug Saf. 2005;4(5):929–48.
38. McAdams MA, Governale LA, Swartz L, Hammad TA, Dal Pan GJ. Identifying patterns of adverse event reporting for four members of the angiotensin II receptor blockers class of drugs: revisiting the Weber effect. Pharmacoepidemiol Drug Saf. 2008;17(9):882–9.
39. Taubes G. Epidemiology faces its limits. Science. 1995;269 (5221):164–9.
40. Livertox: clinical and research information on drug-induced liver injury. Liver Disease Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Division of Specialized Information Services of the National Library of Medicine (NLM), National Institutes of Health. http://www.livertox.nih.gov/index.html. Accessed 12 Mar 2013.
41. Bjornsson E. Drug-induced liver injury: Hy's rule revisited. Clin Pharmacol Ther. 2006;79:521–8.
42. Senior JR. Drug hepatotoxicity from a regulatory perspective. Clin Liver Dis. 2007;11(3):507–24.
43. Weaver J, Grenade LL, Kwon H, Avigan M. Finding, evaluating, and managing drug-related risks: approaches taken by the US Food and Drug Administration (FDA). Dermatol Ther. 2009;22(3):204–15.
44. Weaver J, Willy M, Avigan M. Informatic tools and approaches in postmarketing pharmacovigilance used by FDA. AAPS J. 2008;10(1):35–41.
45. Begaud B, Moride Y, Tubert-Bitter P, Chaslerie A, Haramburu F. False-positives in spontaneous reporting: should we worry about them? Br J Clin Pharmacol. 1994;38(5):401–4.
46. Suzuki A, Andrade RJ, Bjornsson E, Lucena MI, Lee WM, et al. Drugs associated with hepatotoxicity and their reporting frequency of liver adverse events in VigiBase: unified list based on international collaborative work. Drug Saf. 2010;33(6):503–22.