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A pre-marketing ALT signal predicts post-marketing liver safety

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ABSTRACT

Drug induced liver injury during drug development is evidenced by a higher incidence of serum alanine aminotransferase (ALT) elevations in treated versus placebo populations and termed an "ALT signal". We sought to quantify whether an ALT signal in pre-marketing clinical trials predicted post-marketing hepatotoxicity. Incidence of ALT elevations (ALT $\geqslant$ 3 times upper limits normal [$\times$ ULN]) for drug and placebo of new chemical entities and approved drugs associated with hepatotoxicity was calculated using the Food and Drug Administration (FDA) website. Post-marketing liver safety events were identified using the FDA Adverse Event Reporting System (AERS). The association of FDA AERS signal score (EB05 $\geqslant$ 2) and excess risk of pre-marketing ALT elevation (difference in incidence of ALT $\geqslant 3\times$ ULN in treated versus placebo) was examined. An ALT signal of $\geqslant$ 1.2% was significantly associated with a post-marketing liver safety signal ($p \leqslant 0.013$) and a 71.4% positive predictive value. An absent ALT signal was associated with a high likelihood of post-marketing liver safety; negative predictive value of 89.7%. Daily drug dose information improved the prediction of post-marketing liver safety. A cut-off of 1.2% increase in ALT $\geqslant 3\times$ ULN in treated versus placebo groups provides an easily calculated method for predicting post-marketing liver safety.

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1. Introduction

Drug-induced liver injury is the leading cause of death from acute liver failure in the United States (Ostapowicz et al., 2002). Drug-induced liver injury is also a common adverse drug reaction causing drug withdrawal and failure of new drug approvals by the United States Food and Drug Administration (FDA) (FDA Clinical White Paper; FDA Drug Safety Guidance for Industry). It is therefore critical to identify sensitive measures that signal the potential for drug-induced liver injury during drug development.

Severe hepatocellular drug-induced liver injury which leads to liver failure, death, or need for liver transplantation is typically accompanied by elevations of both transaminases and bilirubin (Bjornsson and Olsson, 2005). This observation was initially described by Hy Zimmerman and the FDA now uses "Hy's Law" in the evaluation of investigational drugs with potential hepatotoxicity during drug development (Bjornsson, 2010). Hy's Law is considered to predict serious safety concerns in the post-marketing phase and its validity has been confirmed in several studies. The large Spanish and Swedish Drug-induced Liver Injury Registry datasets reveal that events accompanied by alanine aminotransferase (ALT) $\geqslant$ 3 times the upper limit of normal (x ULN) and concomitant jaundice were associated with a 9–12% mortality (Andrade et al., 2005; Bjornsson and Olsson, 2005). More recently, similar findings have been reported in the United States (Chalasani et al., 2008). Identification of these rare, severe cases pre-marketing can often be difficult however as very large numbers of treated patients are needed to thoroughly assess risk. Therefore, most clinical trials lack sufficient statistical power to use severe liver injury events for detection of hepatotoxicity (FDA Drug Safety Guidance for Industry; Weil et al., 2008).

Abbreviations: DILI, drug induced liver injury; FDA, Food and Drug Administration; AERS, Adverse Event Reporting System; ALT, alanine aminotransferase; ULN, upper limit of normal; NDA, new drug application; EMA, European Medicines Agency; PDR, Physician's Desk Reference; DPA, disproportionality analysis; MedDRA, Medical Dictionary for Regulatory Activities; MGPS, Multi-Item Gamma Poisson Shrinker; EBGM, Empiric Bayes Geometric Mean; EB05, Empiric Bayes lower 95% confidence interval limit; EB95, Empiric Bayes upper 95% confidence interval limit; IQR, interquartile range.

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While severe hepatotoxicity is rare, mild elevations in serum transaminases can commonly be seen during the pre-marketing phase. These elevations are considered reasonably sensitive markers of hepatocellular injury. Accordingly, elevations of ALT $\geqslant 3\times$ ULN have been more commonly used to assess hepatotoxicity potential in clinical trials. A small number of patients receiving placebo may also experience similar ALT elevations. Therefore, a higher incidence of ALT elevation in active treatment groups compared to placebo indicates potential hepatotoxicity. In clinical trials, nearly all drugs associated with hepatotoxicity have been accompanied by an increased frequency of ALT $\geqslant 3\times$ ULN relative to placebo or control (Hunt et al., 2009; Kaplowitz, 2005). Therefore, incidence of ALT $\geqslant 3\times$ ULN may provide a simple metric to identify a drug's pre-marketing hepatotoxicity signal (FDA Clinical White Paper; Hunt et al., 2009).

The problem arises in these signals are not specific for drug-induced liver injury and are occasionally observed in drugs with a low potential to cause severe liver injury (e.g. statins and heparin), where spontaneous resolution or adaptation are seen (Watkins et al., 2008). A higher incidence of ALT $\geqslant 3\times$ ULN in active treatment groups relative to placebo sensitively identifies compounds associated with hepatotoxicity in development but the absolute increased ALT incidence that signals post-marketing severe liver injury remains in question.

Given the many serious consequences of drug-induced liver injury, it is of utmost importance to patient safety to predict hepatotoxic drugs pre-marketing. Clarification as to whether this can be accurately accomplished via liver chemistry data in clinical trials is of great interest. The aim of this investigation was to quantify whether a specific increased incidence of ALT $\geqslant 3\times$ ULN in active treatment groups over placebo in pre-marketing clinical trials could predict post-marketing liver safety signals reported in the FDA Adverse Event Reporting System (AERS). A secondary aim was to investigate whether hepatic metabolism and daily drug dose added utility in predicting hepatotoxicity relative to the increased incidence of ALT $\geqslant 3\times$ ULN alone (Lammert et al., 2010).

2. Materials and methods

2.1. Identification of study drugs

We conducted a retrospective review of FDA new drug applications (NDA) of new chemical entities using publicly available information from the FDA website (FDA Clinical White Paper; FDA Drug Safety Guidance for Industry) and DailyMed (http://dailymed.nlm.nih.gov/dailymed/). From these sources, we identified all NDA between 2001 and 2006 and collected corresponding pre-marketing liver safety information (graded ALT elevations in treatment and placebo groups), daily drug dose, and hepatic metabolic data from medical and statistical reviews and product labeling. This timeframe was utilized to allow at least 3 years of follow up time from drug approval to public use in order to assure accurate post-marketing liver safety signal detection. Daily drug dose and hepatic metabolism information were recorded from the product label. If daily dose range exceeded 50 mg, dose was identified as greater than 50 mg and hepatic metabolism was considered significant if >50% of the drug was metabolized in the liver (Lammert et al., 2008, 2010). Excluded from our analyses were: intranasal, inhaled, or topical drugs; drugs with systemic absorption <25%; and drugs indicated for use in radiology, dialysis, and nutritional supplements (Fig. 1). We expanded the dataset by including drugs associated with hepatotoxicity approved prior to 2006 with available placebo-controlled clinical trial data from a previously published manuscript (Llanos et al., 2010). Finally, due to the broad range and variable ALT signals of comparator drugs in pre-marketing programs, only drugs studied in randomized, placebo-controlled, Phase II or III clinical trials were included in this study.

2.2. Hepatotoxicity assessment

2.2.1. Pre-marketing

In 2000, the FDA provided liver safety guidance for pre-marketing clinical trials in the FDA Clinical White Paper which suggested the following evaluations to detect hepatotoxicity: graded ($3\times$, $5\times$, $10\times$, $20\times$ ULN) transaminases, an overall increased rate of graded transaminase elevations in treated versus placebo/control groups, and any events of concomitant transaminase $3\times$ ULN and bilirubin $1.5\times$ or $2\times$ ULN. Given this, we recorded the number and percentage of patients with ALT $\geqslant 3\times$ ULN elevation in the active drug and placebo treated groups for each NDA. Excess risk (percentage difference) of ALT $\geqslant 3\times$ ULN elevation was calculated by subtracting the incidence in the placebo group from that of the treatment group. This defined the pre-marketing liver safety signal (''ALT signal'') and was utilized as the primary predictor of post-marketing liver signals. The total number of patients receiving placebo and drug treatment was obtained from the safety population in the initial product label. Information on the drug class and indication, year of registration, dosing, route, length of exposure, and information on cases of concomitant bilirubin $\geqslant 2\times$ ULN, jaundice, associated symptoms, liver failure or death due to drug-induced liver injury was also collected from the FDA medical review (www.fda.gov).

2.2.2. Post-marketing

The FDA Adverse Events Reporting System (FDA AERS), a database of over three million spontaneous adverse event reports, was used to assess liver safety of the study drugs in the post-marketing period through the first-quarter of 2009. Spontaneously reported adverse event data are difficult to assess quantitatively because they are derived from voluntary reports and lack a reliable denominator. Therefore, we employed disproportionality analysis (DPA) to examine the reporting frequency of a drug-adverse event pair relative to background reporting in the entire FDA AERS database. The DPA method employs an empirical Bayes data mining algorithm called MGPS (Multi-Item Gamma Poisson Shrinker) which computes the adjusted relative reporting ratio or Empirical Bayes Geometric Mean (EBGM) with associated lower and upper bounds of the 2-sided 90% confidence limits around EBGM (EB05, EB95) (DuMouchel, 1999; Szarfman et al., 2002). This method identifies signals of higher than expected drug-event combinations. For example, an EBGM value of 5 indicates a drug-event combination reported 5 times as frequently as expected. EB05 $\geqslant 2$ has been used as a threshold for signal detection (indicating a 95% confidence the drug-event combination occurred at least twice the expected rate when considering all other drugs and events in the database). We defined a positive post-marketing liver signal as an EB05 $\geqslant 2$ and the primary post-marketing outcome as a dichotomized variable of EB05 $\geqslant 2$ versus EB05 < 2. As a secondary post-marketing outcome variable, we computed the odds ratio (OR) of the relative reporting frequency of liver events after adjusting for age, gender, and co-reported medications. OR05 was defined as the 95% lower confidence interval for the OR.

For these analyses, we used a custom liver event term, combining a group of 'Preferred Terms' from the Medical Dictionary for Regulatory Activities (MedDRA) coding system indicating hepatocellular and/or cholestatic injury with different severity, from liver enzyme elevations to acute liver failure (Suzuki et al., 2010) (Supplemental Table 1). The values of EBGM, OR, and their corresponding 90% confidence intervals were computed using Empirica™ Signal (Oracle, Health Science Global Business Unit; Waltham, MA, USA).