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ORIGINAL REPORT

A proposed modification to Hy's law and Edish criteria in oncology clinical trials using aggregated historical data

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ABSTRACT

Purpose Identifying drug-induced liver injury is a critical task in drug development and postapproval real-world care. Severe liver injury is identified by the liver chemistry threshold of alanine aminotransferase (ALT) >3× upper limit of normal (ULN) and bilirubin >2× ULN, termed Hy's law by the Food and Drug Administration. These thresholds require discontinuation of the causative drug and are seldom exceeded in most patient populations. However, because maintenance of therapy is critical in the treatment of advanced cancer, customized thresholds may be useful in oncology patient populations, particularly for those with baseline liver chemistries elevations.

Methods Liver chemistry data from 31 aggregated oncology clinical trials were modeled through a truncated robust multivariate outlier detection (TRMOD) method to develop the decision boundary or threshold for examining liver injury in oncology clinical trials.

Results The boundary of TRMOD identified outliers with an ALT limit 5.0× ULN and total bilirubin limit 2.7× ULN. In addition, TRMOD was applied to the aggregated oncology data to examine fold-baseline ALT and total bilirubin, revealing limits of ALT 6.9× baseline and bilirubin 6.5× baseline. Similar ALT and bilirubin threshold limits were observed for oncology patients both with and without liver metastases.

Conclusions These higher liver chemistry thresholds examining fold-ULN and fold-baseline data may be valuable in identifying potential severe liver injury and detecting liver safety signals of clinical concern in oncology clinical trials and postapproval settings while helping to avoid premature discontinuation of curative therapy. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—liver toxicity; multivariate outlier detection; Hy's law; liver chemistry elevation; pharmacoepidemiology

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INTRODUCTION

Drug-induced liver injury (DILI) can severely affect patients. It is a leading cause of compound termination during drug development as well as drug withdrawal after the drug is commercially available.[1,2] Most of the drugs withdrawn for hepatotoxicity have caused death or required transplantation at frequencies less than one per 10 000 patients. At this low frequency, typical drug registration databases of 1000 to 3000 patients generally do not demonstrate any events of severe liver injury. Liver chemistries are rigorously monitored during clinical trials to evaluate the safety of compounds in drug development.[3]

The Food and Drug Administration (FDA) has developed liver safety guidelines for use in clinical trials to identify liver safety signals during development[1]. The FDA recommends Hy's law, which says that given alanine aminotransferase (ALT) >3× upper limit of normal (ULN) and total bilirubin >2× ULN, there is potentially a liver event of serious clinical concern[1]. This threshold was derived from Hy Zimmerman's observations[4–6] and confirmed in large DILI registries.[7,8] FDA researchers have developed a graphical

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tool to easily identify liver safety signals in clinical trial populations called eDISH: Evaluation of Drug Induced Serious Hepatotoxicity.[9,10] Lin *et al.*[11] independently assessed these limits, utilizing the multivariate outlier detection method against aggregated clinical trials data of 18 672 patients and affirmed that Hy's law limits are similar to those derived from generally healthy clinical trial populations.

However, both the distribution and clinical significance of liver chemistry elevations may vary in different patient populations. Hy's law does not take into account these differences and may not be optimized for selected patient populations. Specifically, oncology clinical trial patients may require different thresholds for detecting potential DILI due to elevated pretreatment liver chemistries, especially among patients with liver metastases or liver disease and in those receiving prior or concomitant chemotherapy associated with known hepatotoxicity. Liver chemistry elevations may result in treatment discontinuation and subsequent poor control of serious and life-threatening cancer. Therefore, improved understanding of liver chemistries and thresholds in oncology patients may improve disease management. Aggregated clinical trials data serve empirically to help define customized threshold limits for use in subpopulations rather than the fixed limits suggested by Hy's law for generally healthy patient populations.

METHODS

Data sources

Liver chemistry data from aggregated historical clinical trial data provide a reference distribution and are used to establish the decision boundary or threshold limits for examining liver safety signals in selected therapeutic areas. To establish limits pertinent to identifying potential DILI in oncology clinical trials, data from historical oncology trials were extracted from a GlaxoSmithKline (GSK) aggregated clinical trials database containing study data collected between 1985 and 2005. The data set consisted of 3998 patients identified from 31 phase II and III oncology trials as shown in Table 1. The reference data were chosen based on its size and representativeness of several common cancer types. The aggregated data are denoted as the GSK historical oncology patient data (GSK-HOPD) and is 51% men, with median age of 61 years (range 18–90 years).

Baseline liver chemistry inclusion criteria were used in most of these studies; usually, these criteria required transaminases and bilirubin to be less than or equal to 2× ULN if liver metastases were absent or less than or equal to 5× ULN if liver metastases were present at the time of baseline screening. The aggregated data were further divided to distinguish between patients with liver metastases at trial enrollment (29%) and patients without (71%).

Table 1. Aggregated oncology data sources

Cancer type	Number of trials	Number of patients
Colorectal	6	2091
Breast	5	202
Ovarian	5	493
Lung	10	869
Prostate cancer	1	81
Non-Hodgkin's lymphoma	1	7
Kaposi's sarcoma	1	6
Leukemia	2	249

Differences in the distributions of liver chemistry data between oncology and generally healthy patient populations were evaluated by comparing liver chemistry data from GSK-HOPD with another GSK aggregated data set including 18 672 patients without underlying liver disease originating from 28 phase II–IV trials. These aggregated data are referred to as the GSK generally healthy patient data (GSK-GHPD). Patients from the GSK-GHPD were 92.3% women, with mean age of 44.3 years.[12]

Statistical methods

Establish decision boundaries by truncated robust multivariate outlier detection. To identify potential hepatocellular injury, multivariate outlier detection has been studied extensively[13,14] and applied to detect outliers in multivariate safety measures.[15] Multivariate-outlier detection is based on the Mahalanobis distance,[13] which measures the distance of a subject from the center of the data defined by correlated multivariate variables assumed to be normally distributed. Robust distance is obtained using the robust estimate of mean and covariance in the calculation of the Mahalanobis distance. Robust estimates still have reasonable efficiency even when the majority of data come from a multivariate normal distribution and only a few outliers exist. Subjects with a robust distance greater than a given cutoff are considered outliers. Multivariate outliers will include data points in all directions. However, only abnormally high elevations of liver chemistry measurements indicate a potential liver safety issue. Hence, outliers with abnormally small liver chemistry values are not indicative as potential toxicity cases, and therefore, they would not be considered clinically relevant outliers.

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Truncated robust multivariate outlier detection (TRMOD)[16] was proposed as a robust statistical method for identification of clinically relevant outliers in laboratory safety data while automatically excluding clinically irrelevant outliers (Figure 1a). Decision boundaries can be adjusted statistically by controlling the false detection, or tolerance, probability. A false detection probability of 0.001 means that 99.9% of the patients from an underlying normal distribution are expected to be within the decision boundary or only 0.1% of the patients are expected to fall outside of the decision boundary.

TRMOD was applied to the fold-ULN data from the aggregated oncology clinical trials to obtain a decision boundary for ALT and total bilirubin. Similarly, it is applied to fold-baseline data to obtain a decision boundary based on ALT and total bilirubin change from baseline data that may also be useful for monitoring liver safety data during clinical trials.

Modified eDISH based on decision boundaries from historical data. Based on liver chemistry threshold limits consistent with potential Hy's law cases, FDA researchers developed eDISH for liver safety evaluation by graphically plotting both peak ALT and peak total bilirubin for each patient relative to Hy's law limits (Figure 1b).[9,10] A modified version of eDISH (mDISH) was created updating the decision boundaries with thresholds defined by TRMOD using GSK-HOPD rather than the fixed Hy's law limits. By extending the truncation lines on the TRMOD decision boundary for ALT and total bilirubin (Figure 1a), roughly the same decision boundary was calculated as found in the eDISH tool.

Threshold limits for ALT and bilirubin are obtained using the intercept values of the TRMOD decision boundary with the axes of ALT and bilirubin. Therefore, limits based on decision boundaries for both fold-ULN and fold-baseline data may be used instead of the fixed Hy's law limits. TRMOD limits, like eDISH limits, are used to form three regions: Hy's law (severe toxicity), Gilbert's cholestasis (elevated bilirubin), and Temple's corollary (elevated ALT) similar to regions found in the original eDISH and shown in Figure 1a. The mDISH tool was created for both fold-ULN and fold-baseline data. The 95% confidence intervals for these threshold limits are calculated by bootstrapping methods.

RESULTS

Distribution of baseline liver chemistry data. To illustrate the distribution difference of ALT and total

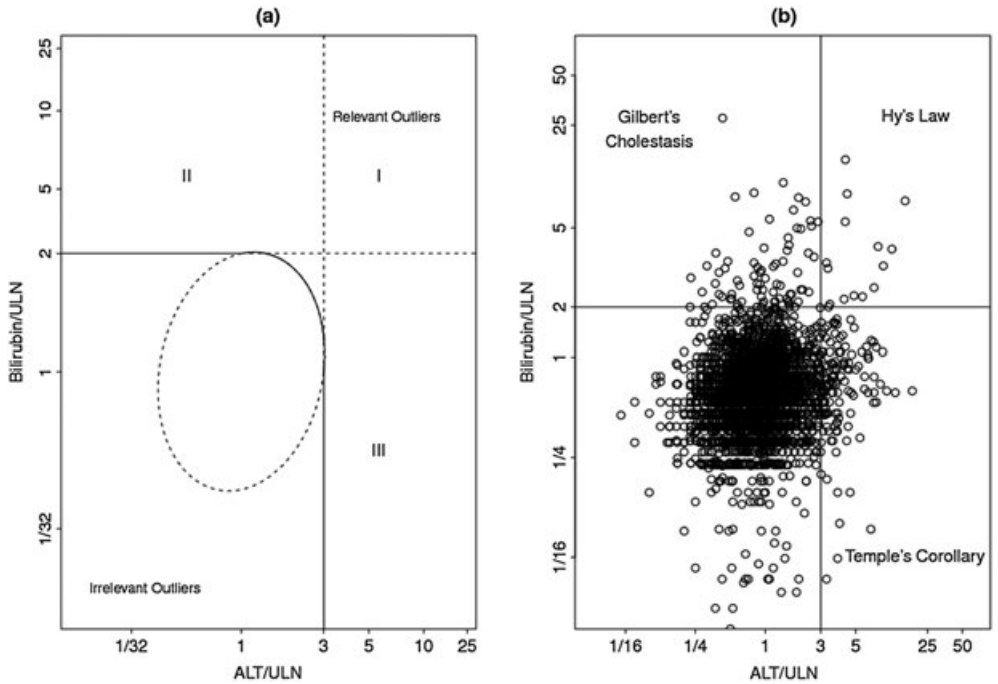

Figure 1. (a) Illustration of TRMOD boundary for two markers. The solid curve is the TRMOD decision boundary, whereas the usual multivariate outlier detection decision boundary is indicated by the dotted eclipse. Regions I–III are formed by the (extended) truncation lines derived from the TRMOD decision boundary. (b) Illustration of eDISH: plot of peak ALT and bilirubin data with the Hy's law limits. Hy's law quadrant: patients with peak ALT >3× ULN and peak bilirubin >2× ULN; Gilbert's cholestasis quadrant: peak bilirubin >2× ULN; Temple's corollary quadrant: patients with peak ALT >3× ULN

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bilirubin, distribution frequencies of each were plotted and compared cancer patients with or without liver metastases at the time of baseline screening in GSK-HOPD with those in GSK-GHPD. Both oncology subsets had a higher percentage of patients with large values of ALT as compared with the liver healthy patient as shown in Figure 2. The percentile plot demonstrates that oncology data have a larger percentile overall than that of the liver healthy data, especially regarding more extreme ALT values, and those with liver metastases possess larger percentiles than do those without liver metastases. Both the histogram and percentile plots indicate that the oncology data demonstrate more extreme values of ALT than do the liver healthy data at baseline, and the oncology data with liver metastases has a slight shift to larger values from the data without liver metastases. This significant shift of distribution of liver chemistry data at baseline suggests that the fixed Hy's law limits might not be suitable in the evaluation of liver safety data and decision making in oncology clinical trials.

Both fold-ULN liver chemistry data and change from baseline liver chemistry data are evaluated for potential elevation. Changes from baseline data are taken into account to note the pretreatment measurements that may reduce the impact of interlaboratory variation and offer greater sensitivity in the identification of safety signals.[11,17] The fold-baseline (defined as a liver chemistry value divided by the corresponding baseline value) values are used to measure the change from baseline liver chemistry data in this study.

Although the populations of GSK-HOPD and GSK-GHPD differ in distributions of age and gender, the results for each were quite similar independent of sex. Previous studies indicate modest associations of ALT with increasing age (Pearson correlation ≤ 0.26) in Asians,[18] and decreasing ALT has been shown among the elderly.[19] By contrast, disease-related liver chemistry differences between the oncology and generally healthy populations were clinically more notable than gender- or age-related influence.

mDISH for oncology patients based on fold-ULN data. To obtain threshold limits of ALT and total bilirubin to be used in mDISH for fold-ULN data for oncology patients, TRMOD decision boundaries were calculated for ALT and bilirubin using GSK-HOPD overall and its subsets. The TRMOD decision boundaries based on the liver metastases subsets with a false detection probability of 0.001 are plotted together with the peak data in Figure 3a–b. Figure 3c plots the TRMOD boundary based on the entire GSK-HOPD data set. The threshold limits calculated are listed in Table 2. The truncation lines of the TRMOD boundary in Figure 3c and Table 2 suggest that the threshold limits of ALT $>5\times$ ULN and total bilirubin $>2.7\times$ ULN may be used in mDISH for oncology patients to define outliers. Separately, threshold limits

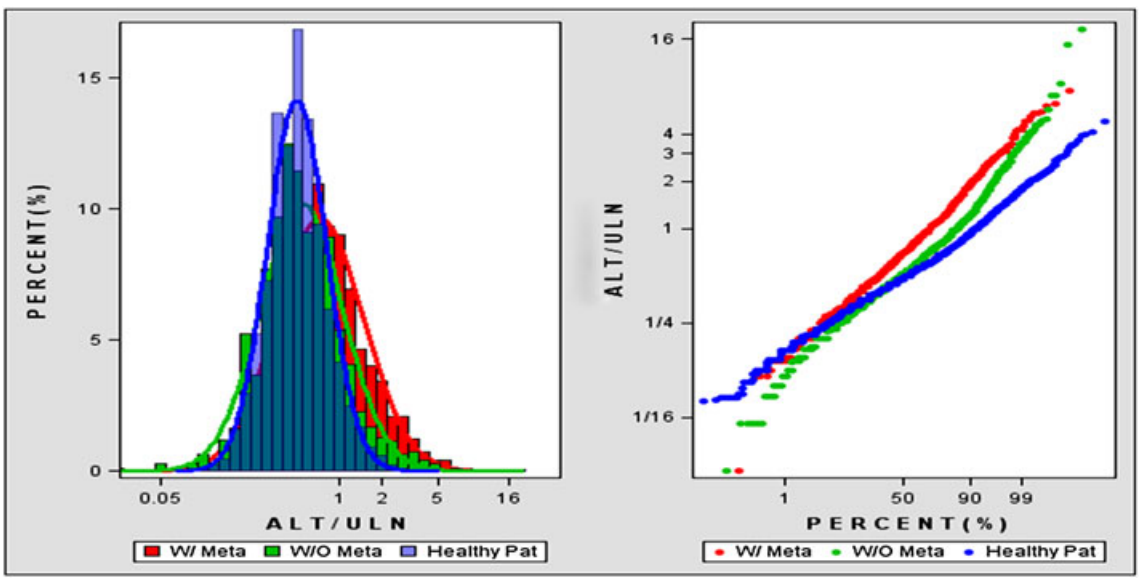

Figure 2. Plot of ALT distributions for GSK oncology historical clinical trial data and generally healthy patient clinical trial data. Left: histograms of fold-ULN ALT at baseline for generally healthy patients (Healthy Pat), oncology data without liver metastases (W/O Meta), and oncology data with liver metastases (W/ Meta); Right: plot of percentile versus cumulative percent (%) of fold-ULN ALT at baseline for each data set

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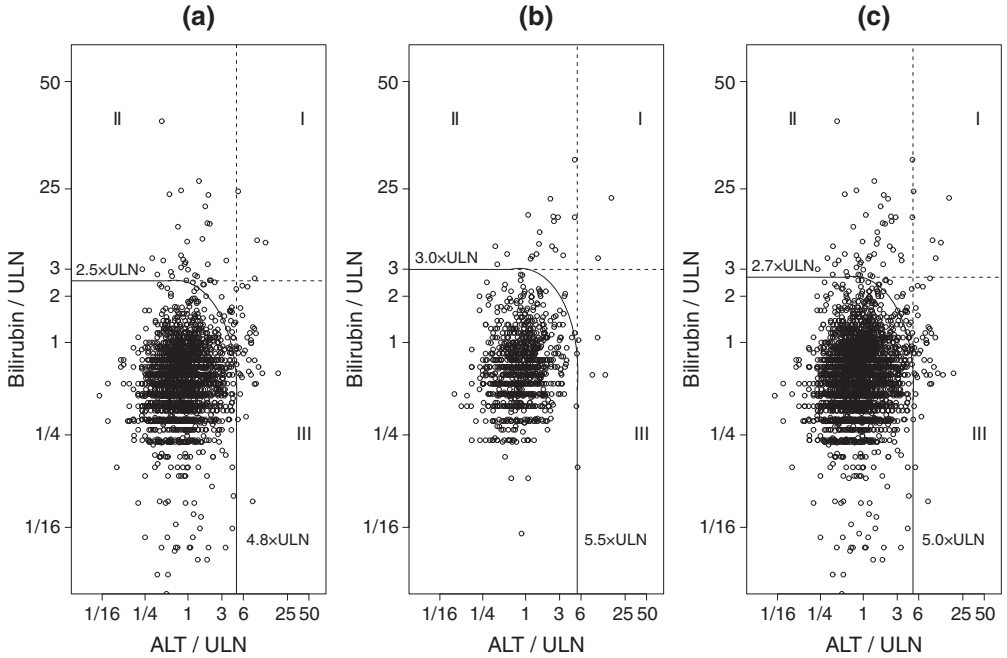

Figure 3. mDISH plots of peak fold-ULN ALT and bilirubin in the two subsets of GSK oncology clinical trial data sets with and without liver metastases, with TRMOD decision boundaries (the false detection probability of 1 in 1000 is used to obtain the TRMOD boundary): (a) data without liver metastases, (b) with liver metastases, and (c) all together

Table 2. Estimate of threshold limits for fold-ULN ALT and bilirubin limit with 95% confidence interval for the GSK oncology historical data (combined) and its two subsets (without and with metastases)

	Without metastases			With metastases			Combined		
Marker	Estimate	95% LL	95% UL	Estimate	95% LL	95% UL	Estimate	95% LL	95% UL
ALT (×ULN)	4.8	4.22	5.63	5.5	4.59	6.09	5.0	4.46	5.72
BILT (×ULN)	2.5	2.25	2.80	3.0	2.65	3.36	2.7	2.48	3.00

LL, lower limit; UL, upper limit.

of ALT >4.8× ULN and total bilirubin >2.5 ULN are calculated for oncology patients without liver metastases and limits of ALT >5.5× ULN and total bilirubin >3.0× ULN for patients with liver metastases.

mDISH for oncology patients based on fold-baseline data. TRMOD was applied to fold-baseline ALT and bilirubin data from GSK-HOPD to calculate decision boundaries based on the two subgroups and are plotted in Figure 4a–b together with both the peak fold-baseline ALT and peak fold-baseline total bilirubin for each individual patient.

Figure 4c plots the TRMOD boundary together with the peak fold-baseline data for the entire GSK-HOPD. Table 3 lists the threshold limits of baseline-adjusted ALT and bilirubin calculated using a false detection probability of 0.001. Based on the truncation lines of the TRMOD boundary in Figure 4 and Table 3, ALT limit of 6.9× baseline and bilirubin limit of 6.5× baseline might be applied in mDISH when examining fold-baseline liver measurements from oncology clinical trials.

Separately, threshold limits of ALT >7.0× baseline and total bilirubin >6.0× baseline may be used for those without liver metastases at baseline, whereas threshold limits of ALT >6.2× baseline and total bilirubin >7.0× baseline may be used for those with liver metastases at baseline.

Employing fold ULN exposes a weakness: Only peak values are considered, whereas any information regarding baseline values is completely

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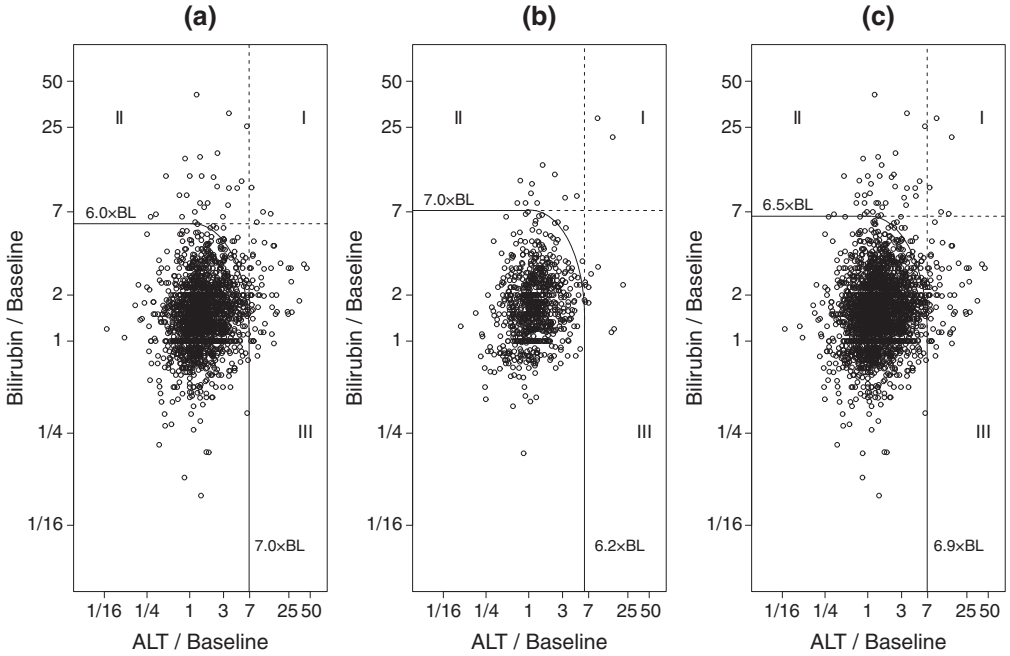

Figure 4. mDISH plots of peak fold-baseline ALT and bilirubin in the two subsets of GSK oncology clinical trial data sets with and without liver metastases, with TRMOD decision boundaries (the false detection probability of 1 in 1000 is used to obtain the TRMOD boundary): (a) patients without liver metastases, (b) patients with liver metastases, and (c) all together

Table 3. Estimate of threshold limits for fold-baseline ALT and bilirubin with 95% confidence interval for baseline-adjusted data

	Without metastases			With metastases			Combined		
Marker	Estimate	95% LL	95% UL	Estimate	95% LL	95% UL	Estimate	95% LL	95% UL
ALT (×baseline)	7.0	6.20	7.85	6.2	5.29	7.13	6.9	6.25	7.51
Bilirubin (×baseline)	6.0	5.34	6.46	7.0	6.29	8.45	6.5	6.00	7.10

LL, lower limit; UL, upper limit.

disregarded.[20] Consideration of baseline values allows drug-induced changes to be directly measured and may also reduce the impact of interlaboratory variation, providing more sensitivity when identifying safety signals.[17]

Examining Hy's law cases with mDISH limits. Hy's law cases were identified during treatment of cancer patients with the HER2/EGFR dual tyrosine kinase inhibitor lapatinib (Tykerb/Tyverb) in a previous study.[21,22] Liver chemistry data of 20 oncology patients with HLA markers meeting the Hy's law threshold in a targeted safety study were examined using mDISH thresholds. Based on pharmacogenetic investigations of lapatinib-associated hepatotoxicity[21,22] and previously reported work implicating HLA-mediated mechanisms in drug-induced liver injury, specified HLA allele association is considered a strong and possibly diagnostic indicator of DILI caused by specific drugs.[23] In the case of lapatinib treatment of breast cancer, a patient who carries at least one copy of the *HLA-DQA**02:01/*DRB1*07:01* alleles is more susceptible to lapatinib-associated liver injury, in comparison with those with homozygous wild-type alleles.

Using mDISH thresholds of ALT >5× ULN and total bilirubin >2.7× ULN in conjunction with the GSK-HOPD data, the patients without the *HLA-DQA**02:01 allele (patients in blue indicated as non-DQA1*02:01/DRB1*07:01 genotype (X_X)) lie within this new threshold, and those patients who exceed this threshold are all specified HLA carriers (Figure 5). The study was also limited by the age and gender differences in the oncology and the generally healthy data sets and the absence of prospective assessment of the mDISH thresholds.

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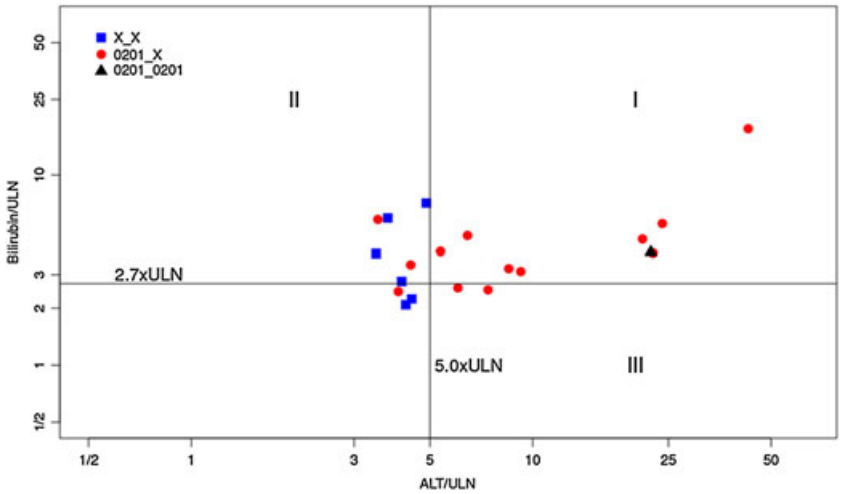

Figure 5. Plot of peak fold-ULN ALT bilirubin of 20 Hy's law events observed in an oncology safety study with the new mDISH limit applied. HLA-DQA*02:01 alleles are associated with lapatinib-related liver injury; heterozygotes are depicted in red circles, and homozygotes are displayed as black triangles. Patients with wild-type HLA alleles appear as blue squares

DISCUSSION

The shift to higher values observed in the distribution of liver chemistry data among patients in GSK-HOPD as compared with the distribution found in GSK-GHPD suggests using higher threshold limits rather than the fixed limit recommended by the FDA (i.e., Hy's law) for select populations such as patients in oncology clinical trials. Threshold limits from patients with and without liver metastases were not found to vary. Application of these thresholds appeared successful in capturing serious DILI cases (adjudicated by hepatologists) with carriage of HLA alleles implicated in lapatinib-associated drug-induced liver injury (however, lapatinib studies were not included in the aggregated oncology data sets). These new limits may be used to modify eDISH to form mDISH to examine both fold-ULN and fold-baseline liver chemistry data in oncology clinical studies. These thresholds are untested in general oncology patients outside of clinical trials where rare events of acute liver failure related to metastatic disease are reported.[24]

The thresholds were as assessed with hepatectomy models and revealed that after more than half of the liver is resected, or in this case, replaced by tumor, bilirubin elevations and evidence of liver functional impairment may be observed.[25] More data are needed to further evaluate and refine these thresholds to assure that key safety outcomes are appropriately captured prior to broad application. Generally, preexisting thresholds work when monitoring liver safety but may require determination on a case-by-case basis, depending on the patient population they are applied to (e.g., oncology, liver disease, or HCV infection). Oncology patients, especially those who exhibit advanced disease, comprise a heavily pretreated population, and baseline liver values may be elevated as a natural byproduct of disease progression.

This evidence-based assessment revealed similar ALT and bilirubin thresholds in oncology patients with and without liver metastases, which may be a result of less severely affected liver metastatic patients being included in the clinical trials. The common practice of varying study inclusion criteria by the presence or absence of liver metastases may be unnecessary and suggests that similar liver chemistry stopping thresholds may also apply. Evidence-based understanding of disease-specific liver chemistry thresholds will improve our ability to sensitively detect safety signals while enabling the continuation of life-saving treatment. Adding additional data will further refine these large, descriptive oncology analyses resulting in enhanced patient safety and optimization for oncology drug development. Moreover, it is noted that these results are hypothesis generating and require follow-up to evaluate the association between revised liver chemistry thresholds and clinically relevant outcomes (e.g., acute liver failure or liver-related death).

Drug-induced liver injury remains a major reason for termination of medicines during development or the withdrawal of clinically important medicines after they are approved.[26] Consequently, new methods are needed to identify liver safety signals and particularly in patient populations exhibiting baseline liver chemistry elevations. These results suggest that current FDA's Hy's law limits should be modified for oncology clinical

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trials to avoid the potential of inappropriate discontinuation of life-saving treatments pending confirmation from larger data sets.

CONFLICT OF INTEREST

All authors of this manuscript are full-time employees of GSK, a pharmaceutical company.

KEY POINTS

- Thresholds for fold-baseline liver chemistry data from the oncology clinical trial data have also been established through the multivariate modeling.
- Multivariate modeling of aggregated historical oncology clinical trial data yielded more extreme thresholds than Hy's law.
- Customized thresholds other than the fixed Hy's law limits may be required in oncology patient populations.

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