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ORIGINAL RESEARCH ARTICLE

Anti-Tuberculosis Drug-Induced Liver Injury in Shanghai: Validation of Hy's Law

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Abstract

Introduction The most reliable liver safety signal in a clinical trial is considered to be 'Hy's Law cases' defined as subjects experiencing hepatocellular injury and serum bilirubin elevations with no more likely cause than study drug. However, there is little published data to support the current biochemical criteria for Hy's Law cases or their use to estimate postmarketing risk of severe liver injury.

Objectives The primary objective of this study was to identify and characterize Hy's Law cases in patients treated for tuberculosis (TB). A secondary objective was to identify patient risk factors for drug-induced liver injuries.

Methods We utilized eDISH (evaluation of Drug-Induced Serious Hepatoxicity) to retrospectively analyze data from 517 patients treated for activeTB, a regimen well known to be capable of causing severe hepatotoxicity.

Results We identified two Hy's Law cases, which is consistent with the treatment's known risk of liver failure. Despite monthly monitoring, neither Hy's Law case experienced a documented elevation in serum alanine aminotransferase exceeding 10 × upper limits of normal. Hepatoprotectant use and infection with chronic hepatitis B were associated with increased risk of liver injury.

Conclusions Our observations support the current biochemical criteria for Hy's Law cases and their use to estimate postmarketing risk.

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1 Introduction

Assessing liver safety of a new drug candidate in clinical trials remains challenging. Of the serum biomarkers routinely employed, alanine aminotransferase (ALT) is the most sensitive to detect liver injury, but serum ALT elevations occur with drugs such as tacrine, heparins, aspirin, and statins that have little or no potential to cause clinically important liver injury [1]. The US FDA guidance document on assessing liver safety in clinical trials [2] states that the most reliable liver safety signal is the elevation in serum total bilirubin (TBil) exceeding 2 times the upper limits of normal (ULN) in the setting of serum ALT elevations exceeding 3 × ULN. These criteria are termed 'Hy's Law' in reference to the late Hyman Zimmerman who first noted that patients with hepatocellular jaundice due to a drug have at least a 10 % chance of developing liver failure [2]. An approximately 10 % incidence of liver failure with hepatocellular jaundice due

to drugs has been confirmed in analyses of large registries of patients who have experienced hepatocellular jaundice due to a drug [3–5].

To facilitate identification of clinical trial subjects meeting Hy's Law biochemical criteria, the FDA typically utilizes a software program called evaluation of Drug-Induced Serious Hepatoxicity (eDISH) [6]. This program graphically displays the peak serum ALT value and the peak serum TBil value for each subject in a clinical trial. All subjects satisfying Hy's Law criteria (ALT $>$ 3 $\times$ ULN and TBil $>$ 2 $\times$ ULN) are then easily identified from the plot and can then be examined in detail to confirm that the injury was hepatocellular and not cholestatic in nature, and that there are no more likely causes for the liver injury than the study drug. If these two additional criteria are satisfied, the subject is considered a 'Hy's Law ase' [2]. The FDA estimates the risk of serious liver injury postmarketing as 10 % of the incidence of Hy's Law cases in a clinical trial [2]. It has been noted that even a single Hy's Law case identified in a liver safety database may result in non-approval for marketing [2]. However, there are few published data that support this 10 % risk extrapolation from clinical trials to the postmarketing setting.

There are also few published data to support the cut off criteria of 3 $\times$ ULN for ALT. In a healthy liver, an acute liver injury must be fairly massive to result in global dysfunction sufficient to cause serum TBil elevations above 2 $\times$ ULN. Such an acute hepatocellular injury would be expected to raise serum ALT levels well above the 3 $\times$ ULN cut-off. For example, patients with acetaminophen liver injuries and who are at risk for liver failure typically experience elevations in serum ALT exceeding 100 $\times$ ULN [7].

Medication treatment of active tuberculosis (TB) is associated with a relatively high incidence of severe and even life-threatening liver injury [8–10]. We retrospectively analyzed liver safety data from Chinese patients who were treated for active TB and who underwent frequent monitoring of liver chemistries. The patient cohort we studied is therefore a model for what might be expected in a clinical trial of a new drug candidate capable of causing severe liver injury. Because published estimates of the incidence of acute liver failure among patients treated for active TB treatment range from 0.01 % [12] to as high as 0.37 % [13], we expected to encounter Hy's Law cases in our cohort. We also expected that the peak serum ALT observed in these cases would greatly exceed 3 $\times$ ULN. A secondary goal of this analysis was to identify patient risk factors for treatment-emergent liver injuries.

2 Methods

This retrospective study was approved by the Ethics Review Committee of the Shanghai Municipal Center for Disease Control and Prevention (SCDC).

2.1 Patient Recruitment and Laboratory Monitoring

The study was conducted in two designated TB hospitals in Shanghai, China. All TB patients, with a total number of 610 diagnosed in the two hospitals during 1 January 2008–31 December 2009, were included in this study. The criteria for TB diagnosis was based on the Chinese national guideline for tuberculosis control [14]. All participants started with a standard anti-TB short-course chemotherapy regimen recommended by the WHO [11], consisting of isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, followed by 4 months of isoniazid and rifampicin [11]. Streptomycin was added to this regimen in re-treatment cases. The regimen could be modified depending on radiological and bacteriological test results and physician's clinical experience. A questionnaire for each patient was used to collect information, including demographics, medical history, co-morbidities, and current use of medication. Serum levels of ALT, alkaline phosphatase (ALP) and TBil were routinely assessed before initiation of anti-TB treatment, and checked twice per month during the first 2 months and once per month during the next 4–6 months after the initiation of anti-TB treatment, or whenever symptoms of hepatitis developed. None of the subjects were known to have HIV infection (this was not routinely tested as this is very rare in the region) and none were being treated for HIV. Serological testing for hepatitis B surface antigen (HBsAg) was not routinely conducted before the initiation of anti-TB treatment, but was conducted for patients who had a history of liver diseases or family contact with people known to carry HBV. Hepatoprotectants are commonly, but not universally, prescribed by Chinese physicians to their patients during treatment for TB with the intention of protecting against drug-induced liver injury (DILI). There was no protocol in effect regarding when to administer hepatoprotectants, and this decision, as well as the choice of hepatoprotectants, was at the discretion of the treating physician. The hepatoprotectants administered were diverse and included traditional Chinese herbal medicines. Patients were excluded if baseline or follow-up liver chemistry test data were missing, which left 517 patients who were enrolled for further study (Fig. 1).

DILI was defined in the current study as the following: for patients with normal baseline liver functions, an increase in serum ALT greater than 3 $\times$ ULN, and/or an

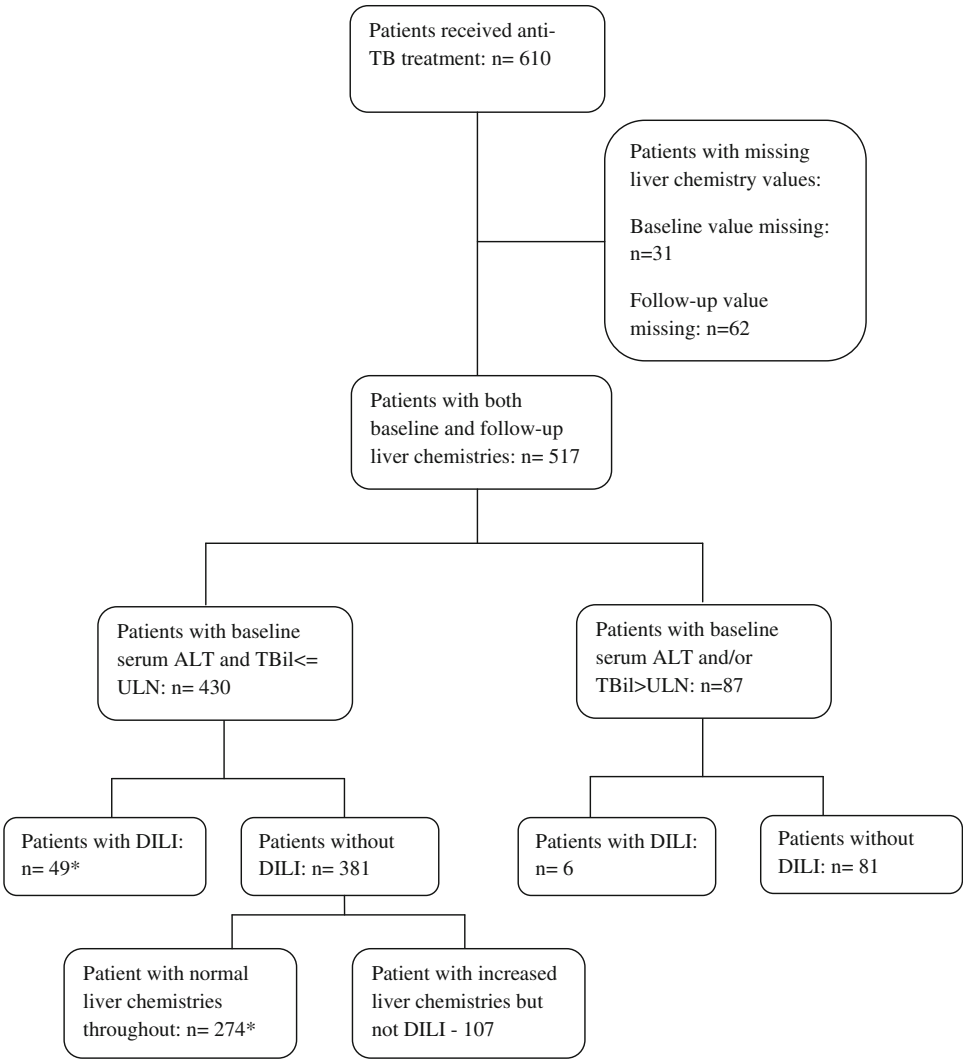

Fig. 1 Subjects entered into the database. For those with normal liver chemistries at baseline, DILI is defined as experiencing a rise in serum ALT >3 × ULN or a rise in serum TBil >2 × ULN. In those patients with abnormal liver chemistries at baseline, liver injury is defined by replacing ULN with the patients' pretreatment (baseline) value. *Those patients used in the risk factor analysis. *ALT* alanine aminotransferase, *DILI* drug-induced liver injury, *TBil* serum total bilirubin, *ULN* upper limits of normal

increase in serum TBil greater than 2 × ULN; for patients with abnormal baseline liver function tests, DILI was defined as an increase in serum ALT greater than three times of the baseline ALT or an increase in serum TBil greater than two times the baseline TBil. The Chinese physicans modify or stop treatment when these criteria for DILI are reached, when lesser biochemical abnormalities occur in patients with symptoms consistent with hepatitis (fatigue, nausea, vomiting and right upper quadrant pain).

2.2 Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) Assessment

eDISH assessment approach was undertaken as previously described [6]. The data were manually manipulated and not loaded into the eDISH program, which is not yet available outside the FDA. The peak serum ALT was plotted along the *x*-axis and the peak serum TBil along the *y*-axis as multiples of (*x*-fold) the ULN on log scale. Each point in the eDISH plot represents the values for a single TB patient. We also plotted each patient stratified by HBsAg status and hepatoprotectant intake to assess the effects of these factors on liver safety assessment.

2.3 Assessment of Potential Hy's Law Cases

Serial liver chemistry values were plotted for each subject satisfying Hy's law criteria (serum ALT exceeding 3 × ULN, and serum TBil exceeding 2 × ULN). The nature of the liver injury was characterized based on using the 'R-value', which is calculated as the ratio of the peak serum ALT value divided by the serum ALP value obtained at that time, with both numerator and denominator expressed as fold ULN. An *R*-value >5.0 denotes a hepatocellular injury, *R* <2.0 denotes a cholestatic injury and *R*-values between 2 and 5 denote a mixed reaction. Each case satisfying Hy's Law biochemical criteria was also examined for likely causes of liver injury other than the TB treatment regimen.

2.4 Statistical Analysis

Baseline characteristics of participants were described as median and interquartile range (IQR) for continuous variables, and percentages for categorical variables. Univariate and multivariable logistic regression analyses were performed to determine the characteristics of the TB patients who were potentially associated with an increased risk of DILI during anti-TB treatment. All independent variables were examined as categorical variables. The following explanatory variables were included in univariate analysis: sex, age group, smoking, drinking, history of liver diseases (including liver cancer, fatty liver, and viral hepatitis A), HBsAg, level of albumin, and prescription of hepatoprotectants. For multivariable analysis, explanatory variables with p-values <0.2 by univariate analysis were included by forward stepwise selection using p-values of 0.05 and 0.1 as cut-off values for entry and removal, respectively. A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using Stata statistical software (version 8.0SE, Stata Corporation, College Station, TX, USA).

3 Results

3.1 Characteristics of Patients

Among the total 610 recruited TB patients, 93 were removed from the cohort due to missing liver chemistry data (Fig. 1). For the remaining 517 patients, 430 had normal liver chemistries and 87 had abnormal liver chemistries prior to TB treatment. All 87 patients with abnormal liver chemistries prior to TB treatment had elevation of baseline serum ALT but normal baseline serum TBil. Characteristics of the 517 patients at baseline were shown in Table 1.

Table 1 Baseline characteristics of the 517 tuberculosis (TB) patients studied

Characteristics	No. of patients	Percentage
Age (years)		
Median (IQR)	43.9 (27–59)	
<65	392	75.8
≥65	125	24.2
Sex		
Male	359	69.4
Female	158	30.6
HBsAg		
Negative	167	32.3
Positive	119	23.0
Unknown	231	44.7
Hepatoprotectants[a]		
No	106	20.5
Yes	395	76.4
Unknown	16	3.9
TB history		
No	420	81.2
Yes	72	13.9
Unknown	25	4.8
Smoking		
No	303	58.6
Yes	187	36.2
Unknown	27	5.2
Habitual drinking[b]		
No	415	80.3
Yes	75	14.5
Unknown	27	5.2

IQR interquartile range, *HBsAg* hepatitis B surface antigen

[a] Hepatoprotectants, both herb products and traditional medicines, were prescribed for patients from the start of anti-TB treatment as a prophylactic measure for hepatotoxity

[b] 'Habitual drinking' includes any kind of alcohol, such as beer, wine, and china spirits

3.2 eDISH Analysis

Following the eDISH analysis approach [6], peak serum ALT and peak serum TBil observed in each of the 517 evaluable subjects were graphed (Fig. 2). The plot was then divided into four quadrants by lines corresponding to a serum ALT value of 3 × ULN and a serum TBil value of 2 × ULN.

Five patients experienced elevations in both ALT >3 × ULN and TBil >2 × ULN, and therefore appeared in the right upper quadrant of the eDISH plot (Fig. 2). The serum bilirubin was fractionated in each case and unconjugated bilirubin comprised at least 50 % of the total in each, excluding Gilbert's syndrome or haemolysis as the cause for the bilirubin rise. To determine whether these subjects fit the criteria for Hy's Law cases [2], the serial liver chemistries for each subject were plotted (Fig. 3). All five patients had baseline liver chemistries within normal limits. None of these five subjects experienced an elevation of serum ALT exceeding 10 × ULN. Four of the potential Hy's Law cases met the criteria for elevation of ALT >3 × ULN and elevation of TBil >2 × ULN on the same calendar day. One patient had a TBil value exceeding 2 × ULN 1 month after the occurrence of ALT >3 × ULN (case 2), and this was also consistent with Hy's Law criteria [2]. The injuries were clearly hepatocellular in two of the patients (case 1 and case 3), with R-values exceeding 5.0, and the injury was largely hepatocellular in two others (cases 4 and 5), with R-values of 4.4 and 4.8, respectively. One subject (case 2) did not have

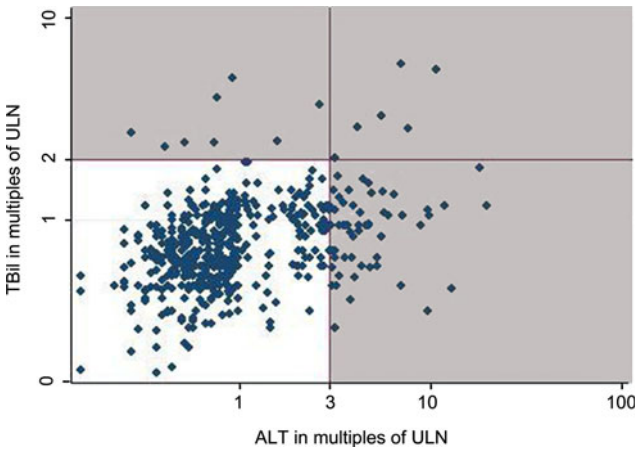

Fig. 2 Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot for each of the 517 patients studied. *Each point in the figure* represents a unique subject's peak serum ALT and peak serum TBil values. Peak serum ALT is shown along the *x*-axis and peak TBil is shown along the *y*-axis as *x*-fold ULN on a log scale. Patients in shadow areas had ALT >3 × ULN and/or TBil >2 × ULN. The arrows indicate the two patients with hepatocellular injury and who were considered to be Hy's Law cases (cases 1 and 3 in Fig. 3). *ALT* alanine aminotransferase, *TBil* serum total bilirubin, *ULN* upper limits of normal

serum ALP values during the ALT elevations so an *R*-value could not be calculated.

Next, the histories and diagnostic evaluations for each of the five patients were scrutinized for alternate causes for the liver injuries. Three of these patients tested positive for HBsAg, but each was known to be a chronic carrier of the virus and each had normal liver chemistries at the start of treatment. It was also noted that the clinical characteristics of the five cases were consistent with the general pattern of treatment-emergent liver chemistry abnormalities among the 44 other subjects with normal baseline liver chemistries, further supporting a causal role for the treatment. Latency was consistent (Fig. 4), and among the 24 cases where serum ALP values were available on the same day as the peak serum ALT was recorded, 21 patients were judged to have hepatocellular injuries, 1 patient a cholestatic injury, and 2 patients had a mixed injury (not shown). None of the five patients were taking concomitant medications suspected to cause DILI. It was concluded that the TB drugs were the most likely cause for the liver injuries observed in all five cases appearing in the right upper quadrant of the eDISH plot. Each of the two cases with hepatocellular injury therefore satisfied the criteria for a 'Hy's Law case'.

All five patients recovered from their liver injuries.

3.3 Risk Factor Analysis

The 430 TB patients with normal baseline liver chemistries were analyzed to investigate risk factors for experiencing DILI (Table 2). Univariate analyses revealed that hepatoprotectant use was significantly associated with increased risk of developing liver injury. Smoking and positive HBsAg status approached but did not meet significance. In a multivariable logistic regression model, use of hepatoprotectants remained a significant risk factor (adjusted odds ratio [OR] 3.0; 95 % CI 1.3–7.2) but positive HBsAg also became significant (adjusted OR 2.8; 95 % CI 1.4–5.4). There was no correlation between taking hepatoprotectants and having positive HBsAg status justifying their use as independent variables in the model. No other variables, including smoking, were significant risk factors in this analysis.

Figure 5 shows the eDISH plot for the 229 patients where status of both HBsAg and hepatoprotectant intake was available.

In an additional analysis, we found that the 87 patients who had abnormal baseline liver chemistries (who were not included in the above analysis) were more likely to take hepatoprotectants than those with normal baseline liver chemistries (OR 3.1; 95 % CI 1.4–6.7; $p = 0.004$).

4 Discussion

In this study, we found a 10.6 % (55/517) cumulative incidence of DILI among treated TB patients who were systematically and frequently monitored with serum liver chemistries. Because the TB treatment regimen employed is associated with a significant risk of life-threatening DILI, we were not surprised to find five cases satisfying the biochemical criteria for Hy's Law currently used by the FDA (i.e. a serum ALT >3 × ULN and a serum TBil elevation >2 × ULN). In each of the five cases, the TB treatment was felt to be the most likely cause for the liver injury. In two of these cases, the injury was confirmed to be hepatocellular, thus satisfying the criteria for Hy's Law cases. In a clinical trial of a new drug candidate, the FDA currently uses the incidence of Hy's Law cases to estimate risk for acute liver failure based on the accepted ~10 % liver failure risk for drug-induced hepatocellular jaundice [2]. Since the total number of patients treated in our cohort was 517, the occurrence of these two Hy's Law cases would therefore support a risk of acute liver failure of approximately 1:2,500 (2/517 × 10 %). This is the middle of the range of liver failure events reported during treatment of active tuberculosis (1:10,000) [12] and 4 in 1,000 [13]. In other words, if our data had been derived from a pre-approval clinical trial of the TB drug regimen, the FDA's estimate of the risk of acute liver failure based on the incidence of Hy's Law cases would approximate the true incidence. Our data therefore support the current FDA approach to estimating liver failure risk.

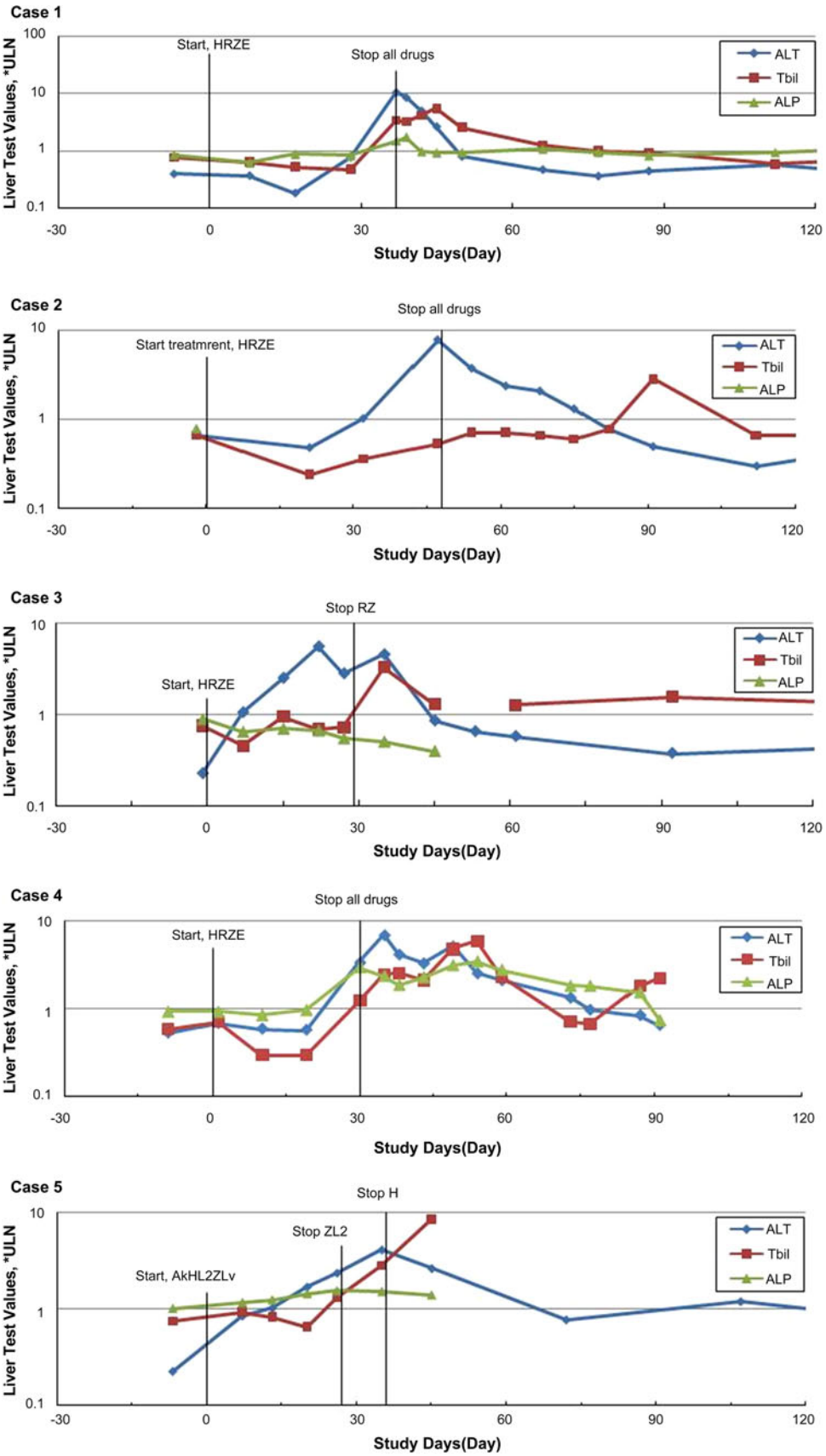

Fig. 3 Serial liver chemistry values in the five potential Hy's Law cases. The *y*-axis represents liver test values as fold of ULN and the *x*-axis represents patient days from the start of treatment. The therapeutic regimen for each patient was shown; cases 1 and 3 were considered Hy's Law cases. ALP levels were not available for case 2 so the nature of the injury could not be determined. *AK* amikacin, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *E* ethambutamol, *H* isoniazid, *HRZE* isoniazid/rifampicin/pyrazinamide/ethambutol, *L2* rifapentine, *Lv* levofloxacin, *TBil* serum total bilirubin, *ULN* upper limits of normal, *Z* pyrazinamide

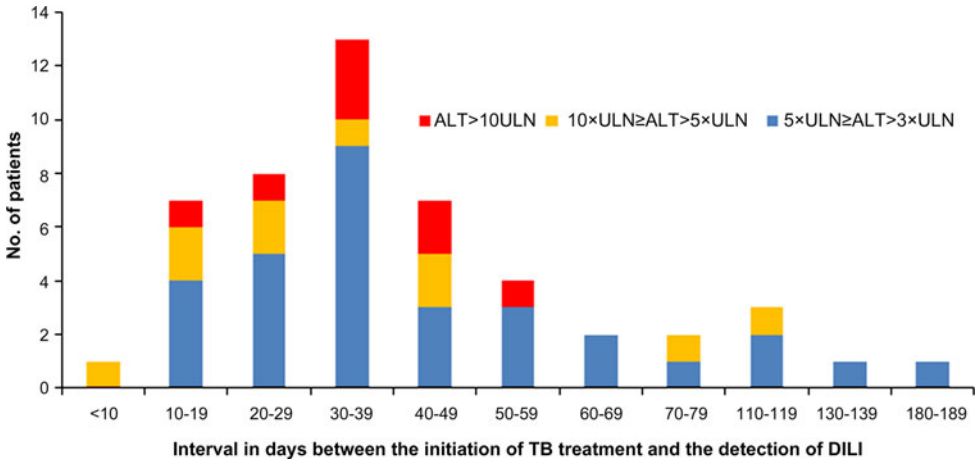

Fig. 4 Interval in days between the initiation of tuberculosis treatment and the detection of serum ALT elevations exceeding 3 × ULN. *ALT* alanine aminotransferase, *ULN* upper limits of normal

Table 2 Results of univariate analysis of the characteristics of patients with normal baseline alanine aminotransferase and total bilirubin who developed drug-induced liver injury during tuberculosis (TB) treatment[a]

Characteristics	Patients with normal liver function ($n = 274$)	Patients with DILI ($n = 49$)	OR (95 % CI)	p-value
Age groups (years)				
<65	202	34	1.0	
≥ 65	72	15	1.2 (0.6–2.5)	0.5287
Sex				
Female	99	14	1.0	
Male	175	35	1.4 (0.7–3.0)	0.3068
Smoking				
No	174	26	1.0	
Yes	86	22	1.7 (0.9–3.3)	
Alcohol				
No	232	39	1.0	
Yes	31	9	1.7 (0.7–4.1)	0.1851
Liver disease history				
Absent	254	44	1.0	
Present	15	5	1.9 (0.5–5.9)	0.2197
Previous TB history				
Absent	213	39	1.0	
Present	48	7	0.8 (0.3–1.9)	0.6048
Hepatoprotectants				
No	77	5	1.0	
Yes	190	42	3.4 (1.3–11.4)	
HBsAg				
Negative	94	16	1.0	
Positive	56	19	2.0 (0.9–4.5)	
Albumin				
<35 g/L	94	14	1.0	
35–55 g/L	100	23	1.5 (0.7–3.4)	0.2356

CI confidence interval, *DILI* drug-induced liver injury, *HBsAg* hepatitis B surface antigen, *OR* odds ratio,

[a] As shown in Fig. 1, the 274 cases chosen as controls had normal (<ULN) liver chemistries throughout treatment

We were surprised that in each of the five cases satisfying Hy's Law biochemical criteria, the peak serum ALT never exceeded 10 × ULN. Although liver chemistry monitoring occurred at least monthly, it is possible that higher levels of serum ALT were missed. Because liver chemistry monitoring more frequent than monthly is unusual in clinical trials involving long-term treatment, our observations can be viewed as supporting the FDA's conservative ALT criteria for Hy's law.

Hepatoprotectant herbs and pharmaceuticals are commonly used by physicians in China, and are often given concomitantly with TB treatment as prophylaxis for liver

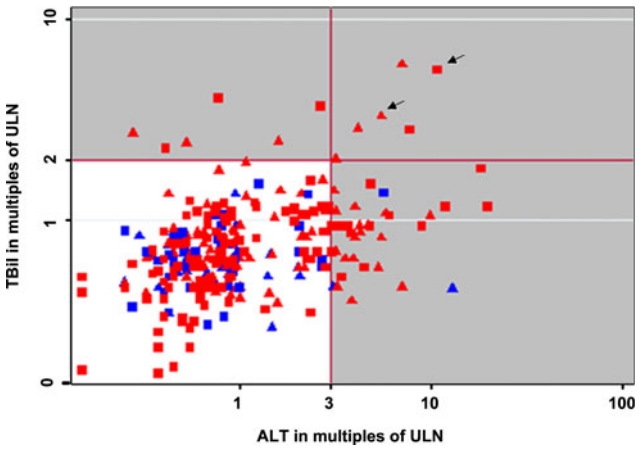

Fig. 5 Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot for the 229 patients where the status of both HBsAg and hepatoprotectant intake was known. *Each point in the figure* represents a unique subject's peak serum ALT and peak serum TBil values. Peak serum ALT is shown along the *x*-axis and peak TBil is shown along the *y*-axis as *x*-fold upper limits of normal on a log scale. Patients with positive HBsAg were plotted with *triangles* ($n = 90$), while patients with negative HBsAg ($n = 139$) were plotted with *squares*. Patients with hepatoprotectant intake are shown in *red* ($n = 163$), while patients without hepatoprotectants intake are shown in *blue* ($n = 66$). The *arrows* indicate the two Hy's law cases. *ALT* alanine aminotransferase, *HBsAg* hepatitis B surface antigen, *TBil* serum total bilirubin, *ULN* upper limits of normal

toxicity. For hepatoprotectants prescribed to TB patients in the current study, 74.9 % were herbal products, of which sedum sarmentosum and baicalin were the two most commonly used, 16.7 % were more traditional medications, including tiopronin and reduced glutathione tablets, diammonium glycyrrhizinate for injection, and ornithine aspartate granules, and 8.4 % were combinations of both herbals and traditional medications. Interestingly, we found that hepatoprotectant intake was associated with increased and not decreased risk of developing DILI among the TB patients. This association did not appear to be related to the presence of pre-existing liver disease, as the association held in patients with normal liver chemistries and those who were HBsAg-negative. We cannot exclude the possibility that the treating physicians were aware of liver issues in specific patients that were not recorded. Whether the hepatoprotectants increase the risk of TB DILI or are simply toxic on their own is unclear from our study. It is interesting that herbal products were recently reported to be the major cause of DILI in China [15].

Previous studies reported that infection with hepatitis B was a risk factor for developing DILI among patients receiving anti-TB treatment, especially in Asia [16–19]. When the effects of hepatoprotectant use were also considered, our study supports this conclusion.

Limitations of our study include the fact that it was retrospective and detailed medical histories were not obtained for all subjects. Chinese physicians also modify or stop treatment when serum ALT exceeds 2 × ULN, and it is possible that higher serum ALT values, and more Hy's Law cases, would have been identified had the stopping criteria been less conservative. Finally, we did not attempt to sub-classify the hepatoprotectants and hence cannot exclude the possibility of benefit from some.

We believe this is the first application of the FDA's current approach to analyzing liver safety in clinical trials to data obtained in a real-world patient care environment. We believe that application of eDISH may be particularly helpful in analyzing the effect of covariates on liver safety, such as was done in Fig. 5, to assess the effects of hepatitis B status and hepatoprotectant intake.

5 Conclusions

Our retrospective analysis of 517 patients treated for active tuberculosis revealed two Hy's Law cases, an incidence that is consistent with the known risk of acute liver failure associated with this treatment regimen. The peak serum ALT recorded in the two Hy's Law cases never exceeded 10 × ULN. Our observations therefore support the FDA's current biochemical criteria for Hy's Law and the use of these events to estimate postmarketing risk of serious liver injury. Because chronic infection with hepatitis B and the use of hepatoprotectants were prevalent among patients and associated with increased DILI risk, and because DILI risk may vary by race and ethnicity, additional studies will be required to test whether our conclusions apply to non-Chinese populations.

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Authorship Xin Shen, Zheng'an Yuan and Jian Mei contributed equally to this work as first author. Paul Watkins and Fan Wu from The Hamner Institutes and the SCDC, respectively, were the two principal investigators and are equally responsible for the content of this manuscript.

Conflict of Interest The authors (Xin Shen, Zheng'an Yuan, Jian Mei, Zurong Zhang, Juntao Guo, Zheyuan Wu, Jie Wu, Haihua Zhang, Jieping Pan, Wenming Huang, Huili Gong, Dong Yuan, Ping Xiao, Yanqin Wang, Yi Shuai, Senlin Lin, Qichao Pan, Tong Zhou, Paul B. Watkins, Fan Wu) have no conflicts of interest that are directly relevant to the content of this study.

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