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Predicting Drug-Induced Liver Injury from Anti-Tuberculous Medications
By Early Monitoring of Liver Tests

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ABSTRACT

Background: Tuberculosis Drug Induced Liver Injury (TB-DILI) is a common and potentially severe complication associated with anti-tuberculous treatment (ATT). Optimal liver test monitoring for standard TB medication has not been established. We describe the predictive value of liver tests (LTs) at pre-treatment and at 2-weeks after initiation of ATT for the detection of TB-DILI.

Methods: Patients initiating ATT were monitored with routine LTs pre-treatment (up to 8 weeks before treatment initiation) and after 2-weeks (1 to 3 weeks after initiation). Logistic regression models were constructed to identify pre-treatment variables associated with 'late' TB-DILI (occurring >2 weeks after treatment initiation) and whether pre-treatment and 2-week alanine aminotransferase (ALT) levels could predict late TB-DILI.

Results: 1247 patients with active tuberculosis managed at 5 sites across north west London between January 2015 and December 2018 were monitored with routine LTs. 103 cases (8.3%) of ATT-associated DILI were diagnosed. 60 cases (58.3%) of TB-DILI occurred later than 2-weeks. The risk of late TB-DILI was 2.2-fold greater for every 30 U/L increment in ALT pre-treatment (OR 2.16, 95% CI 1.38 to 3.29 $p<0.001$) and 2.1-fold greater for every 30 U/L increment in ALT gradient at 2-weeks (OR 2.06, 95% CI 1.52 to 2.76 $p<0.001$).

Conclusion: Routine 2-week LTs capture early TB-DILI and may be valuable in predicting late TB-DILI in patients on ATT.

INTRODUCTION

Drug-induced liver injury (DILI) is the most frequent complication associated with anti-tuberculous therapy (ATT) [1]. TB-DILI incidence ranges from 2-28% of treated active TB cases across a diversity of settings and populations [2-4]. The standard regimen for drug-sensitive TB includes rifampicin, isoniazid and pyrazinamide which are all implicated in TB-DILI as both single agents and when used as components of a multi-drug regimen. Many TB-DILI risk factors have been identified including patient age [5,6,7,8], chronic liver disease [6,7], malnutrition [7], hepatitis B [7], hepatitis C [9], excessive alcohol consumption [2], HIV [7,8,10], extra-pulmonary TB [10], polymorphisms in Cytochrome P450 enzymes (2EI) [11], slow acetylator status [12], certain HLA phenotypes, and Asian ethnicity [9]. Elevated pre-treatment aminotransferases [9] and low pre-treatment albumin [9] have also been reported as independent risk factors for TB-DILI.

Despite these known associations, risk factor-based approaches to predicting the occurrence of TB-DILI in advance of ATT have performed poorly [2,3]. Targeting only risk groups for liver test (LT) monitoring, in line with American Thoracic Society recommendations [2], may therefore be inadequate to minimize harm from TB-DILI. In the absence of reliable *a priori* risk stratification, routine monitoring strategies have been advocated. Optimal timing is yet to be established but investigators have suggested LTs at 2 weeks after ATT initiation corresponding to the median time to TB-DILI [2]. The hypothesis is that early identification of subclinical TB-DILI leading to earlier ATT cessation may, on occasion, prevent acute liver failure. A further advantage would be early detection of mild TB-DILI cases allowing shorter ATT interruption to normalize alanine aminotransaminase (ALT) or bilirubin levels.

Here we assessed the utility of LT monitoring data collected routinely at the time of ATT initiation and at 2-weeks post-initiation in predicting TB-DILI which has become the

standard monitoring practice at the included sites. Data were obtained from patients treated at 5 hospitals in north-west London, UK.

METHODS

Patients and setting

We conducted a multi-centre, retrospective, observational study of adult patients (>18 years) with active tuberculosis diagnosed at Northwick Park Hospital and Central Middlesex Hospital, part of the London North West University Healthcare (LNUWH) NHS Trust and at St. Mary's, Charing Cross and Hammersmith Hospitals in the Imperial College Healthcare (ICH) NHS Trust. Patients who commenced treatment between 1st January 2015 and 31st December 2018 were identified by notification to the Public Health England (PHE) London TB Register.

Data extraction

Patient demographic and clinical data were extracted from hospital electronic medical records including age, sex, ethnicity, site of TB disease, HIV status, hepatitis B/C status.

All LTs recorded from 56 days pre-treatment to completion of treatment were evaluated. Pre-treatment variables for ALT and total bilirubin were established as the closest measurement to initiation but up to 56 days pre-treatment. Individuals who did not have LTs performed within this timeframe or had pre-treatment results meeting biochemical criteria for TB-DILI were excluded from further analysis.

2-week variables for ALT and total bilirubin were established by determining the closest blood test result to 14 days after treatment initiation. Results were only included if they were between 7 and 21 days after initiation. Individuals who did not have LTs performed within this timeframe or already met any criteria for TB-DILI were excluded from further analysis.

In addition, pre-treatment blood test data including C-reactive protein (CRP), haemoglobin, platelet count, albumin, gamma-glutamyl transpeptidase and international normalized ratio (INR) were extracted. Pre-treatment variables were created by determining the closest blood test result to the day of treatment initiation.

TB-DILI Identification

Laboratory results of all TB cases were screened retrospectively to identify patients with a rise in ALT of greater than three multiples of the upper limit of normal (ULN) or a rise in total bilirubin of greater than two multiples of the ULN. The clinical records of the positive screens were then scrutinized to establish a diagnosis of TB-associated DILI (TB-DILI). TB-DILI, in accordance with ATS criteria [2], was defined by an ALT greater than three multiples of the ULN in the presence of typical hepatitis symptoms or an ALT greater than five multiples of the ULN or a rise in total bilirubin greater than two times the ULN regardless of symptoms in the absence of an alternative explanation. Only cases considered at the time to be TB-DILI by the treating clinician were included. The Roussel Uclaf Causality Assessment Method (RUCAM) was performed as an objective assessment of likelihood that the ATT was responsible for the LT abnormalities.

Statistical Analysis

Univariate analyses were performed comparing the pre-treatment characteristics of those who developed TB-DILI to those who did not. Normally distributed continuous variables were

compared using the student t-test and by Wilcoxon rank sum test when not normally distributed. Categorical variables were compared using Fisher's exact test.

For the further analyses blood test data were examined to determine the proportion of missing observations. Missingness was judged to be at random and missing data were therefore imputed using a multivariate imputation with a chained equation method [14]. The proportion of missing observations were as follows: INR (41.5%), haemoglobin (39.8%), total bilirubin at 2-weeks (21.3%), total bilirubin at pre-treatment (9.4%), CRP (8.2%), platelets (7.0%), albumin (7.2%) and alkaline phosphatase (5.9%). Gamma-glutamyl transpeptidase results were 79.7% missing and therefore this variable was excluded. Imputation did not alter the directionality or significance of the main results compared with complete case analysis (see supplementary tables 1 and 2). Pre-treatment variables predicting TB-DILI were assessed using a multivariate logistical regression model (Model 1). Cases where LTs were not recorded before initiation of ATT and where met possible DILI criteria ($ALT \geq 3 \times ULN$ or total bilirubin $\geq 2 \times ULN$) at pre-treatment were excluded (see Fig 1). Initial variables were selected if the p-value was <0.1 in the univariate analyses and a stepwise backward variable selection based on Akaike's information criteria (AIC) was performed to refine the model.

Figure 1. Flow chart demonstrating the number of TB cases including those with TB-DILI used for each stage of the analysis

A further multivariate logistical regression model (Model 2) was constructed using the ALT gradient between pre-treatment and 2-week recordings (normalized to 14 days). Pre-treatment variables, and bilirubin at 2-weeks were also included. The dependent variable was TB-DILI occurring *later* than 2 weeks. Stepwise backward variable selection based on AIC was again performed. Area under the receiver operator curve (AUROC) was calculated.

All analyses were performed using R version 3.6.0 [15]. An alpha of less than 0.05 was pre-defined as significant.

Ethics Statement

Ethical approval was not required since the data were collected retrospectively and did not affect normal clinical practice as such the study is exempt from ethical review and patient consent in the UK [16]

RESULTS

There were a total of 1247 cases of active Tuberculosis and 103 confirmed cases of TB-DILI (8.3%) between January 2015 and December 2018 at all sites (Figure 1). 57 TB-DILI cases (55.4%) were diagnosed by elevation in ALT five times the ULN, 28 (27.2%) by elevation in ALT three times the ULN in conjunction with symptoms of hepatitis, 9 (8.7%) by elevation in total bilirubin and 9 (8.7%) by both ALT and total bilirubin elevations. Of the TB-DILI cases, 43 (41.7%) occurred by the 2-week blood test and 60 (58.3%) occurred after this point. The median number of days from treatment initiation until TB-DILI occurred was 19 (IQR: 8 to 54) (Figure 2).

Figure 2. Histogram showing time from ATT initiation to occurrence of TB-DILI.

Table 1 compares demographic and clinical variables at ATT initiation between individuals who subsequently developed TB-DILI at any point during treatment and those who did not. The median day of measurement for pre-treatment ALT was on the day of ATT initiation (Day 0; IQR: -1 to 0). The median day of measurement for 2-week ALT was 14 days following ATT initiation (Day 14; IQR: 12 to 15). RUCAM scores were 3-5 indicating a

possible adverse drug reaction (ADR) for 25 cases (24.3%), 6-8 indicating a *probable* ADR for 75 (72.8%) and ≥ 9 for 3 (2.9%) indicating a *highly probable* ADR. There were no deaths attributed to TB-DILI and no incidences requiring liver transplantation.

Table 1. Univariate analyses of pre-treatment variables with both datasets combined.

Risk Assessment for TB-DILI

Variables associated with TB-DILI at treatment initiation (Model 1) are shown in Table 2. Associations were found with patient age, pre-treatment INR and platelet count with small effect sizes. For ALT at pre-treatment, after adjusting for confounders, there was 1.4-fold increase in risk of TB-DILI for every 30 U/L increment ($p=0.01$).

Table 2. Odds ratios for variables predicting TB-DILI at treatment initiation

Table 3. Odds ratios for variables predicting TB-DILI at 2-weeks.

At 2 weeks post-treatment initiation, patient age, platelet count and ALT at pre-treatment and the gradient of ALT change were strongly associated with the risk of TB-DILI (Table 3). Model 2 demonstrated that both ALT at pre-treatment and the gradient of ALT change independently represented 2-fold increased risk for late DILI for every 30 U/L increment. There was no significant interaction between the ALT variables ($p=0.11$). The AUROC was 0.70 for model 2 (See supplemental figure 1).

Figure 3. The influence of ALT at pre-treatment and trajectory of change over two weeks on risk of late TB-DILI.

DISCUSSION

This study investigated a role for routine pre-treatment and 2-week LT monitoring to predict DILI in patients on treatment for tuberculosis. Prior to ATT a positive association with TB-DILI was found for pre-treatment ALT after adjustment. These results are in keeping with previous findings for risk factors associated with TB-DILI [8, 9]. Once routine monitoring LTs at 2-weeks were available, the pre-treatment ALT remained significantly associated with later occurring TB-DILI in addition to the ALT gradient over 2-weeks. There was an approximate 2-fold rise in risk of late-occurring TB-DILI for every 30 U/L increment in both initial ALT and the gradient of ALT rise.

Few other studies have addressed ALT kinetics in monitoring TB treatment [16], although a similar method was employed to assess the impact of short-term LT changes in an unselected cohort of general medical admission and was shown to predict 12-month mortality [17]. A notable exception is the investigation by Singanayagam and colleagues reporting outcomes of TB-DILI screening strategies conducted in a similar London population to our study [4].

Comparison was made between the ATS-recommended approach of monitoring only ‘high risk’ patients and routine 2-week monitoring of all patients. The findings highlighted the low sensitivity and specificity of the risk factor approach for identifying TB-DILI both early and late in the treatment course. Pertinent to our study, they also reported that patients with an abnormal 2-week ALT did not have increased rates of late TB-DILI compared to those with normal values. Although contrary to our findings, several differences in their analysis may explain this. Firstly, their study involved fewer patients ($n = 288$) and so had reduced power to detect an effect of a 2-week ALT. Secondly, ALT was treated as a dichotomised variable

with a cutoff (120 U/L) to define an abnormal result. By treating ALT as a continuous variable, our approach maximises the information content and therefore the potential to identify an association. Thirdly, although the Singanayagam study demonstrated a correlation between abnormal pre-treatment ALT and an abnormal 2-week ALT, pre-treatment ALT was not incorporated into a predictive model for late TB-DILI. Thus, the gradient of ALT change, a biologically plausible approach to distinguish resolution of TB liver disease (falling gradient) from incipient TB-DILI (rising gradient), was not investigated.

Complicating the picture, modest elevation in ALT, bilirubin, alkaline phosphatase or gamma-glutamyl transpeptidase early in ATT may be attributable to *hepatic adaptation* [6]. This is a pattern of mild non-progressive liver injury which is of short duration and self-limited even in the presence of continued ATT. This may occur in around a fifth of those exposed to ATT [5] and may even be hepatoprotective [6]. Distinguishing between hepatic adaptation and asymptomatic incipient TB-DILI is not possible with standard LTs. Intensive early monitoring may therefore risk increasing identification of hepatic adaptation which will not progress to meet TB-DILI criteria and may result in unnecessary cessation of treatment. We also note that disseminated TB or TB involvement of the liver complicates assessment of TB-DILI.

There are several important limitations to this study. Many cases were excluded due to an absence of either pre-treatment or 2-week LTs as well as those with possible TB-DILI by LT criteria. Selection bias is therefore possible but seems unlikely since LTs were considered to be standard of care at these sites and the rate of DILI in those excluded for these reasons was similar (9.2%) to the individuals included in the analysis (8.3%). In addition, despite a large initial cohort the reduction of cases at the 2-week point left too few late TB-DILI events to

221 split the data for both a predictive model and a validation cohort. Support for the predictive
222 role of this finding is therefore needed from further studies.

223 **Conclusions**

224 Early LT monitoring may facilitate TB-DILI risk stratification based on the pre-treatment
225 ALT and change in ALT over a 2-week time interval after ATT initiation. Individualised LT
226 testing frequency may therefore be possible with those predicted to be high risk of TB-DILI
227 followed more closely than those at low risk.

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287 **Figures**

288 **Figure 1.** Flow chart demonstrating the number of TB cases including those with TB-DILI used for
 289 each stage of the analysis. (pDILI = possible DILI defined ALT ≥ 3 x ULN or total bilirubin ≥ 2 x
 290 ULN)

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Figure 2. Histogram showing time from ATT initiation to occurrence of TB-DILI.

	DILI	No DILI	p-value
n	103	1144	
Age (mean (SD))	50.53 (19.52)	44.56 (17.67)	0.001
Sex (% Male)	59 (57.3)	657 (57.4)	1.000
Ethnic Group (%)			0.021
South Asian	43 (43.9)	519 (47.1)	
Black	15 (15.3)	215 (19.5)	
Other	14 (14.3)	211 (19.2)	
White	25 (25.5)	147 (13.4)	
East Asian	1 (1.0)	9 (0.8)	
Site of Disease (Pulmonary) (%)	47 (46.1)	487 (42.7)	0.576
Previous TB (%)	3 (3.0)	40 (3.6)	0.995
Drug Sensitivities (%)			0.721
Fully Sensitive	43 (41.7)	496 (43.4)	
Rifampicin Resistant	0 (0.0)	2 (0.2)	
Isoniazid Resistant	3 (2.9)	31 (2.7)	
Multi-Drug Resistant	3 (2.9)	14 (1.2)	
Other Resistance	0 (0.0)	7 (0.6)	
Unknown	54 (52.4)	594 (51.9)	
HIV (% Positive)	6 (6.1)	33 (3.0)	0.187
Hepatitis B (% Positive)	1 (1.2)	22 (2.3)	0.814
Hepatitis C (% Positive)	0 (0.0)	9 (0.9)	0.782
Alanine Aminotransferase U/L	24.50 [15.00, 42.00]	21.00 [15.00, 33.00]	0.029
median [IQR]			
Total Bilirubin U/L	15.16 (18.30)	10.37 (10.63)	<0.001
mean (SD)			
Alkaline Phosphatase U/L	95.00 [65.50, 135.50]	87.00 [71.00, 113.00]	0.171
median [IQR]			
Albumin g/L	33.59 (7.30)	36.66 (7.87)	<0.001
mean (SD)			
Gamma-glutamyl transpeptidase U/L	100.00 [42.50, 325.00]	53.00 [24.00, 127.00]	0.003
median [IQR]			

INR median [IQR]	1.10 [1.00, 1.30]	1.10 [1.00, 1.10]	<0.001
Haemoglobin g/L mean (SD)	116.38 (21.52)	122.21 (19.40)	0.020
Platelet Count 1000/uL mean (SD)	267.05 (112.66)	314.88 (129.19)	<0.001
C-Reactive Protein mg/L median [IQR]	28.45 [4.22, 70.85]	20.20 [4.30, 61.95]	0.357

300

301 **Table 2.** Odds ratios for variables predicting TB-DILI at treatment initiation.

Predictor	Odds Ratio (unadjusted)	95% CI		p-value	Odds Ratio (adjusted)	95% CI		p-value
Age per 10 years	1.19	1.06	1.34	0.003	1.16	1.02	1.31	0.019
INR per 0.1	1.11	1.03	1.19	0.002	1.09	1.01	1.18	0.017
Platelet Count per 10,000 cells/ μ L	0.97	0.95	0.99	0.003	0.97	0.96	0.99	0.009
ALT pre-treatment per 30 U/L	1.40	1.07	1.79	0.008	1.39	1.06	1.78	0.014

302

303 **Supplemental Table 1.** Complete cases analysis for Table 2.

Predictor	Odds Ratio (unadjusted)	95% CI		p-value	Odds Ratio (adjusted)	95% CI		p-value
Age per 10 years	1.24	1.05	1.45	0.008	1.18	0.99	1.40	0.060
INR per 0.1	1.21	1.08	1.37	0.000	1.19	1.07	1.35	0.003
Platelet Count per 10,000 cells/ μ L	0.98	0.95	1.00	0.077	0.98	0.95	1.00	0.094
ALT pre-treatment per 30 U/L	1.45	1.00	2.03	0.033	1.45	1.00	2.06	0.042

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307 **Table 3.** Odds ratios for variables predicting TB-DILI at 2-weeks.

Predictor	Odds Ratio (unadjusted)	95% CI		p-value	Odds Ratio (adjusted)	95% CI		p-value
Age per 10 years	1.19	1.01	1.39	0.033	1.22	1.02	1.44	0.024
Platelet Count per 10,000 cells/ μ L	0.97	0.94	0.99	0.015	0.98	0.95	1.00	0.097
ALT pre-treatment per 30 U/L	1.35	0.90	1.91	0.110	2.09	1.32	3.21	0.001
ALT gradient per 30 U/L	1.67	1.24	2.23	<0.001	2.03	1.50	2.72	<0.001

308

309 **Supplemental Table 2.** Complete cases analysis for Table 3.

Predictor	Odds Ratio (unadjusted)	95% CI		p-value	Odds Ratio (adjusted)	95% CI		p-value
Age per 10 years	1.41	1.10	1.82	0.005	1.47	1.11	1.96	0.007
Platelet Count per 10,000 cells/ μ L	0.97	0.93	1.01	0.136	0.99	0.94	1.02	0.489
ALT pre-treatment per 30 U/L	1.59	0.93	2.54	0.055	2.72	1.41	5.16	0.002
ALT gradient per 30 U/L	1.64	0.94	2.73	0.067	2.11	1.27	3.56	0.004

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313 **Figure 3.** The influence of ALT at pre-treatment and trajectory of change over two weeks on risk of
314 late TB-DILI.

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318 Supplemental Figure 1. ROC curve for the two-week model

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