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Hepatotoxicity during treatment for multidrug-resistant tuberculosis: occurrence, management and outcome

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SUMMARY

SETTING: Multidrug-resistant tuberculosis (MDR-TB) treatment program in Tomsk, Russia.

OBJECTIVE: To describe the incidence and management of hepatotoxicity during treatment of MDR-TB, and to assess risk factors associated with its development and impact on treatment outcomes.

DESIGN: A retrospective case series performed among 608 patients.

RESULTS: Hepatotoxicity, using American Thoracic Society (2006) definitions, was observed in 91/568 patients (16.5%). The median time to the first hepatotoxic event was 196 days post treatment commencement. Baseline factors associated with hepatotoxicity included elevated alanine aminotransferase/aspartate aminotransferase/bilirubin (OR 53.9, 95%CI 6.30–438.7), and renal insufficiency (OR 19.6, 95%CI 2.71–141.6). High treatment adherence (OR 3.25, 95%CI 2.07–5.09) and starting treatment in prison (OR 1.77, 95%CI 1.04–3.01) were associated with treatment success. Smoking (OR 0.44, 95%CI 0.21–0.92) and bilateral cavitary disease (OR 0.51, 95%CI 0.34–0.77) were associated with worse outcomes. For alcohol users, developing hepatotoxicity was associated with better outcomes (OR 4.40, 95%CI 1.79–10.81) than not (OR 0.42, 95%CI 0.25–0.68). One or more medications were permanently stopped in 10/91 patients, but in no case was treatment entirely discontinued.

CONCLUSION: MDR-TB treatment in the face of hepatotoxicity during therapy did not result in a statistically significant increase in poor outcomes.

KEY WORDS: hepatitis; hepatotoxicity; drug-resistant tuberculosis; MDR-TB; Tomsk; Russia

TUBERCULOSIS (TB) is one of the leading infectious causes of adult deaths globally, accounting for an estimated 1.7 million deaths each year. Multidrug-resistant tuberculosis (MDR-TB), defined as strains of TB with in vitro resistance to isoniazid (INH) and rifampin (RMP), is a form of the disease that has rising morbidity and mortality. The treatment of MDR-TB is more complex than for pan-susceptible disease, requiring multiple second-line anti-tuberculosis agents given over a period of 18–24 months.[1] One of the main concerns about MDR-TB regimens is their potential for causing adverse effects, particularly in vulnerable populations.[2–5] The development of hepatotoxicity—including hepatitis (hepatocellular necrosis), cholestasis (impairment of bile flow), and zonal necrosis—is one of the most commonly reported adverse effects associated with first- and second-line anti-tuberculosis treatment.[6,7] Rates of hepatotoxicity of between 1% and 80%—with varying definitions used to define the condition—have been reported in patients undergoing treatment for TB and MDR-TB.[8–11] In the case of anti-tuberculosis treatment, a number of first- and second-line anti-tuberculosis drugs have been implicated as potential causative agents of drug-induced liver injury (DILI; Table 1). Patient responses to DILI can be idiosyncratic, and can range from simple adaptation with no further negative effect to fulminant hepatitis and death.[27]

The use of alcohol is often considered to be a major predisposing risk factor for the development of hepatitis among patients on anti-tuberculosis treatment,[28–30] as is co-infection with the human immunodeficiency virus (HIV) or viral hepatitides.[31–36] This is of particular concern in the setting of the former Soviet Union, where rates of alcoholism and injecting drug use are high.[37–39] In the present study, we describe the incidence and management of hepatotoxic events during MDR-TB treatment in a cohort of patients in Tomsk, Russia, and assess risk factors associated with the occurrence of this adverse event. We also explore

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Table 1 Anti-tuberculosis drugs that present a risk for hepatotoxicity

Medication	Rate of hepatotoxicity %	Comments
INH*	5–10[12]	Reported to be fatal in some cases[13]
PZA	2–30[14]	Hepatotoxicity is the most common adverse event of this agent, and is dose-related[15]
EMB	Rare[16]	
Aminoglycosides and capreomycin	Rare[17]	
Fluoroquinolones	2–41[18,19]	Numerous case reports in the literature[20]
Ethionamide/ prothionamide	5–37[21]	More common when given in combination with other agents[22]
Para-aminosalicylic acid	0.3[23]	
Cycloserine	Rare[6]	
Amoxicillin-clavulanate	Up to 23[24]	Numerous case reports in the literature[25,26]

*INH is sometimes used in high doses to treat MDR-TB. PZA and EMB are often included in MDR-TB treatment regimens.
INH = isoniazid; PZA = pyrazinamide; EMB = ethambutol; MDR-TB = multidrug-resistant tuberculosis.

whether the development of hepatotoxicity after the commencement of treatment was associated with poor treatment outcome.

METHODS

Setting

Tomsk Oblast (population in 2006: 1 036 000) is located in western Siberia, in the Russian Federation. Between 1993 and 2000, the tuberculosis notification rate in Tomsk increased from 80.6 per 100 000 population to 116.7, an estimated 15–20% of which were MDR-TB (Tomsk Oblast Tuberculosis Services, unpublished data). In the face of this growing epidemic,[40,41] in 2000 Tomsk Oblast expanded its TB program to include the treatment of MDR-TB.*

Study design

This was a retrospective case series of 608 patients with confirmed MDR-TB at baseline enrolled for MDR-TB treatment between 10 September 2000 and 1 November 2004. Patients were included if they had active TB evidenced by positive culture and drug susceptibility testing (DST) results showing MDR-TB.† There were no exclusion criteria. Treatment regimens were designed using a standard algorithm.[1,42,43] Patients received quality-assured second-line anti-tuberculosis drugs procured through the Green Light Committee.[44] Patient management and treatment outcomes of this cohort have been reported elsewhere.[45] Laboratory data, including serum potassium, liver function tests, creatinine, and thyroid stimulating hormone, were monitored at least monthly. Physicians reported adverse reactions and management—according to protocols disseminated in training courses—using a real-time reporting form.[43] Patient charts were reviewed retrospectively. Laboratory data were electronically imported into the study database.

All patients initiating TB treatment in Tomsk are routinely tested for HIV infection. Alcohol use and illicit drug use were considered to be present if documented by the treating physician in the patient chart. Baseline alcohol use was defined as a recording of a diagnosis of 'alcoholism' at intake by a physician or mental health provider. Use during treatment was defined as recording of patient intoxication in the chart. 'Hepatoxicity' was defined as per the 2006 American Thoracic Society guidelines: documented elevations of either transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and/or bilirubin above five times the upper limit of normal (ULN) at any point after commencing treatment, or three times the ULN with either recorded clinical symptoms or a change of more than twice the baseline levels.[27,46] 'Baseline hepatitis' was defined as laboratory results showing signs of hepatotoxicity within 60 days prior to treatment commencement and/or a clinical diagnosis from the admitting physician. Tests for hepatitis B and hepatitis C were performed among the majority of patients in the second patient cohort.‡ Other comorbid conditions, such as chronic renal insufficiency, diabetes mellitus, and seizure disorder, were considered to be present if documented in the patient chart by a physician. Low body mass index (BMI) was defined as <18.5 kg/m^2 for women and <20 for men.[47] Non-adherence to treatment was defined as missing more than 20% of the prescribed doses (a dose was defined as any single administration of all prescribed medications) during the entire treatment period. Treatment outcomes were defined according to international consensus definitions.[48] 'Good' outcomes were defined as cure or treatment completion. 'Poor' treatment outcomes were defined as default, failure, or death from any cause during MDR-TB treatment.

Continuous data were assessed for normality using a skewness-kurtosis test. Univariable and multivariable logistic regression were conducted to assess factors associated with good treatment outcomes. A final model was determined using likelihood ratio testing. Variables included in the multivariable analysis were assessed for interaction and effect modification. Base-

*This was a joint program of the Tomsk Oblast Tuberculosis Services, the Federal Penitentiary Service of the Ministry of Justice, and the international non-profit Partners In Health, and included treatment of MDR-TB in the prison and civilian sectors.

†An additional 28 patients were enrolled in the treatment program with suspected MDR-TB based on a history of treatment failure without DST-confirmed MDR-TB; they are not included in this analysis.

‡We were unable to collect these data for the first 241 patients treated in the program due to the collection instrument used at the time.

line drug regimens were assessed using the first regimen assigned to each patient within the study time frame. Drug regimens at the time of the first episode of hepatotoxicity were assessed using the closest documented regimen on or prior to the laboratory date. If no regimen was listed prior to the laboratory date, the baseline regimen was assumed to be the regimen the patient was on at the time of elevated transaminases/bilirubin.

RESULTS

Laboratory data were unavailable for 40 patients, who were not included in the analysis. These 40 patients were not significantly different from the remaining cohort with respect to treatment outcomes (data not shown). The analysis was performed among the remaining 568 individuals. Properties and characteristics of the cohort as a whole and those developing hepatotoxicity during treatment vs. those who did not are presented in Table 2. This was a young, predominantly male (82%) population, with very low rates of HIV co-infection (0.7%); 28% of the cohort started treatment within the prison system. As could be expected, this cohort consisted of very ill people: 60% had both bilateral and cavitary disease, and 43% had low BMI at baseline. Only 13 people (2.3%) in the cohort had baseline hepatitis. Ninety-one patients (16.5%) developed hepatotoxicity during treatment.

Table 2 Selected clinical and treatment characteristics of patient cohort and associations with development of elevated transaminases/bilirubin during treatment (n = 568)

Characteristic	All patients (n = 568) n (%)	Individuals without elevated transaminases during treatment (n = 477) n (%)	Individuals with elevated transaminases (3× ULN) during treatment (n = 91) n (%)	P value*
Male sex	467 (82)	384 (82.2)	83 (91.2)	0.02
Age, years, median [range]	34 [17–71]	34 [17–71]	32 [19–65]	0.36
Married at baseline	235 (42.5)	198 (42.6)	37 (42.0)	0.92
Prison sector (at start of treatment)	161 (28)	122 (25.6)	39 (42.8)	0.001
Number of years with TB, mean [range]	4.6 [0.5–36.4]	4.5 [0.1–21.6]	4.7 [0.1–36.4]	0.94
Number of drugs to which patients were resistant, median [IQR]	4 [3–6]	5 [4–6]	4 [3–7]	0.29
Low baseline BMI (<18.5 kg/m^2 if female, <20 if male; n = 567)	246 (43.4)	203 (42.6)	43 (47.2)	0.42
Homeless at treatment start	23 (4)	18 (3.7)	5 (5.5)	0.39
Baseline comorbid conditions†	166 (29.2)	143 (30.0)	23 (25.3)	0.37
HIV-positive	4 (0.7)	4 (0.8)	0	
Renal insufficiency	5 (0.9)	2 (0.4)	3 (3.3)	0.03
Respiratory insufficiency	306 (54.4)	272 (57.7)	34 (37.4)	0.001
Diabetes mellitus	24 (4.2)	21 (4.4)	3 (3.3)	0.78
Baseline cerebrovascular disease	50 (8.8)	44 (9.3)	6 (6.6)	0.41
Seizure disorder	21 (3.7)	18 (3.8)	3 (3.3)	0.85
Psychiatric disorder	29 (5.4)	26 (5.5)	3 (3.3)	0.60
Gastritis/ulcer	67 (11.7)	58 (12.2)	9 (10.0)	0.53
Elevated transaminases at baseline (laboratory value 3× normal AST/ALT/bilirubin)‡	13 (2.2)	1 (0.2)	12 (13.2)	0.00
Substance use				
Baseline injecting drug use	79 (15.4)	64 (14.9)	15 (18.0)	0.49
Baseline alcohol use	204 (35.9)	178 (37.3)	26 (28.6)	0.11
Baseline positive smoking history	496 (87.6)	411 (86.5)	85 (93.4)	0.06
Extent of disease				
Cavitary disease	502 (89.7)	424 (89.6)	78 (86.7)	0.41
Bilateral and cavitary disease	342 (60.2)	291 (61.0)	51 (56.0)	0.38
History of prior TB treatment default	21 (3.7)	17 (3.5)	4 (4.4)	0.76
Number of previous treatment regimens, median [IQR]	2 [1–3]	2 [1–3]	2 [1–3]	0.53
Average number of drugs at start of treatment [range]	5.8 [3–8]	5.8 [4–8]	5.8 [3–7]	0.98
Adherent (took at least 80% of doses)	437 (76)	368 (77.2)	69 (75.8)	0.78
Treatment outcome				
Cured/completed	372 (65.5)	302 (63.3)	70 (76.9)	0.01
Defaulted	112 (19.7)	100 (21.0)	12 (13.2)	0.08
Died	29 (5.1)	26 (5.4)	3 (3.3)	0.39
Failed treatment	55 (9.7)	49 (10.3)	7 (6.6)	0.33

*Pearson's χ^2, Fisher's exact, t-test or Wilcoxon rank-sum as appropriate.
†Any of the following: diabetes mellitus, renal insufficiency, cardiovascular disorder, seizure diagnosis, gastritis/ulcer, psychiatric disorder.
‡Most recent laboratory value within 60 days prior to treatment start.
ULN = upper limit of normal; TB = tuberculosis; IQR = interquartile range; BMI = body mass index; HIV = human immunodeficiency virus; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 3 Laboratory AST, ALT and bilirubin values at time of first hepatotoxic event (n = 91)*

	Mean mmol/l	Median mmol/l	Minimum mmol/l	Maximum mmol/l
AST value at first hepatotoxicity	2.19	1.92	0.08	9.42
ALT value at first hepatotoxicity	2.34	2.18	0.08	10.8
Bilirubin at first hepatotoxicity	23.4	11.7	4	250.8
Time to first abnormal value, days (SD)	231 (184)	196	0	651

*AST normal values 0.45–0.68 mmol/l; ALT normal values 0.45–0.68 mmol/l; bilirubin normal values 7.5–20.5 mmol/l.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; SD = standard deviation.

Mean and median AST, ALT and bilirubin values at the time of elevated transaminases for those patients are presented in Table 3. The median time to first hepatotoxic event was approximately 6 months after the start date (196 days, interquartile range 68–370; Table 3, Figure). Baseline factors associated with the development of hepatotoxicity in multivariable logistic regression included documentation of elevated transaminases at baseline (odds ratio [OR] 53.9, 95% confidence interval [CI] 6.30–438.68), and renal insufficiency (OR 19.6, 95%CI 2.71–141.58), although the numbers were small (n = 13 and n = 5, respectively) and the CIs were wide (Table 4).

We also looked at the subset of individuals who had been tested for viral hepatitis. Of 327 patients, 281 (85.9%) were tested for hepatitis B or C, or both. Of these, 21 (7.5%) tested positive for hepatitis B, 43 (15.3%) were positive for hepatitis C, and 13 (4.6%) were positive for both. Among all patients tested for hepatitis, 48 (17.4%) developed hepatotoxicity during MDR-TB treatment. Baseline diagnosis of hepatitis C showed a trend towards association with the development of hepatoxicity, with borderline statistical significance (OR 2.19, 95%CI 0.99–4.98).

Univariable analysis of the full cohort (Table 5) found that good treatment outcome was associated

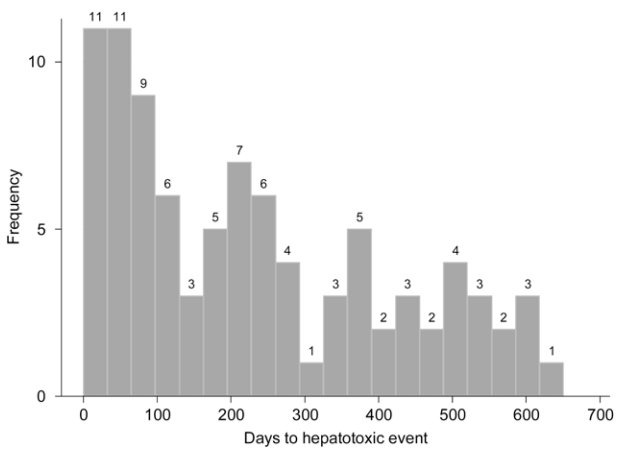

Figure Time to first hepatotoxic event (n = 91).

Table 4 Multivariable analysis of baseline factors associated with the development of elevated transaminases during multidrug-resistant tuberculosis treatment, Tomsk, Russian Federation (n = 568)

	OR for developing hepatotoxicity	95%CI	*P* value
Alcohol use at baseline (per physician diagnosis)	0.73	0.42–1.27	0.27
Prison sector (at start of treatment)	1.23	0.67–2.26	0.49
Male sex	0.55	0.23–1.30	0.17
Positive smoking history at baseline	2.37	0.87–6.43	0.09
Renal insufficiency at baseline	19.60	2.71–141.58	<0.01
Elevated transaminases at baseline	53.95	6.3–438.68	<0.01
Respiratory insufficiency at baseline	0.63	0.36–1.11	0.11

OR = odds ratio; CI = confidence interval.

Table 5 Results of the univariable logistic regression models predicting positive multidrug-resistant TB treatment outcomes (n = 568)

	Cure or treatment completion OR (95%CI)	*P* value
Hepatoxicity during treatment		
Yes		
No	1.93 (1.14–3.25)	0.01
Alcohol use during treatment		
Yes		
No	0.27 (0.19–0.39)	0.00
Prison sector (at start of treatment)		
Yes		
No	2.24 (1.48–3.43)	0.00
Adherent to >80% of doses overall		
Yes		
No	3.50 (2.33–5.24)	0.00
Sex		
Male		
Female	1.10 (0.69–1.74)	0.67
History of default from anti–tuberculosis treatment*		
Yes		
No	0.31 (0.13–0.76)	0.01
Smoker at baseline		
Yes		
No	0.30 (0.15–0.59)	0.00
Cavitary and bilateral disease		
Yes		
No	0.40 (0.27–0.58)	0.00
Low BMI at baseline		
Yes		
No	0.88 (0.62–1.24)	0.48
Respiratory insufficiency at baseline*		
Yes		
No	0.42 (0.30–0.61)	0.00
Seizure diagnosis at baseline*		
Yes		
No	0.46 (0.19–1.11)	0.08

*Included in preliminary main effects model but dropped before final model.
TB = tuberculosis; OR = odds ratio; CI = confidence interval; BMI = body mass index.

Table 6 Results of the multivariable logistic regression model predicting positive multidrug-resistant tuberculosis treatment outcomes (n = 568)

	Cure or treatment completion OR (95%CI)
Prison sector (at start of treatment)	1.77 (1.04–3.01)
Adherent to >80% of doses overall	3.25 (2.07–5.09)
Smoker at baseline	0.44 (0.21–0.92)
Cavitary and bilateral disease	0.51 (0.34–0.77)

OR = odds ratio; CI = confidence interval.

Table 7 Interaction between alcohol and hepatotoxicity among people who drank alcohol during treatment (n = 271)

	Cure or completion among people who drank alcohol	
	Unadjusted OR	Adjusted OR*
No hepatotoxicity	0.23 (0.15–0.35)	0.42 (0.25–0.68)
Hepatotoxicity	3.34 (1.44–7.74)	4.40 (1.79–10.81)

*Adjusted for adherence levels, prison sector start, bilateral and cavitary disease at baseline and smoking status at baseline.
OR = odds ratio.

with a diagnosis of hepatotoxicity (OR 1.93, 95%CI 1.14–3.25), starting treatment in prison (OR 2.24, 95%CI 1.48–3.43), and adherence to anti-tuberculosis treatment (OR 3.5, 95%CI 2.33–5.24). Worse outcomes were associated with alcohol use (OR 0.27, 95%CI 0.19–0.39), smoking at baseline (OR 0.3, 95%CI 0.15–0.59), a diagnosis of respiratory insufficiency (OR 0.42, 95%CI 0.30–0.61) or seizure disorder at baseline (OR 0.46, 95%CI 0.19–1.11), and a prior history of non-adherence to treatment (OR 0.31, 95%CI 0.13–0.76).

In the multivariable model (Table 6), treatment adherence (OR 3.25, 95%CI 2.07–5.09), and starting treatment in the prison system (OR 1.77, 95%CI 1.04–3.04) were associated with good outcomes. Baseline smoking (OR 0.44, 95%CI 0.21–0.92) and bilateral cavitary disease (OR 0.51, 95%CI 0.34–0.77) were both associated with worse outcomes. An interaction existed between hepatotoxicity and alcohol use during treatment: compared to patients who did not use alcohol or develop hepatotoxicity during treatment, alcohol use was associated with worse outcomes (OR 0.42, 95%CI 0.25–0.68) in patients who did not develop hepatotoxicity. However, among those with a hepatotoxic event, alcohol use did not influence treatment outcome (OR 1.83, 95%CI 0.69–4.82; Table 7).* Information was available for treatment regimen just prior to first recorded elevated transaminases/bilirubin for 85/91 patients (Table 6). Of these 91 patients, 31 (34%) had an unanticipated change made to their regimens within 45 days after the date of detection of elevated liver enzymes. Ten patients had one or more drugs permanently dropped from the regimen specifically because of hepatitis or elevated transaminases; in none of these cases was treatment entirely discontinued due to hepatotoxicity (Table 8). The drugs most often stopped permanently by clinicians were pyrazinamide (PZA) and ethionamide (ETH)/prothionamide (PTH).

Table 8 Drugs in regimen at the time patients experienced a hepatotoxic event (n = 91), and drugs stopped by clinicians after event*

	Patients taking the drug at the time of event as part of a multidrug regimen (n = 91) n (%)	Drugs permanently stopped by clinician due to hepatitis or transaminase elevation within 45 days after a hepatotoxic event†
Isoniazid	0	0
Rifampin	0	0
Ethambutol	25 (27)	0
Pyrazinamide	69 (76)	7
Kanamycin	27 (30)	0
Amikacin	0	0
Capreomycin	46 (50)	0
Fluoroquinolones	90 (99)	1
PAS	78 (86)	0
Cycloserine	81 (89)	1
Ethionamide/ prothionamide	75 (72)	8

*Drugs were permanently stopped in 10 patients based on the clinician's assessment of toxicity.
†Drugs in regimen within 2 weeks of laboratory hepatotoxic event if listed in chart (n = 85). If no regimen was listed (n = 6), the last documented regimen was used.
PAS = para-aminosalicylic acid.

Other management strategies included the use of ancillary medications and supportive care to control symptoms of side effects, such as nausea or dehydration. In addition, 'hepato-protectors' were ubiquitously used (not only among those experiencing hepatotoxicity) in this cohort. These include 'karsil' and 'hepatoprotektor', which are commonly used in Russian medicine,[49,50] although no clinical benefit of these agents has been demonstrated.

DISCUSSION

The treatment of MDR-TB using currently available tools is clinically complex and challenging. Clinicians treating patient populations with a high prevalence of concomitant alcohol use during treatment and/or viral hepatitis face additional concerns about adverse events from the use of some first- and second-line anti-tuberculosis drugs. In patients with baseline hepatitis and those who develop hepatotoxicity during

*Interestingly, for patients who did use alcohol, development of hepatotoxicity was associated with good outcomes (OR 4.40, 95%CI 1.79–10.81) compared to those who did not develop hepatotoxicity. Patients who did not develop elevated transaminases/bilirubin during treatment presented a different picture: in multivariable analysis, alcohol use, smoking history, bilateral and cavitary disease at baseline and respiratory insufficiency at baseline were associated with worse treatment outcomes. High levels of treatment adherence were associated with good outcomes.

treatment, physicians should seriously weigh the dangers of continued treatment vs. intermittently treated or untreated MDR-TB. In this study of MDR-TB treatment in Tomsk, Russia, in a patient population with high alcohol use, and presence of both hepatitis B and C, hepatotoxicity was not, in general, associated with poor treatment outcomes. In many ways, these findings are expected. Watkins describes 'adaptation' among patients with drug-induced transaminitis upon continued exposure to the drug.[51]

Management of hepatotoxicity in patients with TB can be complicated. As patients receive multidrug regimens, it can be difficult to pinpoint the precise agent responsible for the hepatotoxic effects.[52] Some studies have found that gradually re-introducing the medications or re-introducing them in a stepwise fashion leads to less repeat hepatotoxicity, although most data have been limited to individuals without MDR-TB.[53] To date, few data are available on how to manage adverse events among MDR-TB patients, in particular whether to suspend any or all anti-tuberculosis agents and how to re-instate these medications. As with management of pan-susceptible TB, there are often several potential offenders, and identification of the culprit drug requires sequential re-initiation of anti-tuberculosis drugs. In general, the management approach to hepatotoxicity adopted by this community of Tomsk physicians was to suspend all medications and, once liver function tests normalized, to initiate the anti-tuberculosis drugs one by one, saving the most likely offenders for the end. Such an approach enabled the physicians to reinstate the full MDR-TB regimen in the vast majority of hepatoxicity cases. In the 10 patients in whom medications were stopped, PZA and/or ETH/PTH were the most frequent agents selected, a finding consistent with the literature (Table 1). Importantly, none of these cases required complete discontinuation of MDR-TB treatment. This is especially important for MDR-TB patients, for whom few therapeutic options may be available and for whom continuation of appropriate multi-drug regimens is critical. In this cohort, such an aggressive approach in the management of hepatotoxicity, even among individuals with chronic viral hepatitis and active alcohol users, resulted in final treatment outcomes that were comparable to those among individuals without hepatoxicity.

Patients experienced hepatotoxic events quite late in their treatment (mean = 196 days). In general, patients were hospitalized for the early 4–6 months of treatment, after which they received ambulatory treatment. The hepatotoxicity observed during this period may have been linked to increased access to alcohol. This is an area that will require further study.

The finding that alcohol use during treatment was associated with poor treatment outcome among those who did *not* experience hepatotoxicity, but was not associated with poor outcome in people *with* hepatotoxicity, may reflect an increased level of health system attention to patients with this side effect. If this is the case, then it supports the contention that being closely followed by health workers can lead to a mitigation of the negative biological and social effects of alcohol on successful TB treatment.[54] However, the alcohol use variable was imprecise; any documentation of intoxication was sufficient to be included as a drinker. If alcohol use was overestimated in those with hepatotoxicity, but not in those without, this finding might be reflective of bias, and the well-known negative effects of alcohol use on outcome underestimated.

Cigarette smoking history and more severe illness (bilateral and cavitary disease) were also associated with poorer treatment outcomes, after controlling for alcohol use and other factors. Although smokers were no more likely to have respiratory insufficiency at baseline than non-smokers, they were more likely to die or fail treatment than non-smokers (data not shown). These findings for patients with MDR-TB corroborate published data that cigarette smoking is associated with poor treatment outcomes in the treatment of drug-susceptible disease.[55,56]

Our study does have several important limitations. First, as mentioned above, assessment of alcohol use was imprecise, and based on the physician documenting intoxication in the chart, and did not allow for assessment of quantity or duration of alcohol use or time relationships to the hepatotoxic events. Second, tests for hepatitis B and C were not collected for the early cohort of patients. Small numbers may have precluded measurement of the true effect of this comorbidity, as this was not an outcome the original protocol was powered to detect. Another limitation of the study is that we only followed the patients during treatment and were therefore unable to assess whether those with hepatotoxicity had longer-term health problems secondary to this. Strengths of the study include the fact that adverse events and treatment adherence data were captured prospectively, and our assessment of hepatitis is based on laboratory confirmation.

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RÉSUMÉ

CONTEXTE : Le programme de traitement de la tuberculose à germes multirésistants (TB-MDR) à Tomsk, Russie.

OBJECTIF : Décrire l'incidence et la prise en charge de l'hépatotoxicité au cours du traitement de la TB-MDR, et évaluer les facteurs de risque associés à son développement ainsi que son impact sur les résultats du traitement.

SCHÉMA : Série rétrospective de cas portant sur 608 patients.

RÉSULTATS : On a observe une hépatotoxicité selon les définitions de l'American Thoracic Society (2006) chez 91 des 568 patients (16,5%). La durée médiane avant le premier effet hépatotoxique a été de 196 jours après le début du traitement. Les facteurs initiaux associés à l'hépatotoxicité ont comporté un taux élevé d'alanine aminotransférase/aspartate aminotransférase/bilirubine (OR 53,9 ; IC95% 6,30–438,7) et l'insuffisance rénale (OR 19,6 ; IC95% 2,71–141,6). Les succès du traitement sont en association avec une adhésion thérapeutique marquée (OR 3,25 ; IC95% 2,07–5,09) et avec la mise en route du traitement en prison (OR 1,77 ; IC95% 1,04–3,01). Sont en association avec des résultats plus défavorables le tabagisme (OR 0,44 ; IC95% 0,21–0,92) et une maladie cavitaire bilatérale (OR 0,51 ; IC95% 0,34–0,77). Chez les consommateurs d'alcool, l'apparition d'une hépatotoxicité est en association avec des résultats favorables (OR 4,40 ; IC95% 1,79–10,81) par rapport aux sujets n'ayant pas développé cette hépatotoxicité (OR 0,42 ; IC95% 0,25–0,68). Un ou plusieurs médicaments ont dû être interrompus définitivement chez 10 des 91 patients, mais le traitement n'a été totalement interrompu dans aucun cas.

CONCLUSION : La présence d'une hépatotoxicité au cours du traitement de la TB-MDR n'entraîne pas chez ces patients une augmentation statistiquement significative des résultats défavorables.

RESUMEN

MARCO DE REFERENCIA: El programa contra la tuberculosis multidrogorresistente (TB-MDR) en Tomsk, Rusia.

OBJETIVO: Describir la incidencia y el manejo de la hepatotoxicidad durante el tratamiento de la TB-MDR y evaluar los factores de riesgo asociados con esta complicación y su repercusión en el desenlace terapéutico.

MÉTODO: Fue este un estudio retrospectivo de una serie de casos de 608 pacientes.

RESULTADOS: Con base en la definición de hepatotoxicidad de la American Thoracic Society (2006), 91 de los 568 pacientes presentaron la complicación (16,5%). La mediana del lapso hasta la aparición de la primera manifestación de hepatotoxicidad fue 196 días a partir del comienzo del tratamiento. Las características iniciales de los pacientes correlacionadas con la toxicidad hepática fueron las concentraciones altas de alanina aminotransferasa, aspartato aminotransferasa y bilirrubinas (OR 53,9; IC95% 6,30–438,7) y la insuficiencia renal (OR 19,6; IC95% 2,71–141,6). Los factores asociados con el éxito del tratamiento fueron un buen cumplimiento terapéutico (OR 3,25; IC95% 2,07–5,09) y el haber comenzado el tratamiento en la prisión (OR 1,77; IC95% 1,04–3,01). Se asociaron con los desenlaces más desfavorables el tabaquismo (OR 0,44; IC95% 0,21–0,92) y la presencia de cavernas bilaterales (OR 0,51; IC95% 0,34–0,77). En los pacientes que ingirieron alcohol durante el tratamiento, los que presentaron una toxicidad hepática alcanzaron desenlaces más favorables (OR 4,40; IC95% 1,79–10,81) que los consumidores de alcohol que no padecieron hepatotoxicidad (OR 0,42; IC95% 0,25–0,68). En 10 de los 91 pacientes se interrumpió en forma definitiva la administración de uno o varios medicamentos, pero en ningún caso se suspendió completamente el tratamiento.

CONCLUSIÓN: La aparición de hepatotoxicidad durante el tratamiento de la TB-MDR no aumentó en forma significativa los desenlaces desfavorables de los pacientes.