INT J TUBERC LUNG DIS 16(7):891–896

http://dx.doi.org/10.5588/ijtld.11.0795
E-published ahead of print 9 April 2012

Alcohol use and the management of multidrug-resistant tuberculosis in Tomsk, Russian Federation

A. C. Miller,* I. Y. Gelmanova,† S. Keshavjee,*‡ S. Atwood,‡ G. Yanova,§ S. Mishustin,§ J. J. Furin,¶ S. S. Shin‡

***Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, USA; †Partners In Health, Tomsk Oblast, Russian Federation; ‡Division of Global Health Equity, Brigham and Women's Hospital, Boston, Massachusetts, USA; §Tomsk Oblast Clinical Tuberculosis Hospital, Tomsk, Russian Federation; ¶Department of Medicine, Case Western Reserve University, Cleveland, Ohio, USA**

SUMMARY

SETTING: Alcohol use increases the risk of multidrug-resistant tuberculosis (MDR-TB) and poses challenges for successful MDR-TB treatment, including the potential for additional adverse events.

AIM: To investigate the association between alcohol consumption during MDR-TB treatment and adverse events and treatment outcomes in a cohort of patients in Tomsk, Russia.

DESIGN: From 2000 to 2004, retrospective data were collected on 407 MDR-TB patients in Tomsk. Factors associated with treatment outcomes were assessed using logistic regression.

RESULTS: Of the 407 patients, 253 (62.2%) consumed alcohol during treatment ('drinkers'), and 367 (90.2%) had at least one documented adverse advent. No significant differences were noted in frequency of adverse events in drinkers vs. non-drinkers. Drinkers had less favourable treatment outcomes (OR 0.28, 95%CI 0.18–0.45). Among drinkers, favourable treatment outcome was associated with adherence to at least 80% of prescribed doses (OR 2.89, 95%CI 1.30–6.43) and the occurrence of an adverse event requiring treatment interruption (OR 2.49, 95%CI 1.11–5.59).

CONCLUSIONS: Alcohol use did not appear to increase the risk of adverse events during MDR-TB treatment; however, alcohol consumption was associated with poor outcome. Our findings suggest that individuals who drink alcohol should receive aggressive attention to optimise treatment adherence and manage adverse events.

KEY WORDS: adverse effects; alcohol; outcomes; tuberculosis; multidrug-resistant; Russia

TUBERCULOSIS (TB) is a major cause of infectious global mortality, with an estimated 9.4 million new cases and 1.7 million deaths in 2009.[1] Heavy alcohol use is associated with an increased risk of tuberculosis infection and active disease.[2–3] Alcohol use has been documented to increase the risk of certain adverse events during TB treatment, including hepatotoxicity,[4–5] neuropathy,[6] and psychosis,[7] and may potentially increase the risk of additional adverse events (i.e., electrolyte disturbance, depression, seizure and gastric intolerance) due to overlapping toxicities.[8] Finally, alcohol use disorders are associated with worse treatment outcomes. The mechanisms by which alcohol contributes to unfavourable outcomes are both biological and social in nature, including death from alcohol-related causes and default or failure due to non-adherence and adverse events.[9–16]

Multidrug-resistant tuberculosis (MDR-TB) is defined as *Mycobacterium tuberculosis* bacilli resistant to at least isoniazid and rifampicin. Treatment for MDR-TB is more difficult, costly and yields worse outcomes than for drug-susceptible TB.[17,18] Alcohol use disorders (AUDs) increase the difficulty of MDR-TB management and control. Alcohol use is associated with a greater risk of MDR-TB and extensively drug-resistant TB (XDR-TB) in several settings,[9,19,20] and worse outcomes among MDR-TB cohorts.[21,22]

Challenges in MDR-TB treatment due to alcohol use are particularly salient in settings with 'converging epidemics' of MDR-TB and AUDs. As the only country that ranks on both the World Health Organization's (WHO's) list of high TB burden countries and the 'top ten' countries with the highest per capita alcohol consumption, the Russian Federation is an illustrative example from this perspective.[1,23] In 2011, furthermore, the WHO estimated that 18% of new TB and 46% of recurrent TB cases in the Russian Federation were MDR-TB cases.[24] According to the

Correspondence to: Ann C Miller, Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Avenue, Boston, MA 02115, USA. Tel: (+1) 617 432 7297. Fax: (+1) 617 432 2565. e-mail: ann_miller@hms.harvard.edu

Article submitted 29 November 2011. Final version accepted 10 January 2012.

WHO's 2011 Global Status Report on Alcohol and Health, approximately 16% of men and 2.5% of women aged >15 years in the Russian Federation have an AUD.[23] Rehm et al. have estimated that the proportion of TB in Russia attributable to alcohol exposure ranges from 37% to 54% in men and from 9% to 17% in women.[25]

In Russia and other settings, providers are faced with the dilemma of whether to offer MDR-TB treatment to individuals with AUDs given the potentially elevated risk of adverse events, poor adherence and unfavourable outcomes among this 'difficult to manage' population. Providers who do treat such patients must weigh decisions regarding the choice of drug and toxicity management in this population, with minimal insight available from the published literature. Responding to this knowledge gap, we sought to describe the frequency of second-line drug treatment related adverse events among individuals who drank alcohol during MDR-TB treatment in Tomsk, Russia, compared with those who did not drink alcohol, and to explore the impact of these adverse events on treatment outcomes.

STUDY POPULATION AND METHODS

Study setting and treatment programme

Tomsk oblast is located in Western Siberia, Russian Federation. About 50% of its 1 035 000 population live in remote rural areas. As in the rest of the former Soviet Union, MDR-TB is a significant problem in the region. Between 1998 and 2002, rates of MDR-TB rose from 6.5% to 16% for new cases, and from 26.7% to 43.6% among retreatment cases,[26] despite the introduction and expansion of WHO's DOTS strategy. In 2000, the prison and civilian TB programmes in Tomsk incorporated MDR-TB treatment for patients with either documented MDR-TB or probable MDR-TB (i.e., based on history of treatment failure). The programme was scaled up throughout the oblast from 2000 to 2004, and influenced national norms for the treatment of MDR-TB in Russia and other countries of the former Soviet Union.

Procedures for bacteriology and drug susceptibility testing (DST) are described elsewhere.[22,27] In brief, prior to the start of treatment, smear microscopy and culture on Löwenstein-Jensen media were performed at local laboratories. DST was initially performed by the Massachusetts State Laboratory Institute, and later transferred to the Tomsk reference laboratory.

Patient treatment and adverse reaction management have been described elsewhere.[22,27–28] Regimens were individualised based on drug resistance data and prior treatment history, with efforts to include at least five drugs to which the infecting isolate was confirmed or likely to be susceptible. All treatment was provided under directly observed therapy. Adverse reactions were aggressively managed at no cost to the patient. All TB physicians were trained using standardised protocols for the diagnosis and management of adverse events associated with anti-tuberculosis drugs. Routine laboratory monitoring of liver function tests, creatinine and potassium was conducted monthly, and thyroid stimulating hormone monitoring was conducted bi-monthly, with pre-established thresholds for laboratory-defined adverse events. Adverse events not defined by laboratory data were determined on a clinical basis.

Patients

Between 10 September 2000 and 1 November 2004, 636 patients from both the civilian and incarcerated population were consecutively enrolled in the programme. Of these, 608 had documentation of MDR-TB at baseline. To assess the impact of alcohol use during treatment, analysis was limited to the 407 patients with confirmed MDR-TB who started treatment in the civilian sector.

Ethical considerations

The study was reviewed and approved by the Institutional Review Boards of Harvard School of Public Health (Boston, MA, USA) and the Siberian State Medical University in Tomsk, Russia.

Data collection and analysis

Clinical data were captured on forms prospectively completed by TB providers, abstracted through retrospective chart review and entered into an electronic medical record, which used a Microsoft SQL server 2000 (Microsoft Corporation, Seattle, WA, USA). Chart reviews were supplemented by laboratory and TB registry data from Tomsk oblast.

Alcohol use during treatment was defined as a physician documenting alcohol consumption and/or inebriation during treatment in the patient's chart. A baseline AUD was defined as documentation of a diagnosis of alcoholism at intake by a physician or mental health provider (e.g., psychiatrist, psychologist, addiction specialist). Body mass index (BMI) was calculated as kg/m^2, and was considered low if $<$18.5 in females or $<$20 in males.

XDR-TB was defined as documented MDR-TB plus resistance to any second-line aminoglycoside or capreomycin, plus any fluoroquinolone.[29] A patient was considered to be 'adherent' to treatment if he/she took $\geq$80% of prescribed doses, as recorded on the treatment administration forms.

Definitions of specific adverse events are presented in Table 1. We collected all relevant laboratory data, as well as clinically defined events as recorded by the treating physician. Treatment outcomes were defined as in Laserson et al.[30] A 'favourable' outcome was defined as cure or treatment completion. 'Poor' treatment outcomes included default, failure or death from any cause during MDR-TB treatment.

Table 1 Definition of adverse reactions

Adverse reaction	Definition of specific adverse reaction
Nausea and vomiting	Documentation of nausea/vomiting by physician
Diarrhoea	Documentation of diarrhoea by physician
Depression	As diagnosed by a TB physician and/or as judged by a psychiatrist, based on ICD-10 criteria
Psychosis	As diagnosed by a TB physician and/or as judged by a psychiatrist, based on ICD-10 criteria
Seizure	Witnessed or unwitnessed event consistent with seizure, e.g., tonic-clinic movement, bowel-bladder incontinence, post-ictal confusion, etc.
Ototoxicity	Hearing loss confirmed by physical examination or audiometry
Arthralgia	Joint pain as reported by patient and documented by physician, with or without presence of arthritis
Rash	Dermatological reaction felt to be related to anti-tuberculosis medicines, as documented by the physician
Neuropathy	Symptoms and findings consistent with neuropathy, e.g., pain or numbness of distal extremities, as diagnosed by physician or electromyography
Nephrotoxicity	Elevation of at least one creatinine value >141 mmol/l
Hepatotoxicity	Elevation of either serum transaminase or serum bilirubin at least 3 times ULN (AST/ALT ULN 0.45 or 0.68 mmol/l, depending on technique; bilirubin ULN 20.5 mmol/l)
Hypokalaemia	At least one serum potassium value of <3 mEq/l
Hypothyroidism	At least one measure of TSH >10.0 IU/ml

TB = tuberculosis; ICD = International Classification of Diseases; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal; TSH = thyroid-stimulating hormone.

Analyses were conducted using Stata version 11.1 (College Park, TX, USA). Continuous data were assessed for normality using a skewness-kurtosis test. Demographic data and specific adverse reactions were compared in 2×2 tables using Student's *t*-test or Wilcoxon rank sum tests, as appropriate, for continuous variables, and using Pearson's χ^2 or Fisher's exact test for categorical variables. Univariable and multivariable logistic regression were conducted to assess factors associated with treatment outcomes. Variables included in univariable analysis were included based on existing literature and factors of prior significance in an earlier version of this cohort. Variables significant at $P = 0.1$ were considered for inclusion in the multivariable analysis. A final model was determined using likelihood ratio testing. Variables included in the multivariable analysis were assessed for interaction and effect modification.

RESULTS

Table 2 shows baseline demographic and clinical information for the cohort. Of 407 non-incarcerated civilian patients treated for documented MDR-TB, 253 (62%) used alcohol during treatment. Patients who used alcohol during treatment ('drinkers') were strikingly different from those who did not ('non-drinkers'). Drinkers were more likely to be male, older, unemployed, smokers, have a past history of incarceration and/or homelessness, and have the following baseline characteristics: bilateral and cavitary disease and a diagnosis of alcoholism (*P* for all characteristics < 0.01).

Table 2 Baseline characteristics among individuals who drank alcohol vs. those who did not during MDR-TB treatment, 2000–2004, in Tomsk, Russian Federation (*N* = 407)

Baseline characteristic	Drinkers (*n* = 253) *n* (%)	Non-drinkers (*n* = 154) *n* (%)	*P* value
Male sex	206 (81.4)	100 (64.9)	<0.01
Age, years, median [range]	40 [17–65]	30 [17–71]	<0.01
History of incarceration	111 (44.22)	39 (26.0)	<0.01
Married or living together	128 (50.6)	87 (56.5)	0.26
Employed at treatment start	46 (18.3)	60 (38.5)	<0.01
Homeless	20 (7.9)	0	<0.01
Smoking history	241 (95.3)	102 (66.2)	<0.01
Diagnosis of alcoholism	192 (75.9)	14 (9.1)	<0.01
Baseline comorbidity*	198 (78.2)	127 (82.4)	0.31
Low BMI	119 (47.0)	58 (32.8)	0.06
Years since TB diagnosis, mean ± SD	4.9 ± 5.7	3.3 ± 5.1	<0.01
Bilateral and cavitary disease	183 (72.3)	66 (42.8)	<0.01
Number of drugs resistant at baseline, median [range]	5 [2–9]	5 [3–12]	0.48
XDR-TB	12 (4.7)	8 (5.2)	0.83

*Any of the following at baseline: diabetes mellitus, seizure disorder, renal failure, hepatitis or elevated transaminases, psychiatric disorder as reported by intake physician.
MDR-TB = multidrug-resistant tuberculosis; BMI = body mass index; TB = tuberculosis; SD = standard deviation; XDR-TB = extensively drug-resistant tuberculosis.

Clinical management

Baseline drug regimens for drinkers and non-drinkers were similar (Table 3), as were rates of laboratory monitoring per protocol (data not shown).

Table 3 Drugs in baseline regimens for individuals who drank alcohol vs. those who did not during MDR-TB treatment in Tomsk, Russian Federation (*N* = 407)

Drug	Drinkers (*n* = 253) *n* (%)	Non-drinkers (*n* = 154) *n* (%)	*P* value
OFX	249 (98.4)	150 (97.4)	0.47
CS	248 (98.0)	150 (97.4)	0.68
PAS	224 (88.5)	127 (82.4)	0.09
PZA	207 (81.8)	118 (76.6)	0.21
THA	206 (81.4)	125 (81.2)	0.28
CM	157 (62.1)	84 (54.5)	0.13
KM	90 (35.6)	65 (42.2)	0.18
EMB	71 (28.1)	42 (27.3)	0.8
AMOX-CLAV	8 (3.2)	8 (5.2)	0.31
RFB	2 (0.7)	2 (1.3)	0.61
INH	2 (0.7)	4 (2.6)	0.18
MFX	1 (0.4)	2 (1.3)	0.3
AMK	0	2 (1.3)	0.07

MDR-TB = multidrug-resistant tuberculosis; OFX = ofloxacin; CS = cycloserine; PAS = para-aminosalicylic acid; PZA = pyrazinamide; THA = thiamide; CM = capreomycin; KM = kanamycin; EMB = ethambutol; AMOX-CLAV = amoxicillin-clavulanate; RFB = rifabutin; INH = isoniazid; MFX = moxifloxacin; AMK = amikacin.

Frequency and type of adverse events in drinkers vs. non-drinkers

The majority of the cohort (90.2%) had at least one documented adverse event during treatment. The total number of different adverse events experienced by each patient over the course of treatment ranged from zero to seven. The most frequent adverse events were gastrointestinal: of those who had an adverse event, approximately 78% experienced either nausea and vomiting or diarrhoea. Other frequently occurring adverse events included arthralgia (44.2%) and hypokalaemia (38.3%). Table 4 provides a comparison of adverse events between drinkers and non-drinkers. Drinkers and non-drinkers did not significantly differ with respect to development or number of adverse events in general; 90.9% of drinkers vs. 88.9% of non-drinkers experienced an adverse event ($P = 0.52$); the mean number of different events was 2.7 for drinkers (standard deviation [SD] 1.6) and 2.8 for non-drinkers (SD 1.6, $P = 0.4$). There was no difference in time to presentation among drinkers vs. non-drinkers for all types of adverse events except diarrhoea, which occurred later among drinkers vs. non-drinkers (median 2.5 months vs. 1 month after treatment start, $P = 0.002$). Among adverse events diagnosed with laboratory data (nephrotoxicity, hepatotoxicity, hypokalaemia and hypothyroidism), the severity of each event at the time of presentation did not differ significantly among drinkers vs. non-drinkers. Permanent interruptions of anti-tuberculosis drugs due to adverse events were generally uncommon. Overall, and for each type of reaction, the rate of drug discontinuation due to adverse events among drinkers vs. non-drinkers did not differ significantly.

Treatment outcomes

Table 5 provides treatment characteristics for the cohort. Overall, 247/407 (61%) had favourable treatment outcomes. Alcohol use during treatment was negatively associated with favourable outcome ($P < 0.001$), and positively associated with death ($P < 0.0001$) and default ($P < 0.05$). As alcohol use was associated with non-adherence during treatment, we explored whether the adverse impact of drinking on treatment outcome could be mediated by non-adherence. Controlled for non-adherence, drinking was still negatively associated with favourable treatment outcome (adjusted odds ratio [OR] 0.38, 95% confidence interval [CI] 0.23–0.61). We also explored whether there were differences in time to default based on alcohol use ($n = 93$ defaulters), and found a non-significant trend toward earlier default among drinkers vs. non-drinkers (mean [± SD] 230 ± 124 days vs. 248 ± 154 days, $P = 0.77$).

We explored factors associated with poor treatment outcome, stratified by alcohol use. Among drinkers, a diagnosis of alcoholism at baseline and severe TB (bilateral and cavitary disease at baseline) were associated with worse treatment outcomes (Table 6). Interruption of treatment due to side effects and adherence to at least 80% of prescribed doses were associated with favourable treatment outcomes in drinkers. In multivariable analysis, greater adherence (OR

Table 4 Adverse events among individuals who drank alcohol vs. those who did not during MDR-TB treatment in Tomsk, Russian Federation ($N = 407$)

Characteristic	*n*	Drinkers ($n = 253$) *n* (%)	Non-drinkers ($n = 154$) *n* (%)	*P* value
Any adverse reaction		230 (90.9)	137 (88.9)	0.52
Nausea and vomiting	246	145 (57.3)	101 (65.6)	0.1
Diarrhoea	163	88 (34.8)	75 (48.7)	0.005
Depression	33	26 (10.3)	7 (4.6)	0.04
Psychosis	13	23 (9.1)	14 (9.1)	1.00
Seizure	45	31 (12.2)	14 (9.1)	0.32
Ototoxicity	60	42 (16.6)	27 (17.5)	0.81
Arthralgia	180	119 (47.0)	61 (39.6)	0.14
Rash	44	31 (12.2)	13 (8.4)	0.23
Neuropathy	27	20 (7.9)	7 (4.6)	0.19
Nephrotoxicity	36	17 (6.7)	19 (12.3)	0.05
Hepatotoxicity	55	32 (12.7)	23 (14.9)	0.51
Hypokalaemia	156	96 (37.9)	60 (39.0)	0.83
Hypothyroidism	28	14 (5.5)	14 (9.1)	0.17

MDR-TB = multidrug-resistant tuberculosis.

Table 5 Treatment characteristics among individuals who drank alcohol vs. those who did not during MDR-TB treatment in Tomsk, Russian Federation ($N = 407$)

Characteristic	Drinkers ($n = 253$) *n* (%)	Non-drinkers ($n = 154$) *n* (%)	*P* value
Adherent to TB treatment	171 (67.6)	144 (93.5)	<0.001
Favourable outcome	127 (50.2)	120 (77.2)	<0.001
Treatment outcome			
Cured	117 (46.6)	115 (74.6)	<0.001
Completed treatment	10 (3.9)	5 (3.2)	0.71
Died	19 (7.5)	3 (1.9)	0.016
Defaulted	74 (29.2)	19 (12.3)	<0.001
Failed treatment	33 (11.1)	12 (7.8)	0.10

MDR-TB = multidrug-resistant tuberculosis.

Table 6 Factors associated with favourable MDR-TB treatment outcomes among drinkers ($n = 253$) in Tomsk, Russian Federation

Characteristic	Univariable OR (95%CI)	Final model OR (95%CI)
Male sex	1.46 (0.77–2.76)	
Prior incarceration	0.95 (0.58–1.57)	
Diagnosis of alcoholism*	0.52 (0.29–0.94)	
Smoking history	1.00 (0.32–3.20)	
Baseline XDR-TB	0.48 (0.14–1.63)	
Bilateral and cavitary disease at baseline*	0.44 (0.26–0.83)	0.45 (0.24–0.82)
Adherence to 80% of doses*	2.78 (1.56–4.96)	2.89 (1.30–6.43)
Any AEs requiring treatment interruption*	3.06 (1.41–6.61)	2.49 (1.11–5.59)

*Entered into main effects multivariable model.
MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; XDR-TB = extensively drug-resistant tuberculosis; AEs = adverse events.

Table 7 Factors associated with favourable MDR-TB treatment outcomes among non-drinkers (n =154) in Tomsk, Russian Federation

Characteristic	Univariable OR (95%CI)	Final model OR (95%CI
Male sex*	0.32 (0.12–0.83)	
Prior incarceration*	0.22 (0.10–0.51)	0.34 (0.14–0.79)
Diagnosis of alcoholism	0.39 (0.10–1.49)	
Smoking history*	0.14 (0.04–0.48)	0.19 (0.05–0.71)
Baseline XDR-TB	0.25 (0.06–1.09)	
Bilateral and cavitary disease at baseline	0.62 (0.28–1.35)	
Adherence to 80% of doses*	6.21 (1.64–23.51)	4.27 (1.06–17.11)
Any AEs requiring treatment interruption	2.96 (0.97–9.05)	

*Entered into main effects multivariable model.
MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; XDR-TB = extensively drug-resistant tuberculosis; AEs = adverse events.

2.89, 95%CI 1.30–6.43), and interruption of treatment due to side effects (OR 2.49, 95%CI 1.11–5.59) were associated with better outcomes, while bilateral and cavitary disease (OR 0.45, 95%CI 0.24–0.82) were associated with unfavourable outcomes.

In non-drinkers, univariate analysis showed that male sex, smoking at baseline and a history of prior incarceration were associated with worse outcomes (Table 7), and adherence to at least 80% of prescribed doses was associated with better outcomes. In multivariable analysis, a history of prior incarceration (OR 0.34, 95%CI 0.14–0.79), baseline history of smoking (OR 0.19, 95%CI 0.05–0.71) and treatment adherence (OR 4.27, 95%CI 1.06–17.11) were all significantly associated with treatment outcome.

DISCUSSION

In this non-incarcerated population of MDR-TB patients with high levels of alcohol use during treatment, alcohol use did not confer an increased risk of adverse events during MDR-TB treatment. Notably, despite the well-known effects of alcohol on the liver, alcohol use during treatment was not significantly associated with development of hepatotoxicity. We tested this finding at elevations of both three and five times the normal limits of transaminases, with no difference in findings. Given that treatment regimens and frequency of laboratory monitoring did not differ significantly among drinkers vs. non-drinkers, these data provide reassurance that individuals who drink alcohol during MDR-TB treatment can be managed using the same principles of regimen design, without necessarily incurring excess toxicity due to interactions or synergy between anti-tuberculosis drugs and alcohol consumption.

However, alcohol use during treatment was associated with poor treatment outcome, in large part due to increased rates of death and default. Non-adherence was associated with poor treatment outcome for both drinkers and non-drinkers. Recognition of this unsurprising factor led to the development of a programme to address those TB patients at risk for non-adherence in Tomsk. The 'Sputnik' programme, implemented in December 2006, provides intensive programmatic support to those most at risk of non-adherence and default, and has been very successful, with cure rates of 71% and mean adherence improving from 52% to over 80%.[31]

Other characteristics associated with treatment outcome differed among those who did and did not consume alcohol during treatment. Cigarette use was associated with worse treatment outcomes in non-drinkers, but not in drinkers. Smoking is known to be associated with worse TB treatment outcomes in general;[32–34] however, we were only able to document this for the non-drinkers. A possible reason for this finding is that almost all of the drinkers were also smokers (96%); any additional burden of tobacco use would probably have been masked.

Interestingly, we found that treatment interruption due to an adverse event was associated with favourable treatment outcomes in drinkers. It is possible that greater attention was paid to individuals who developed adverse events, resulting in improved management and treatment outcome. An alternative explanation is that those who were followed more closely were subsequently more likely to have an adverse event identified and appropriately managed by providers, resulting in improved outcomes.

This study provides some of the first data on adverse events in a population with high rates of alcohol use. One major limitation of the study is the retrospective nature of the data collection. Alcohol use during treatment and alcoholism diagnosis were captured based on physician diagnosis and documentation. We were unable to assess amounts and frequency of alcohol use, or relate the chronology of drinking episodes with respect to adverse events. The Alcohol Use Disorders Identification Test (AUDIT), which has been validated in this population, could provide an instrument to gauge degree of alcohol use;[35] future prospective studies may be able to capture some of these important nuances.

CONCLUSIONS

Alcohol use during treatment was not associated with increased risk or number of adverse events during MDR-TB treatment. High treatment adherence and development of an adverse event requiring treatment interruption were associated with favourable outcomes in alcohol users. Interventions to promote high treatment adherence and retention among drinkers, aggressive management of adverse events and integrated alcohol care within TB services[36,37] could result in lessening the imbalance in favourable treatment outcomes for those who use alcohol.

Acknowledgements

The authors acknowledge the work of the doctors, nurses and community health workers from the Tomsk oblast TB programme and Partners In Health, Russia.

References

1 World Health Organization. WHO report 2010. Global tuberculosis control. WHO/HTM/TB/2010.7. Geneva, Switzerland: WHO, 2010.
2 Lönnroth K, Williams B G, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis—a systematic review. BMC Public Health 2008; 8: 289.
3 Fok A, Numata Y, Schulzer M, FitzGerald M J. Risk factors for clustering of tuberculosis cases: a systematic review of population-based molecular epidemiology studies. Int J Tuberc Lung Dis 2008; 12: 480–492.
4 Dossing M, Wilcke J T, Askgaard D S, Nybo B. Liver injury during antituberculosis treatment: an 11-year study. Tubercle Lung Dis 1996; 77: 335–340.
5 Grant A D, Mngadi K T, van Halsema C L, Luttig M M, Fielding K L, Churchyard G J. Adverse events with isoniazid preventive therapy: experience from a large trial. AIDS 2010; 24 (Suppl 5): S29–S36.
6 Patel A M, McKeon J. Avoidance and management of adverse reactions to antituberculosis drugs. Drug Saf 1995; 12: 1–25.
7 Goldman A L, Braman S S. Isoniazid: a review with emphasis on adverse effects. Chest 1972; 62: 71–77.
8 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2008.402. Geneva, Switzerland: WHO, 2008.
9 Pablos-Mendez A, Knirsch C A, Barr R G, Lerner B H, Frieden T R. Nonadherence in tuberculosis treatment: predictors and consequences in New York City. Am J Med 1997; 102: 164–170.
10 Amuha M G, Kutyabami P, Kitutu F E, Odoi-Adome R, Kalyango J N. Non-adherence to anti-TB drugs among TB/HIV co-infected patients in Mbarara Hospital Uganda: prevalence and associated factors. Afr Health Sci 2009; 9 (Suppl 1): S8–S15.
11 Gelmanova I Y, Keshavjee S, Golubchikova V T, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. Bull World Health Organ 2007; 85: 703–711.
12 Burman W J, Cohn D L, Rietmeijer C A, Judson F N, Sbarbaro J A, Reves R R. Noncompliance with directly observed therapy for tuberculosis. Epidemiology and effect on the outcome of treatment. Chest 1997; 111: 1168–1173.
13 Jakubowiak W M, Bogorodskaya E M, Borisov S E, Danilova I D, Kourbatova E V. Treatment default among new smear-positive pulmonary TB patients in Russian regions. Int J Tuberc Lung Dis 2007; 11: 353–354.
14 Franke M F, Appleton S C, Bayona J, et al. Risk factors and mortality associated with default from multidrug-resistant tuberculosis treatment. Clin Infect Dis 2008; 46: 1844–1851.
15 Waitt C J, Squire S B. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis 2011; 15: 871–885.
16 Mathew T A, Ovsyanikova T N, Shin S S, et al. Causes of death during tuberculosis treatment in Tomsk Oblast, Russia. Int J Tuberc Lung Dis 2006; 10: 857–863.
17 Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. Eur Respir J 2009; 33: 1085–1094.
18 Cox H S, Kalon S, Allamuratova S, et al. Multidrug-resistant tuberculosis treatment outcomes in Karakalpakstan, Uzbekistan: treatment complexity and XDR-TB among treatment failures. PLoS One 2007; 2: e1126.
19 Massi M N, Wahyuni S, Halik H, et al. Drug resistance among tuberculosis patients attending diagnostic and treatment centres in Makassar, Indonesia. Int J Tuberc Lung Dis 2011; 15: 489–495.
20 Suarez-Garcia I, Rodriguez-Blanco A, Vidal-Perez J L, et al. Risk factors for multidrug-resistant tuberculosis in a tuberculosis unit in Madrid, Spain. Eur J Clin Microbiol Infect Dis 2009; 28: 325–330.
21 Johnston J C, Shahidi N C, Sadatsafavi M, Fitzgerald J M. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One 2009; 4: e6914.
22 Shin S S, Pasechnikov A D, Gelmanova I Y, et al. Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia. Int J Tuberc Lung Dis 2006; 10: 402–408.
23 World Health Organization. Global status report on alcohol and health. Geneva, Switzerland: WHO, 2011.
24 World Health Organization. WHO report 2011. Global tuberculosis control. WHO/HTM/TB/2011.16. Geneva, Switzerland: WHO, 2011.
25 Rehm J, Samokhvalov A V, Neuman M G, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health 2009; 9: 450.
26 World Health Organization. Anti-tuberculosis drug resistance in the world. Fourth global report. WHO/HTM/TB/2008.394. Geneva, Switzerland: WHO, 2008.
27 Keshavjee S, Gelmanova I Y, Farmer P E, et al. Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. Lancet 2008; 372: 1403–1409.
28 Shin S S, Pasechnikov A D, Gelmanova I Y, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. Int J Tuberc Lung Dis 2007; 11: 1314–1320.
29 Centers for Disease Control and Prevention. Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004. MMWR 2006; 55: 301–305.
30 Laserson K F, Thorpe L E, Leimane V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2005; 9: 640–645.
31 Gelmanova I Y, Taran D V, Mishustin S P, Golubkov A A, Solovyova A V, Keshavjee S. 'Sputnik': a programmatic approach to improve tuberculosis treatment adherence and outcome among defaulters. Int J Tuberc Lung Dis 2011; 15: 1373–1379.
32 Kittikraisak W, Burapat C, Kaewsa-ard S, et al. Factors associated with tuberculosis treatment default among HIV-infected tuberculosis patients in Thailand. Trans R Soc Trop Med Hyg 2009; 103: 59–66.
33 Gajalakshmi V, Peto R, Kanaka T S, Jha P. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43 000 adult male deaths and 35 000 controls. Lancet 2003; 362: 507–515.
34 Jiang J, Liu B, Nasca P C, et al. Smoking and risk of death due to pulmonary tuberculosis: a case-control comparison in 103 population centers in China. Int J Tuberc Lung Dis 2009; 13: 1530–1535.
35 Mathew T, Shields A, Yanov S, et al. Performance of the alcohol use disorders identification test among tuberculosis patients in Russia. Subst Use Misuse 2010; 45: 598–612.
36 Greenfield S F, Shields A, Connery H S, et al. Integrated management of physician-delivered alcohol care for tuberculosis patients: design and implementation. Alcohol Clin Exp Res 2010; 34: 317–330.
37 Mathew T A, Yanov S A, Mazitov R, et al. Integration of alcohol use disorders identification and management in the tuberculosis programme in Tomsk Oblast, Russia. Eur J Public Health 2009; 19: 16–18.

RÉSUMÉ

CONTEXTE : L'utilisation d'alcool augmente le risque de tuberculose multirésistante (MDR-TB) et constitue un défi pour un traitement de la TB-MDR couronné de succès, y compris la possibilité d'effets indésirables supplémentaires.

OBJETIF : Investiguer l'association entre la consommation d'alcool au cours du traitement de la TB-MDR et d'autre part les effets indésirables (AE) et les résultats du traitement dans une cohorte de patients à Tomsk, Russie.

SCHÉMA : On a recueilli les données rétrospectives de 2000 à 2004 concernant 407 patients TB-MDR à Tomsk. On a évalué par régression logistique les facteurs en association avec les résultats du traitement.

RÉSULTATS : Au cours du traitement, il y a eu 253 (62,2%) personnes ayant consommé l'alcool (« les buveurs ») et 367 chez lesquels au moins un effet indésirable a été documenté. On n'a pas noté de différences significatives en matière de fréquence des effets indésirables entre les buveurs et les non-buveurs. Les résultats finaux du traitement sont moins favorables chez les buveurs (OR 0,28 ; IC95% 0,18–0,45). Chez les buveurs, un résultat favorable du traitement est en association avec l'adhésion à au moins 80% des doses prescrites (OR 2,89 ; IC95% 1,30–6,43) et avec l'apparition d'un effet indésirable exigeant l'arrêt du traitement (OR 2,49 ; IC95% 1,11–5,59).

CONCLUSION : Au cours du traitement de la TB-MDR, l'utilisation d'alcool ne semble pas accroître le risque d'effets indésirables. Elle est toutefois en association avec de médiocres résultats. Nos observations suggèrent que les individus buvant de l'alcool doivent être suivis de très près pour optimiser l'adhésion thérapeutique et prendre en charge les effets indésirables.

RESUMEN

MARCO DE REFERENCIA: El consumo de alcohol aumenta el riesgo de padecer tuberculosis multidrogorresistente (TB-MDR) y constituye un obstáculo al tratamiento exitoso de esta enfermedad, entre otras razones por la posibilidad de aparición de reacciones adversas adicionales. En el presente estudio se investigó la asociación entre el consumo de alcohol durante el tratamiento de la TB-MDR, las reacciones adversas y los desenlaces terapéuticos en una cohorte de pacientes en Tomsk, en Rusia.

MÉTODOS: Se recogieron en forma retrospectiva los datos de 407 pacientes registrados con TB-MDR entre el 2000 y el 2004 en Tomsk. Se evaluaron los factores asociados con los desenlaces terapéuticos mediante un análisis de regresión logística.

RESULTADOS: De los 407 pacientes, 253 (62,2%) consumían alcohol durante el tratamiento ('bebedores') y 367 (90,2%) presentaron como mínimo una reacción adversa documentada. No se observaron diferencias en la frecuencia de reacciones adversas entre los pacientes bebedores y los no bebedores. Los bebedores alcanzaron desenlaces terapéuticos menos favorables (OR 0,28; IC95% 0,18–0,45). En los bebedores, un desenlace favorable se asoció con un cumplimiento terapéutico mínimo del 80% de las dosis previstas (OR 2,89; IC95% 1,30–6,43) y con la aparición de una reacción adversa que hubiese precisado la interrupción del tratamiento (OR 2,49; IC95% 1,11–5,59).

CONCLUSIÓN: El consumo de alcohol no pareció aumentar el riesgo de aparición de reacciones adversas durante el tratamiento de la TB-MDR. Sin embargo, este consumo se asoció con desenlaces desfavorables. Los resultados del estudio indican que los consumidores de alcohol deberían recibir una atención enérgica, con el objeto de lograr el máximo cumplimiento terapéutico y tratar las reacciones adversas.