Smoking and 2-month culture conversion during anti-tuberculosis treatment

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SUMMARY

OBJECTIVE—To investigate risk factors for delayed sputum culture conversion to negative during anti-tuberculosis treatment, with an emphasis on smoking.

DESIGN—Nested case-control study of adults with non-cavitary, culture-confirmed pulmonary tuberculosis (TB) participating in an anti-tuberculosis treatment trial in Brazil. A case of delayed culture conversion was a patient who remained culture-positive after 2 months of treatment. Odds ratios with 95% confidence intervals were calculated.

RESULTS—Fifty-three cases and 240 control patients were analyzed. Smokers had three-fold greater odds of remaining culture-positive after 2 months of treatment ($P = 0.007$) than non-smokers, while smokers and ex-smokers who smoked >20 cigarettes a day had two-fold greater odds of remaining culture-positive after 2 months of treatment ($P = 0.045$).

CONCLUSION—Cigarette smoking adversely affects culture conversion during anti-tuberculosis treatment. Support for smoking cessation should be considered to improve outcomes in TB control programs.

Keywords

pulmonary tuberculosis; smoking; culture conversion

TOBACCO USE is among the leading preventable causes of death worldwide,[1] and is a major contributor to respiratory diseases, including tuberculosis (TB).[2] Smoking reduces normal mucociliary clearance of tracheobronchial secretions and impairs alveolar macrophage function against *Mycobacterium tuberculosis*.[3]

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Culture conversion to negative after the first 2 months of treatment is a widely used measure of bacteriologic response to therapy in anti-tuberculosis treatment trials, and is associated with long-term cure.[4] Delayed sputum conversion prolongs the time during which patients are infectious and capable of transmitting TB to others in their community. Several studies have examined the impact of smoking on sputum smear and culture conversion and outcomes of TB treatment.[2] Smoking did not affect smear conversion in a study from Kuwait,[5] whereas smoking and bilateral cavitary disease increased the risk of culture positivity two fold after the first 2 months of treatment in a cohort of non-human immunodeficiency virus (HIV) infected patients with drug-susceptible TB in Spain.[6] Batista et al. recently reported that smoking was associated with a 2.5-fold increased risk of relapse after treatment in 754 patients in Brazil.[7] However, most earlier studies did not control for confounding by other factors associated with delayed response to treatment, such as non-adherence to treatment, alcohol use and cavitary disease.[8] To further examine the impact of smoking and other factors on bacillary clearance and response to anti-tuberculosis treatment, we analyzed sputum culture status during the first 2 months of treatment in adults with non-cavitary pulmonary TB participating in a TB treatment trial.

METHODS

Patients screened in Brazil for a Phase 2 anti-tuberculosis treatment trial between December 2002 and August 2006 were evaluated for the analysis. The parent trial was a randomized multicenter trial assessing whether anti-tuberculosis treatment with available first-line drugs could be shortened from 6 to 4 months in HIV-negative adults aged 18–60 years with smear-positive or -negative, culture-confirmed initial episodes of newly diagnosed, drug-susceptible, non-cavitary pulmonary TB whose sputum cultures converted to negative after the first 2 months of treatment. Relatively normal hematologic, renal and hepatic function (serum aspartate aminotransferase and total bilirubin) was required for enrollment. The study treatment regimens consisted of 2 months of daily isoniazid (H), rifampin (R), pyrazinamide (Z) and ethambutol (E), followed by 4 months of daily HR (6-month standard short-course chemotherapy), or 2 months of daily HRZE, followed by 2 months of daily HR. At least 5 of the 7 weekly doses of anti-tuberculosis treatment were administered by directly observed therapy (DOT). All patients were followed monthly during treatment by examination and sputum smear and culture on solid and Mycobacteria Growth Indicator Tube (MGIT) media, and every 3 months thereafter for a total of 30 months after beginning anti-tuberculosis treatment.

Information on demographic characteristics, including alcohol use and symptoms of TB, was collected using standardized questionnaires by trained study physicians and nurses. Smears and cultures were performed in quality controlled laboratories. Chest X-rays (CXR) were read by qualified clinicians using standardized reporting forms. Full particulars about the parent clinical trial have been published,[9] and are also available at www.clinicaltrials.gov (ClinicalTrials.gov Identifier NCT00130247).

The study protocol was approved by the local and national ethics committees at all trial sites. All participants gave informed consent for participation, including HIV testing, which was performed using an approved HIV enzyme immunoassay.

Patients were divided into cases and controls based on sputum culture status after 2 months of treatment. Cases were patients who remained culture-positive after 2 months of treatment. At least four age- (within 5 years) and sex-matched patients whose sputum cultures had converted to negative after 2 months were selected as controls for comparison. This substudy was approved by the Ethics Committee of the Universidade Federal do Espírito Santo, Vitoria, Brazil.

Continuous variables were compared using the Mann-Whitney test, and categorical variables were compared using the χ^2 test with SPSS version 15.0 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA). Univariate logistic regression was performed for each variable of interest. To examine the relationship between the number of cigarettes smoked daily and culture conversion, the variable number of cigarettes was analyzed using the median value to dichotomize this variable. All variables with an odds ratio (OR) and P value < 0.10 were then included in a multivariate logistic regression for the calculation of adjusted ORs (OR_{adj}).

RESULTS

Of 714 patients screened in Brazil for the parent clinical trial,[9] 360 were available for the analysis; 354 were excluded due to other medical comorbidities, including diabetes mellitus, asthma, rheumato-logic disease and HIV infection, or negative pretreatment cultures for *M. tuberculosis*.

Of the 360 patients eligible for the analysis, 53 (15%) were sputum culture-positive after 2 months of anti-tuberculosis treatment and were considered as cases; 240 age- and sex-matched controls who were culture-negative after 2 months of treatment were selected for comparison. The median age of all subjects was 37 years; 66% were males. Demographic characteristics, including educational, marital and employment status, did not differ between cases and controls (Table 1); 21% of the cases consumed alcohol compared to 19% of controls ($P = 0.74$). The amount of alcohol consumed did not differ between cases and controls.

In a univariate analysis (Tables 1 and 2) comparing never smokers and current smokers, the extent of disease on CXR[10] (OR 1.90, 95% confidence interval [CI] 0.84–4.08, $P = 0.07$) and smoking status (OR 2.28, 95%CI 1.02–5.33, $P = 0.04$) were associated with significantly increased odds for remaining culture-positive after 2 months of treatment.

Among smokers and ex-smokers, the median number of cigarettes a day was 20 (interquartile range [IQR] 8–20). The median number of cigarettes smoked was greater (20 per day, IQR 10–20) among cases than among controls (15 per day, IQR 5–20, Mann-Whitney test $P = 0.036$). The number of years of smoking did not differ between cases and controls.

In a multivariate analysis, which included pretreatment extent of disease on CXR, smoking status and the number of patients who smoked >20 cigarettes a day, we found that current smoking at the time of TB diagnosis (OR_{adj} 3.04, 95%CI 1.35–6.83) and smoking >20

cigarettes a day (OR_{adj} 2.09, 95%CI 1.02–4.33) were independently associated with 2-month culture conversion.

DISCUSSION

Effective anti-tuberculosis treatment and reduced risk of infecting others in the community rely on rapid killing of tubercle bacilli during combination chemotherapy.[11] Culture conversion after the first 2 months (intensive phase) of treatment is a widely used surrogate measure of response to anti-tuberculosis treatment. Delay in 2-month culture conversion is associated with treatment failure and relapse.[4]

In our study, we found that patients who smoked had three-fold greater odds of remaining sputum culture-positive after 2 months of treatment than non-smokers, and that smokers who smoked more cigarettes each day were also more likely to have delayed culture conversion than those who smoked fewer cigarettes each day. In earlier studies from Kuwait and India, smoking did not affect smear conversion during treatment,[5,12] whereas time to conversion was longer among smokers than among non-smokers in South Africa.[13] Smoking and bilateral cavitary disease increased the risk of culture positivity after the first 2 months of treatment by two fold in a cohort of non-HIV-infected patients with drug-susceptible TB in Spain.[6] Batista et al. also recently reported that smoking was associated with a 2.5-fold increased risk for relapse after treatment in a cohort of 754 patients in Brazil.[7] However, most studies did not control for potential confounding by other factors associated with delayed response to anti-tuberculosis treatment, such as cavitary disease and alcohol use, and patients were not treated under DOT.[2] We observed a significant negative impact of smoking on culture conversion in patients without destructive cavitary TB. Forty per cent of the patients in our study consumed alcohol; the proportion of drinkers did not differ between cases and controls. This suggests that concomitant alcohol use is unlikely to be a confounder in our case-control study.

Our study had several limitations. Due to the design of the parent trial, we were unable to examine differences in culture conversion after 2 months, and studied only patients with non-cavitary TB. Smoking status was based on self-report, and was not confirmed by biochemical testing. We did not collect data regarding whether patients stopped smoking after beginning anti-tuberculosis treatment. As culture non-conversion occurred in 15% of the patients in the analysis and was not rare, the OR may overestimate the relative risk of the association between smoking and culture conversion. Strengths of this study include the use of standardized questionnaires and patient follow-up, treatment under DOT and the use of a quality controlled TB laboratory for cultures.

In conclusion, we found that smoking significantly reduced bacillary clearance during anti-tuberculosis treatment in patients with non-cavitary disease. Our data add to increasing evidence of the adverse impact of smoking on response to anti-tuberculosis treatment, and support the need for integrated action on smoking cessation by national TB and tobacco control programs.[1,2,14] Health care systems need to create opportunities to encourage and assist patients diagnosed with TB to stop smoking to improve treatment outcomes.[1]

Acknowledgements

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Table 1

Odds ratio for positive sputum culture at 2 months according to patients' demographic characteristics

Variable	Cases (n = 53) n (%) or median [IQR]	Controls (n = 240) n (%) or median [IQR]	OR (95%CI)	*P* value
Male	34 (64)	158 (66)	0.93 (0.40–1.83)	0.82
Age, years	37 [32–43]	36 [27–44]	—	0.85
Body mass index, kg/m^2	20 [18–23]	21 [19–25]	—	0.48
Education				
None	30 (57)	117 (49)	1.00	—
Primary school	15 (28)	73 (31)	1.25 (0.60–2.67)	0.52
Middle or high school	8 (15)	48 (20)	1.54 (0.63–4.16)	0.21
Marital status				
Single	23 (43)	80 (34)	1.00	—
Steady partner	23 (43)	116 (49)	1.45 (0.72–2.90)	0.25
Divorced	7 (13)	40 (17)	1.64 (0.61–4.91)	0.29
Employed	33 (62)	165 (69)	0.75 (0.39–1.48)	0.36
Alcohol consumption	11 (21)	35 (19)	1.53 (0.65–3.40)	0.26
Smoking status				
Never smoked	12 (23)	78 (33)	1.0	0.04
Current smoker	26 (49)	74 (31)	2.28 (1.02–5.33)	
Ex-smoker	15 (28)	88 (37)	1.11 (0.45–2.76)	

IQR = interquartile range; OR = odds ratio; CI = confidence interval.

Table 2

OR for positive sputum culture at 2 months according to patients' clinical status

Variable	Cases (*n* = 53) *n* (%)	Controls (*n* = 240) *n* (%)	OR (95%CI)	*P* value
Extent on chest radiograph[10]				
Minimal	13 (24.6)	35 (14.6)	1.90 (0.84–4.08)	0.07
Moderately or far advanced	40 (75.4)	205 (85.4)		
Symptoms				
Cough	45 (84)	202 (84)	1.05 (0.44–2.80)	0.89
Sputum production	40 (75)	192 (80)	0.77 (0.37–1.69)	0.46
Fever	35 (66)	155 (64)	1.06 (0.55–2.12)	0.84
Chills	30 (56)	113 (47)	1.46 (0.77–2.80)	0.21
Night sweats	28 (52)	140 (58)	0.8 (0.42–1.52)	0.46
Poor appetite	29 (54)	116 (48)	1.29 (0.68–2.46)	0.40
Weight loss	38 (73)	176 (73)	0.98 (0.48–2.10)	0.96
Hemoptysis	13 (24)	74 (31)	0.72 (0.34–1.49)	0.36
Chest pain	39 (73)	156 (65)	1.5 (0.74–3.16)	0.23
TB contact	20 (37)	95 (39)	0.92 (0.47–1.77)	0.80

OR = odds ratio; CI = confidence interval; TB = tuberculosis.