

Characterization of hepatitis C infection in tuberculosis patients in an urban city in the USA

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SUMMARY

The impact of hepatitis C virus infection (HCI), the most common bloodborne virus infection in the USA, on outcome of active tuberculosis (TB) treatment is largely unknown. We aimed to describe characteristics of TB patients with hepatitis C virus infection (TB-HCI) in King County, Washington, including TB treatment duration and outcome. We reviewed 1510 records of patients treated for active TB at the Public Health – Seattle & King County Tuberculosis Control Program between 2000 and 2010, and identified 53 with HCI. Advanced age, being born in the USA, HIV infection, homelessness and injection drug use were independently associated with HCI in TB cases. Independent factors associated with increased treatment duration included HIV infection, excess alcohol use, extrapulmonary TB, and any drug-resistant TB disease. Our findings suggest that TB-HCI patients can be successfully treated for active TB without extending treatment duration.

Key words: Hepatitis C, tuberculosis (TB).

INTRODUCTION

Worldwide, 8·8 million incident cases and 1·45 million deaths from tuberculosis (TB) were reported in 2010. Despite falling TB incidence rates, the World Health Organization's Stop TB Partnership objective of halving TB prevalence rates by 2015 compared to 1990 is unlikely to be achieved [1]. Recent approaches to improving TB control include targeted interventions, such as active case-finding in specific high-risk groups. Identification and characterization of the determinants of TB disease progression are necessary,

so that healthcare efforts can be aimed at those who are most likely to develop and transmit TB.

Hepatitis C infection is a prevalent disease that may influence TB outcome. The global burden of chronic hepatitis C virus infection (HCI) is increasing; current prevalence is estimated at 130–170 million persons, with more than 350 000 deaths each year [2]. Hepatitis C is the most common chronic bloodborne virus infection in the USA [3, 4], with about 75% of cases unaware of their infection [5]. Despite the prevalence of HCI globally, and the potential to affect the clinical course of TB by increasing liver toxicity [6–10], the impact of HCI on risk of TB disease and outcome of active TB treatment has received little attention [11, 12].

We hypothesized that TB patients with hepatitis C virus infection (TB-HCI) might have

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socio-demographic characteristics such as homelessness that differentiate them from TB-only patients and may influence TB treatment outcome. Of homeless people, factors that favour TB transmission such as alcohol and substance abuse, and crowded living situations have been reported in recent TB outbreaks in the USA [13, 14]. These same factors may impact the timely completion of TB treatment in HCI-TB patients, requiring increased resources, and increasing the potential for further transmission in a community. In this study, we evaluated patients in King County, Washington, where the annual rate of reported chronic HCI cases is 95/100 000 and has been stable from 2000 to 2010 [15, 16], and where the annual rate of TB continues to be higher than the incidence rate in the USA (3.6/100 000 in 2010) [17]. We characterized the patients with dual hepatitis C and TB infections, compared to patients infected with TB-only receiving care in the Public Health – Seattle & King County Tuberculosis Control Program, and determined whether hepatitis C infection influenced active TB treatment outcome.

STUDY POPULATION AND METHODS

Study population

We reviewed the case records of all the patients treated for active TB at the Public Health – Seattle & King County Tuberculosis Control Program from January 2000 to December 2010. We identified patients with known HCI, the majority having chronic infection, from the Public Health – Seattle & King County Hepatitis C Surveillance Program. Using probabilistic matching of demographic variables, we identified 53 with known HCI at the time of active TB treatment in the records of 1510 TB and 13 218 HCI cases.

Data collection

We collected data on all TB patients in King County through the Report of Verified Case of Tuberculosis (RVCT) form used in the US National Tuberculosis Surveillance System [17] and from retrospective medical record review in the TB-HCI patients. We extracted characteristics of the population, focusing on known and potential risk factors for TB and HCI, from the RVCT at the time of TB diagnosis [17]. These characteristics included: age at the time of TB diagnosis, gender, race/ethnicity, US born *vs.* foreign born, HIV status, resident of correctional

facility at the time of diagnosis and, within the year prior to TB diagnosis: any homelessness, injection drug use (IDU) or excess alcohol use. Characteristics of TB disease included: pulmonary *vs.* extrapulmonary disease, positive *vs.* negative initial smear and culture results, any initial drug resistance, and the presence of cavitary disease on chest radiograph (CXR). Outcomes of TB treatment were captured in the RVCT as completion of therapy, death, or loss to follow-up. TB therapy administration was defined as directly observed therapy (DOT), DOT and self-administered, or self-administered only. Duration of treatment of active TB depends primarily on the location of the disease and drug susceptibility testing. The recommendations of the most recent guidelines are 6 months (26 weeks) of treatment for susceptible pulmonary and extrapulmonary TB except for bone and joint involvement and tuberculous meningitis for which they recommend 6–9 and 9–12 months, respectively [18]. For drug-resistant TB, the length of treatment is guided by culture data. We calculated actual treatment duration by determining the time elapsed from the start date of anti-TB medications until the end date using RVCT data. In addition, we examined aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and medication side-effects in a subset of 48 TB-HCI patients who completed treatment and had data available.

Statistical analysis

Baseline characteristics were compared between TB-HCI and TB-only patients using *t* tests or Wilcoxon rank-sum tests for continuous parametric or non-parametric variables, respectively, or χ^2 to compare categorical variables. We used logistic regression to analyse patient characteristics and potential risk factors for HCI in patients with TB. We examined the relationship between the clinical presentation of TB disease and the duration of active TB treatment between TB-HCI and TB-only groups using linear regression.

To identify independent factors associated with treatment duration in TB patients, we generated a multivariable linear regression model with risk factors selected *a priori*, namely: age, gender, race, birth place, site of disease, drug resistance, HIV status, IDU, alcohol use, and homelessness as well as HCI status. We compared a complete case analysis with a model where we imputed missing values. Assuming that data were missing at random, we created a

Table 1. *Socio-demographic characteristics of tuberculosis (TB) cases by hepatitis C status*

Characteristics	TB, hepatitis C (<i>n</i> = 52)	TB only (<i>n</i> = 1369)
Age (yr) at the time of TB diagnosis, median (IQR)	48 (43–53)	41 (28–58)
Gender (male)	36 (69)	789 (58)
Race		
White	15 (29)	164 (12)
American Indian or Alaskan Native	14 (27)	44 (3)
Asian	6 (12)	605 (44)
Black or African American	13 (25)	373 (27)
Pacific Islander	2 (4)	36 (3)
Hispanic	2 (4)	141 (10)
US born	42 (81)	253 (19)
HIV infected	12 (24)	66 (6)
Homelessness	37 (71)	165 (12)
Intravenous drug use	14 (29)	15 (1)
Excess alcohol use	29 (59)	128 (10)
Resident in correctional facility	2 (4)	22 (2)

Values given are *n* (%) unless stated otherwise.

IQR, Interquartile range.

multiple imputations by chained equation (MICE) model to account for missing data using the same variables that we included in the full model (age, gender, race, birth place, site of disease, drug resistance, HIV status, IDU, alcohol use, homelessness). Data were missing on drug susceptibility testing (8.1% in TB-HCI and 15.3% in TB-only groups), HIV (5.6% in TB-HCI and 19.4% in TB-only groups), excess alcohol use (5.6% in TB-HCI and 3.9% in TB-only groups), and IDU (7.4% TB-HCI and 4% in TB-only groups). The imputation model was repeated 10 times. The estimates were calculated taking into account both inter- and intra-variation of imputed datasets. The level for determining statistical significance was set at $P < 0.05$. We performed all data analyses using Stata version 11 (StataCorp., USA). The Internal Review Board of the University of Washington approved this study.

RESULTS

Between January 2000 and December 2010, 1510 cases of active TB were reported in King County; 53 patients were also listed in the hepatitis C registry. After excluding 22 cases that were missing outcome data and 67 cases that were aged <15 years, our analytical cohort consisted of 1421 patients of whom 52 were in the TB-HCI group.

Characteristics of TB-HCI patients

The TB-HCI patients had significantly different socio-demographic characteristics compared to the TB-only patients (Table 1). TB-HCI patients were more likely to be white and American Indian compared to the TB-only group. In addition, TB-HCI patients were more likely to be US-born, HIV-infected, and homeless compared to TB-only patients. TB-HCI patients were also more likely to have a history of IDU and excess alcohol use during the year prior to TB diagnosis. These differences were statistically significant ($P < 0.001$ for both).

In multivariable logistic regression, independent risk factors for HCI in persons with TB included older age at time of TB diagnosis [odds ratio (OR) 1.40, 95% confidence interval (CI) 1.08–1.81]; being born in the USA (OR 3.94, 95% CI 1.28–12.1); homelessness (OR 3.44, 95% CI 1.27–9.27) and IDU (OR 6.64, 95% CI 2.45–18.0), controlling for race, HIV status, residence in a correctional facility, and excess alcohol use (Table 2).

Clinical characteristics of TB disease presentation by HCI status

TB disease limited to pulmonary involvement was significantly more common in the TB-HCI group (79% vs. 53%). In addition, the TB-HCI group was

Table 2. Unadjusted and adjusted odds ratios for risk factors associated with hepatitis C infection in tuberculosis patients

Characteristics	Unadjusted			Adjusted		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.13	1.0–1.02	0.07	1.40	1.08–1.81	0.01
Race						
White	6.45	1.45–28.7	0.014	1.60	0.29–8.74	0.59
American Indian or Alaskan Native	22.4	4.9–102.5	<0.001	1.75	0.30–10.0	0.53
Asian	0.67	0.14–3.50	0.663	1.23	0.21–7.27	0.82
Black or African American	2.45	0.55–11.0	0.241	0.98	0.18–5.22	0.98
Pacific Islander	3.92	0.53–28.8	0.180	3.79	0.44–32.8	0.23
Hispanic	Ref.			Ref.		
US born	18.5	9.17–37.4	<0.001	3.94	1.28–12.1	0.02
HIV infected	5.10	2.55–10.2	<0.001	2.22	0.81–6.06	0.12
Homelessness	17.9	9.65–33.5	<0.001	3.44	1.27–9.27	0.02
Intravenous drug use	34.9	15.7–77.8	<0.001	6.64	2.45–18.0	<0.001
Excess alcohol use	13.56	7.46–24.7	<0.001	1.60	0.63–4.07	0.32

OR, Odds ratio; CI, confidence interval.

more likely to have smear-positive and culture-positive disease at the time of diagnosis compared to the TB-only group. There was no difference in the proportion of patients presenting with drug-resistant strains or cavitory disease on CXR (Table 3).

Treatment outcome of TB-HCI patients

Next, we analysed treatment outcome for the 1421 patients who were started on treatment for active TB. From the TB-HCI group, 45 (87%) patients completed treatment, four (8%) patients died, three (6%) were lost to follow-up; from the TB-only group 1230 (90%) completed treatment, 66 (5%) patients died and 73 (5%) were lost to follow-up. These differences were not significant ($P=0.63$). Exclusive DOT was significantly higher in the TB-HCI group than the TB-only group (94% vs. 66%; OR 7.27, 95% CI 1.76–30.1). There was no difference in proportion with negative culture conversion between the two groups (Table 3).

Duration of TB treatment by HCI status

Of the 45 TB-HCI and 1230 TB-only patients who completed therapy, the TB-HCI group took 34 weeks (IQR 20–45) to finish treatment on average, whereas TB-only patients spent 30 weeks (IQR 27–41) to finish active TB treatment; this difference was not statistically significant ($P=0.3$). In a multivariable linear regression, independent factors associated with increased treatment duration included HIV infection

($\beta=5.70$, 95% CI 1.78–9.62), excess alcohol use ($\beta=4.29$, 95% CI 0.73–7.85), extrapulmonary TB ($\beta=2.80$, 95% CI 1.14–4.43) and any drug-resistance pattern ($\beta=8.89$, 95% CI 6.36–11.4), controlling for age, gender, race, birth place, IDU and homelessness (Table 4). HCI status was not a significant independent factor for increased duration of treatment ($\beta=0.863$, 95% CI –4.5 to 6.23). We found similar results when accounting for missing data with an imputation model (Table 4).

Side-effects of therapy in TB-HCI patients treated with shorter vs. longer duration of therapy

In a subset of TB-HCI patients that had transaminase and side-effect data available, we examined differences according to shorter vs. longer duration of therapy, dichotomized as treatment duration less than or greater than the overall median value of 33.8 weeks. We found that there was no significant difference in AST or ALT baseline values between these groups. Similarly, there was no significant difference in side-effects (nausea and vomiting, rash, diarrhoea, peripheral neuropathy, vision changes) in patients with shorter vs. longer duration of therapy (Table 5).

DISCUSSION

To our knowledge, this is the first study to compare differences in clinical presentation and in treatment

Table 3. Clinical characteristics of tuberculosis (TB) disease presentation and treatment outcome by hepatitis C status

Characteristics	TB, hepatitis C n (%)	TB only n (%)	OR	95% CI	P value
Site of TB disease					
Pulmonary	41 (79)	727 (53)	3.29	1.68–6.46	0.001
Extrapulmonary	11 (21)	642 (47)			
Initial smear					
Positive	29 (60)	447 (40)	2.30	1.27–4.14	0.006
Negative	19 (40)	673 (60)			
Initial culture					
Positive	43 (90)	807 (73)	3.26	1.28–8.31	0.013
Negative	5 (10)	306 (28)			
Initial drug susceptibility testing					
Any drug resistance	3 (6)	191 (16)	0.37	0.11–1.19	0.095
Drug sensitive	44 (94)	1025 (84)			
Cavitary disease on CXR					
Present	12 (28)	245 (24)	1.25	0.63–2.47	0.519
Not present	31 (72)	792 (76)			
Culture conversion documented					
Yes	37 (93)	720 (87)	1.83	0.55–6.05	0.320
No	3 (8)	107 (13)			
Reason to discontinue TB medications					
Completed treatment	45 (87)	1230 (90)			
Died	4 (8)	66 (5)	1.67	0.58–4.75	0.347
Loss/other	3 (6)	73 (5)	1.12	0.34–3.70	0.848
TB therapy administration					
Direct observed therapy (DOT)	49 (94)	897 (66)	7.27	1.76–30.1	0.006
DOT and self-administered	1 (2)	202 (15)	0.66	0.06–7.31	0.734
Self-administered only	2 (4)	266 (20)			

OR, Odds ratio; CI, confidence interval, CXR, chest radiograph.

outcome for active TB in patients with and without HCl in the USA. We found that TB-HCl patients are a distinct group compared to patients with TB-alone in this cohort from a US urban setting. In a multivariable analysis, independent factors associated with HCl in TB patients included older age, HIV infection, IDU, and homelessness. In addition, we found that the clinical presentation of TB disease was different in HCl-infected patients, with a greater proportion of co-infected patients having pulmonary, smear- and culture-positive TB. Finally, most TB-HCl patients successfully completed therapy, and outcomes such as smear conversion, death and lost to follow-up were no different when comparing HCl-TB patients to TB-only patients. Although the treatment duration was on average longer (34 vs. 30 weeks), TB-HCl patients did not have a statistically significant increase in the duration of active TB treatment compared to TB-only patients.

Previous studies have shown the association of HCl with other infectious diseases including TB, even when excluding HIV or other immunocompromised patients [19, 20]. Several studies around the world have outlined the prevalence and risk factors for HCl in patients with active TB. In Eastern Europe a high prevalence of HCl (12–22.4%) has been reported with low rates of HIV infection (0.7–1.1%) in TB patients in the Republic of Georgia [21, 22]. In Thailand, Argentina, and Brazil, HCl infection has been reported to have a prevalence as high as 31.5% in TB patients, accompanied by high prevalence of HIV infection [23–25]. A recent meta-analysis revealed substantial heterogeneity in the prevalence estimates for TB, HCl and HIV in homeless people around the world, which highlights the need for locally based studies to inform specific public health measures [11]. In our study the proportion of patients with HCl in the active TB patients was lower than in

Table 4. Factors associated with prolonged tuberculosis treatment duration in King County, 2000–2010

Characteristics	Complete case analysis (n=918)			Multiple imputations analysis (n=1130)		
	β coeff.	95% CI	P value	β coeff.	95% CI	P value
Hepatitis C virus infection	0.86	−4.50 to 6.23	0.80	−0.701	−5.55 to 4.15	0.78
Age	0.49	−0.05 to 1.02	0.08	0.532	0.08 to 0.98	0.02
Gender	1.86	−0.05 to 3.77	0.06	1.409	−0.25 to 3.07	0.10
HIV infected	5.70	1.78 to 9.62	0.01	4.212	0.74 to 7.69	0.09
Excess alcohol use	4.29	0.73 to 7.85	0.02	4.02	0.74 to 7.31	0.02
Extrapulmonary tuberculosis	2.81	0.95 to 4.67	0.01	2.784	1.14 to 4.43	0.01
Any drug resistance	8.89	6.36 to 11.4	<0.001	8.035	5.72 to 10.4	<0.001

Adjusted for race, birth place, intravenous drug use, and homelessness.

Table 5. Side-effects of tuberculosis treatment on patients with tuberculosis and hepatitis C co-infection

Characteristics	Duration of treatment		P value
	Shorter (n=24)	Longer (n=24)	
Baseline AST ($\mu\text{g/dl}$)	38 (27–55)	25 (15–43)	0.14
Baseline ALT ($\mu\text{g/dl}$)	42 (27–73)	37 (29–54)	0.73
Highest AST ($\mu\text{g/dl}$)	75 (45–145)	92 (38–126)	0.58
Highest ALT ($\mu\text{g/dl}$)	62 (33–174)	60 (28–88)	0.23
Side-effects			
Nausea/vomiting	10 (59)	15 (71)	0.42
Rash	7 (41)	14 (67)	0.12
Diarrhoea	6 (35)	11 (52)	0.29
Peripheral neuropathy	10 (59)	12 (57)	0.92
Vision changes	3 (27)	2 (22)	0.80

AST, Aspartate aminotransferase; ALT, alanine aminotransferase.

Values presented as median (interquartile range) or n (%).

these other reported settings. This may be due to under-reporting of HCI, as chronic HCI became reportable in Washington State in 2000, and recommendations for chronic HCI screening have been promoted since 2012 [26]. Nevertheless, we identified similar factors such as age, IDU and homelessness as the main risk factors associated with HCI infection in patients with active TB, which similarly have been described in previous studies [11, 27]. Other reports have identified the association of TB with HCI in incarcerated patients [28, 29], whereas in our study incarceration was not a significant risk factor.

Despite having a higher prevalence of behavioural risk factors that might influence the clinical course of TB therapy, we did not find a statistically significant difference in TB treatment outcome when comparing TB-HCI and TB-only patients. TB-HCI patients spent an average of 34 weeks completing

active TB treatment. The majority of TB-HCI patients had pulmonary TB and were sensitive to standard first-line therapy, which may have contributed to a less pronounced difference in treatment duration when comparing TB-HCI and TB-only patients. TB-only patients spent an average of 30 weeks completing treatment, including patients with extrapulmonary TB and drug resistance. These numbers are comparable to a current report [30] where TB-only patients with drug-susceptible TB spent 36 weeks (252 days) on average, to finish active TB treatment. Mitruka and colleagues [27] identified that the highest risk factors for failure to achieve timely completion of TB treatment were combined pulmonary and extrapulmonary disease, homelessness, incarceration and HIV infection. In our study, we also found that extrapulmonary TB and HIV infection were independent factors associated with prolonged treatment duration.

In addition, we found that history of excess alcohol consumption the year prior to TB diagnosis was a significant factor associated with prolonged treatment duration. In Mitruka *et al.*'s study, excess alcohol consumption was combined with IDU and non-IDU within 12 months of diagnosis, and therefore the effect could have been masked.

Our study has several limitations to consider when interpreting its findings. We used a retrospective cohort in which measured HCl serology or viral load were not systematically available. Information about HCl status was obtained from HCl case reporting. It is possible that the TB-only group could have included patients without recognized HCl, which could have resulted in misclassification of patients and biased us away from finding a significant difference in treatment duration between the TB-HCl and TB-only groups. Our dataset did not include liver function tests in TB-only patients, limiting our ability compare degree of liver injury during therapy between TB-only and TB-HCl groups. Finally, our results are limited by sample size, given the relatively small number of patients with TB-HCl despite our large sample size of TB-only patients.

Nonetheless, this is the first study investigating the impact of HCl on risk factors and outcome of active TB treatment in the USA. Our findings draw attention to several behavioral risk factors of TB-HCl patients; they also demonstrate that well executed guideline-based therapy leads to successful treatment for active TB in patients co-infected with TB and HCl. These data are important for TB control programmes to consider in allocating resources for infection control and TB surveillance for programmes that care for a significant number of HCl-infected persons. First, we found a greater likelihood of smear-positive TB in this group. Second, we found that TB-HCl patients were more likely to receive DOT, which may have facilitated the TB therapy completion in a timely manner. In addition, TB-HCl patients were more likely to be homeless; frequently, these patients are placed in housing during treatment. Taken together, these data suggest that TB-HCl patients may require a more intensive level of intervention and greater resource utilization to achieve successful completion of therapy compared to TB-only patients.

CONCLUSIONS

We found that age, being born in the USA, homelessness and IDU were independently associated with

HCl infection in TB cases. Additionally we found that excess alcohol use, HIV infection, extrapulmonary disease and drug-resistant TB were independent predictors of prolonged TB treatment duration. Although the TB-HCl co-infected population had a higher occurrence of social and behavioural factors that can complicate TB treatment, they did not have prolonged TB treatment duration. In our cohort, TB-HCl did not play a statistically significant role in outcome for TB treatment.

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DECLARATION OF INTEREST

None.

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