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The effects of alcohol on spontaneous clearance of acute hepatitis C virus infection in females versus males

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ABSTRACT

Background: Approximately one quarter of persons exposed to hepatitis C virus (HCV) will spontaneously clear infection. We undertook this study to investigate the impact of alcohol on likelihood of HCV spontaneous viral clearance stratified by sex groups.
Methods: Pooled data from an international collaboration of prospective observational studies of incident HIV and HCV infection in high-risk cohorts (the InC3 Study) was restricted to 411 persons (or 560.7 person-years of observation) with documented acute HCV infection and data regarding alcohol use. The predictor of interest was self-reported alcohol use at or after estimated date of incident HCV infection and the outcome was HCV spontaneous clearance. Sex stratified Cox proportional hazards models were used to evaluate the association between alcohol and spontaneous clearance, adjusting for age, race/ethnicity, and *IFNL4* genotype.
Results: The median age was 28.5 years, 30.4% were women, 87.2% were white, and 71.8% reported alcohol use at or after incident infection. There were 89 (21.6%) cases of spontaneous clearance observed, 39 (31.2%) among women and 50 (17.5%) in men ($p < 0.01$). Overall, spontaneous clearance occurred less frequently among participants who drank alcohol compared to those who did not drink (18.9% v. 28.5%, $p = 0.03$). After adjustment for other covariates, alcohol was significantly and independently associated with lower relative hazards for spontaneous clearance of HCV in women (AHR = 0.35; 95% CI: 0.19–0.66; $p = 0.001$) but not in men (AHR = 0.63; 95% CI: 0.36–1.09; $p = 0.10$).
Conclusion: Results indicate that abstaining from drinking alcohol may increase the likelihood of spontaneous clearance among women.

1. Introduction

Hepatitis C virus (HCV) infection is conservatively estimated to affect 1% of the world's population (Gower et al., 2014) and continues to be a global health issue primarily associated with unsafe parenteral injections and injection drug use (Nelson et al., 2011). Effective treatments are available, yet are extremely costly, and many barriers to uptake remain, particularly among people who inject drugs (PWID; Bruggmann, 2012). Approximately 25% of persons exposed to HCV will spontaneously clear the infection without treatment (Micallef et al., 2006; Page et al., 2009). Understand-

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ing the mechanisms underlying clearance can inform strategies to control HCV.

To date, a number of factors have been found to impact HCV spontaneous clearance. CD4+ and CD8+ T-cell responses enhance HCV clearance (Cox et al., 2005; Shoukry et al., 2003), and females are more likely to clear HCV than males (Page et al., 2009), especially if they are homozygous for the C allele of the single nucleotide polymorphism (SNP) rs12979860 (Grebely et al., 2014), which is located within intron 1 of the interferon lambda 4 (*IFNL4*) gene (Prokunina-Olsson et al., 2013). The impact that behavioral exposures, including the effects of alcohol, have on HCV spontaneous clearance is less well studied. In vitro, alcohol increases HCV replication in some models through modulation of interferon signaling pathways and microRNA expression (Bukong et al., 2013; Osna et al., 2015; Ye et al., 2010). Alcohol has been shown to impair adaptive immune responses that are essential for eliminating HCV, including the altering of antigen presentation on immune cells (Osna, 2009; Osna et al., 2009), interfering with key proteasomes involved with degradation of HCV (Osna et al., 2014), and enhancing the effects of HCV on dendritic cell function (Szabo et al., 2006), Prevalence of concurrent alcohol use is high among PWID: one study of young adult injectors found that 68% reported current alcohol use meeting or exceeding cutoffs for hazardous use (Le Marchand et al., 2013).

Observational studies that have examined the impact of alcohol on HCV clearance have shown mixed results. In a large cross-sectional study of HCV-seropositive veterans, individuals with a clinical diagnosis of an alcohol use disorder were half as likely to have an undetectable viral load indicating prior spontaneous clearance (Piasecki et al., 2004). However, two community-based studies did not find significant associations between any alcohol use and HCV clearance (Grebely et al., 2007; Shah et al., 2012). To date, no studies of acute HCV infection have prospectively ascertained the impact of alcohol use on HCV viral clearance or the effect of alcohol on HCV clearance separately among females versus males. Men are more likely to drink alcohol and drink in larger amounts; however, women absorb alcohol more quickly and take longer to metabolize it (Center for Disease Control and Prevention, 2014). Patterns of alcohol consumption have been shown to have differential effects on markers of liver damage in women, compared to men (Stranges et al., 2004), and alcohol has been shown to be associated with more advanced fibrosis at lower levels of intake among women compared to men (Hezode et al., 2003). Furthermore, alcohol use can potentially impact sex hormone levels (Gill, 2000), which have been shown to be important mediators of immune responses to infectious diseases (Bouman et al., 2005).

This study examined the impact of drinking alcohol on likelihood of HCV spontaneous clearance in a large sample of merged cohorts of persons with documented acute HCV who were prospectively followed over time with repeated measures of HCV viral load and drinking self-report. In addition, we assessed whether associations between alcohol and spontaneous clearance differed among women compared to men.

2. Material and methods

2.1. Study design and population

The InC3 study, a collaboration of nine prospective cohorts in the United States, Australia, Canada, and The Netherlands, evaluates HCV and HIV outcomes among people at high risk of HCV, the majority of who have a history of injection drug use, and has been previously described in detail (Grebely et al., 2013). Participants were recruited and prospectively followed between 1979 and 2012. For the current study, only individuals from longitudinal cohorts with documented acute HCV and data on alcohol use are included. Acute HCV was defined as either: 1) HCV seroconversion with an anti-HCV negative test followed by either an anti-HCV positive or HCV RNA-positive test within two years or 2) documented symptomatic HCV infection, defined by a positive anti-HCV/HCV RNA test, jaundice or alanine aminotransferase (ALT) elevation >400 U/L, or history of high-risk exposure within three months of clinical manifestation of acute HCV. Individuals treated for HCV within 26 weeks of incident HCV were excluded, as they were treated within the acute window during which spontaneous clearance could occur.

2.2. Study procedures and laboratory testing

The data collected at each site every one to six months included baseline and longitudinal information on socio-demographic and exposure variables (such as date of birth, sex, ethnicity, housing, parenteral/injecting, and sexual exposures) and HCV testing (anti-HCV and HCV RNA testing). The choice of qualitative and quantitative HCV RNA testing varied by cohort but was consistent at each site. Qualitative HCV RNA testing was performed using the following assays: Versant TMA (<10 IU/mL; Bayer, Pymble, New South Wales, Australia), COBAS AmpliPrep/COBAS Taq-Man (<15 IU/mL; Roche, Branxhburg, NJ), COBAS Aplicore HCV Test (v2.0; <50 IU/mL: Roche Diagnostics, Mannheim, Germany), or discriminatory HCV transcription-mediated amplification component of the Procleix HIV-1/HCV (<12 copies/mL; Gen-Probe, San Diego, CA). Quantitative HCV RNA testing was performed using the Versant HCV RNA 3.0 (<615 IU/mL: Bayer), Cobas Amplicor HCV Monitor (version 2.0; <600 IU/mL; Roche), or an in-house polymerase chain reaction (<1000 IU/mL). HCV genotype was determined by line-probe assay (Versant LiPa1/LiPa2; Bayer) or HCV sequencing at acute HCV detection. Among those with undetectable HCV RNA and available samples, Murex HCV serotyping was performed to determine HCV genotype (Murex Biotech Limited, Dartford, UD). *IFNL4* genotype was determined by sequencing of the RS12979860 single-nucleotide polymorphism, as previously described (Grebely et al., 2014). The total number of participants, those lost to follow-up, and the number defined as having HCV acute infection by different methods and spontaneous clearance outcomes are presented in Fig. 1. All participants provided written informed consent, and cohort protocols were approved by local ethics committees. Approval was also obtained for the merged dataset, which contained no identifiers.

2.3. Study measures

2.3.1. Outcomes. Spontaneous clearance was defined by two consecutive undetectable HCV RNA test results greater than or equal to four weeks apart after date of acute infection. The methods for estimating the date of infection have been previously described (Grebely et al., 2014). Briefly, the date of HCV infection was estimated as either: (1) the midpoint between last negative and first positive anti-HCV test for those whose new infection was identified via anti-HCV seroconversion or (2) the date of first HCV RNA positive visit minus 28 days for those whose new infection was identified via a RNA positive/anti-HCV negative test. The estimated date of clearance was defined as the midpoint between the first of two consecutive undetectable qualitative HCV RNA tests and the last sample with detectable HCV RNA (or the estimated date of infection, in the event that the sample collected at the time of acute detection was HCV RNA undetectable). Time to clearance was calculated as the time from the estimated date of infection to the estimated date of clearance. For those without clearance, follow-up time was calculated from the estimated date of infection until the date of the last therapy-naïve detectable HCV RNA test. For participants with only one undetectable HCV RNA as their last mea-