Drug and Alcohol Dependence 154 (2015) 125–131

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Evidence of continued injecting drug use after attaining sustained treatment-induced clearance of the hepatitis C virus: Implications for reinfection☆

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ARTICLE INFO

Article history:
Received 29 January 2015
Received in revised form 15 June 2015
Accepted 16 June 2015
Available online 2 July 2015

Keywords:
Hepatitis C
Sustained viral response
People who inject drugs
Reinfection
Record linkage

ABSTRACT

Background: People who inject drugs (PWID) are at the greatest risk of hepatitis C virus (HCV) infection, yet are often denied immediate treatment due to fears of on-going risk behaviour. Our principal objective was to examine evidence of continued injecting drug use among PWID following successful treatment for HCV and attainment of a sustained viral response (SVR).
Methods: PWID who attained SVR between 1992 and June 2012 were selected from the National Scottish Hepatitis C Clinical Database. Hospitalisation and mortality records were sourced for these patients using record linkage techniques. Our primary outcome variable was any hospitalisation or death, which was indicative of injecting drugs post-SVR.
Results: The cohort comprised 1170 PWID (mean age at SVR 39.6y; 76% male). The Kaplan Meier estimate of incurring the primary outcome after three years of SVR was 10.59% (95% CI, 8.75–12.79) After adjusting for confounding, the risk of an injection related hospital episode or death post-SVR was significantly increased with advancing year of SVR: AHR:1.07 per year (95% CI, 1.01–1.14), having a pre-SVR acute alcohol intoxication-related hospital episode: AHR:1.83 (95% CI, 1.29–2.60), and having a pre-SVR opiate or injection-related hospital episode: AHR:2.59 (95% CI, 1.84–3.64).
Conclusion: Despite attaining the optimal treatment outcome, these data indicate that an increasing significant minority of PWID continue to inject post-SVR at an intensity which leads to either hospitalisation or death and increased risk of reinfection.

1. Introduction

It is well established that people who inject drugs (PWID) are at the greatest risk of hepatitis C virus (HCV) infection. Globally, there are an estimated 16 million PWID who are currently injecting (Mathers et al., 2008) and of these, 10 million are estimated to have been infected with HCV (Nelson et al., 2011). Chronic HCV infection is a major cause of liver-related morbidity and

☆ Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:10.1016/j.drugalcdep.2015.06.032.

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http://dx.doi.org/10.1016/j.drugalcdep.2015.06.032
0376-8716/

mortality but can be cleared with antiviral treatment and establishment of sustained viral response (SVR). Currently, there is low initiation of HCV antiviral treatment among PWID, which likely relates to concerns of adherence to and reinfection post-treatment (Martin et al., 2013; Iversen and Maher, 2012). Regardless, recent studies have indicated treatment outcomes to be acceptable and risk of HCV reinfection to be relatively low among PWID, albeit based on only a few small-scale studies conducted among selected populations in clinical and harm reduction settings often with limited follow-up (Aspinall et al., 2013; Arain and Robaeys, 2014; Grady et al., 2013). Modelling work has further demonstrated that treating PWID is cost-effective and has the potential to reduce HCV transmission and prevalence in this population (Martin et al., 2011a, 2013). Therefore, recommendations state that treatment is not to be withheld from an individual based on injection status alone (EASL, 2015).

After being deemed one of the greatest public health challenges of our time, HCV was made a priority by the Scottish Government and a comprehensive Action Plan was formulated to curb the predominately injecting-related epidemic (Chisholm, 2004; Scottish Government Health Department, 2008). As a result, the overall number of people initiated on antiviral therapy in Scotland more than doubled between 2007 and 2010 with ~1000 now treated per year and the vast majority (>80%) of these report having ever injected drugs (Health Protection Agency (HPA), 2013).

Given this recent and anticipated future upscale in treatment provision among PWID a better understanding is needed of the injecting risk behaviours and potential for reinfection post-SVR. Our principal objective, therefore, was to establish evidence and predictors of continued engagement in injection drug use post-SVR using a record-linkage approach involving both HCV treatment and injecting-related hospitalisation data for a large nationally representative cohort of over 1000 PWID.

2. Methods

2.1. Study population, data sources, and linkage procedure

This paper utilised a retrospective cohort of Scottish PWID derived from the HCV Clinical Database using data linked from four additional national databases. Health Protection Scotland (HPS) holds and maintains individual patient data for all HCV diagnosed persons who attended a specialist centre for HCV treatment and management across Scotland, referred to as the HCV Clinical Database. This database includes information on patient demographics, virology, treatment episodes, epidemiological exposures, and liver disease investigations. Inclusion criteria for the study were a history of injection drug use, SVR attained by June, 2012, and sufficient identifiers for record-linkage. To enable further database linkage (described below), the HCV Clinical Database was first linked to the Scottish HCV Diagnosis Database, as previously described (Innes et al., 2011); this linkage also allowed for scrutiny of patient record accuracy, such that patients were dropped if flaws in treatment records were detected (e.g., missing diagnosis dates [$n = 68$] or nonsensical treatment dates [$n = 95$]).

Hospital episode data were obtained by sourcing Information Services Division (ISD) Scotland's Scottish Morbidity Records (SMR) 01 and 04, which provide general, non-obstetric hospital discharge data and psychiatric hospital admissions data, respectively. Hospital episodes are coded using the World Health Organisation's International Classification of Disease (ICD) Ninth Revision for all hospitalisations prior to 1996, and Tenth Revision for hospitalisations thereafter. SMR records include six possible diagnostic fields, all of which were included in analysis.

Mortality data were obtained through sourcing deaths registrations collated by National Records of Scotland. Date and up to eleven causes of death are recorded for each registered death using ICD-9 and ICD-10 codes.

2.2. Linkage procedure

ISD Scotland annually link the Scottish HCV Diagnosis Database to SMR and deaths data. This probabilistic linkage technique is estimated to have a rate of false positives or false negatives under 5% (Kendrick and Clarke, 1993); the probabilistic linkage has also been previously described (McDonald et al., 2008).

Thereafter, this linked dataset, containing SMR/deaths data on all HCV diagnosed persons, was transferred to HPS and combined with the Clinical and Diagnosis dataset via the HCV Diagnosis Database record number to enable extraction of hospitalisation and mortality data for all those who had attended a specialist clinic for HCV. The final linked dataset included all relevant demographic, behavioural, morbidity, and mortality data for 1170 Scottish PWID who had received antiviral treatment for HCV and attained SVR in the over 20 year period between 1992 and June 2012.

2.3. Outcome measures

Our primary outcome was an injection-related hospitalisation (IRH) or death (IRD) post-SVR. We defined an injection-related cause based on ICD codes present in the primary or supplementary diagnostic position. Heroin has been and remains the predominant drug injected in Scotland (University of the West of Scotland et al., 2015), therefore the relevant outcome codes comprised opiate-related: *mental and behavioural disorders due to opiate* misuse (ICD-10: F11), *poisoning due to opium* (ICD-9: 965.0; ICD-10: T40.0), *poisoning due to heroin* (ICD-10: T40.1), *accidental poisoning due to heroin* (ICD-9: E8500; ICD-10: X42.4), *accidental poisoning due to opium* (ICD-10: X42.9), *intentional self-poisoning by exposure to opium* (ICD-10: X62.9), *opiate dependence* (ICD-9: 3040), *non-dependent opiate use* (ICD-9: 3055), *finding opiates in blood* (ICD-10: R781), and injection-related as defined in previous literature: *endocarditis* (ICD-9: 421.0; ICD-10: I33), *deep vein thrombosis* (ICD-9: 451, 453; ICD-10: I80), *cellulitis/abscesses* (ICD-9: 682; ICD-10: L02, L03) (Lloyd-Smith et al., 2008; Irish et al., 2007).

2.4. Explanatory variables

Behavioural and demographic exposure variables of interest were recorded for each patient pre-SVR and were obtained from clinical and SMR records.

Behavioural variables included presence of an acute alcohol intoxication-related hospital episode, and history of an IRH pre-SVR (using the above listed codes). Alcohol intoxication-related hospital episodes have been previously defined and include hospital episodes due to *problems related to lifestyle alcohol use* (ICD-10: Z72.1), *mental and behavioural disorders due to use of alcohol* (ICD-10: F10), *toxic effect of alcohol (ethanol, methanol, unspecified)* (ICD-9: 980.0, 980.1, 980.9; ICD-10: T51.0, T51.1, T51.9), *blood alcohol level 100–240+/100 ml* (ICD-9: 790.3; ICD-10: Y90.5–Y90.9), *evidence of alcohol involvement determined by level of intent* (ICD-10: Y91), *finding of alcohol in blood* (ICD-10: R78.0), *poisoning by and exposure to alcohol* (ICD-9: E8600-02, E8609; ICD-10: X45, X65, Y15), *alcohol deterrents* (ICD-10: Y57.3), *alcohol abuse counselling and surveillance* (ICD-10: Z71.4), *non-dependent alcohol abuse* (ICD-9: 305.0).

Additional explanatory variables for each PWID included age at SVR, gender, year of SVR (date of SVR was defined as negative HCV RNA reading 24 weeks post-treatment completion), and presence of cirrhosis at treatment initiation. Age at SVR was categorised