Research paper

Efficacy of response-guided directly observed pegylated interferon and self-administered ribavirin for people who inject drugs with hepatitis C virus genotype 2/3 infection: The ACTIVATE study

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ABSTRACT

Background: There are few data on treatment for hepatitis C virus (HCV) infection among people with ongoing injecting drug use. This study evaluated the efficacy of response-guided therapy for chronic HCV genotypes 2/3 infection among people with ongoing injecting drug use or receiving opioid substitution therapy (OST). A secondary aim was to identify predictors of HCV treatment response.
Methods: ACTIVATE was a multicentre clinical trial recruited between 2012 and 2014. Participants with genotypes 2/3 were treated with directly observed peg-interferon alfa-2b and self-administered ribavirin for 12 (undetectable HCV RNA at week 4) or 24 weeks (detectable HCV RNA at week 4). Participants were recruited from drug treatment clinics, private practices, hospital clinics and community clinics in Australia, Canada, and five countries in Europe. The primary study outcome was sustained virological response (SVR, undetectable HCV RNA >12 weeks post-treatment).
Results: Among 93 people with ongoing injecting drug use or receiving OST treated for HCV genotype 2/3, 59% had recently (past month) injected drugs, 77% were receiving OST and 56% injected drugs during therapy. Overall SVR was 66% (61/93). SVR was 84% in those with undetectable HCV RNA at week 4

(12 weeks) compared to 38% in those without (24 weeks). In adjusted analysis, cirrhosis vs. no/mild fibrosis [adjusted OR (aOR) 0.33, 95% CI 0.13, 0.86] predicted reduced SVR, while response at week 4 was associated with increased SVR [aOR 8.11, 95% CI 2.73, 24.10]. Recent injecting drug use at baseline or during therapy was not associated with SVR.

Conclusion: This study demonstrates that people with recent injecting drug use or OST with chronic HCV can achieve responses to interferon-based therapy similar to other populations, despite injecting drugs prior to or during therapy. Cirrhosis was predictive of reduced response to HCV therapy, while response at week 4 (despite shortened therapy) was predictive of improved response.

Introduction

The morbidity and mortality due to hepatitis C virus (HCV) infection among people who inject drugs (PWID) continues to increase (Hajarizadeh, Grebely, & Dore, 2013; Kielland et al., 2014). New highly effective, simple, and tolerable HCV therapies have the potential to enhance treatment uptake. However, strategies for delivering HCV therapy will be required to achieve maximum impact among PWID.

Interferon-based HCV therapy is safe and effective for PWID (Aspinall et al., 2013; Hellard, Sacks-Davis, & Gold, 2009) and international recommendations support HCV treatment for PWID (AASLD/IDSA, 2017; EASL, 2017; Grebely et al., 2015; Robaeys et al., 2013; WHO, 2016). Despite these recommendations, some HCV clinicians remain concerned that adherence, efficacy (including re-infection), and competing morbidity still provide barriers to HCV treatment for PWID (Litwin et al., 2007; Myles, Mugford, Zhao, Krahn, & Wang, 2011).

Successful strategies to optimize adherence to therapy include directly observed therapy (with the morning dose of ribavirin and/or weekly interferon injections observed) and multidisciplinary support programmes (Meyer et al., 2015). The major limitations of studies evaluating interventions to enhance HCV treatment among PWID is that they rely on retrospective data collection, are single-centre, or consist of small numbers. PWID are usually excluded from Phase II/III trials (Grebely, Dore et al., 2016; Grebely, Mauss et al., 2016). There is a need for larger, multicentre, prospective studies evaluating strategies to enhance HCV treatment among PWID with ongoing drug use.

Given that interferon-based HCV therapy is poorly tolerated, and associated with neuropsychiatric side-effects, efforts have been made to identify patients responding to shorter treatment. A rapid virologic response (RVR) after 4 weeks of therapy is predictive of a sustained virological response (SVR) (Jensen et al., 2006). Among patients with genotypes 2/3 and an RVR, SVR may be achieved in 80–95% as compared to 50% of those without RVR (Dalgard et al., 2008; Jensen et al., 2006; Mangia et al., 2005). In patients with genotypes 2/3 and RVR treated for 12–14 weeks, SVR is comparable to 24 weeks of therapy (Dalgard et al., 2004, 2008; Dalgard, Bjøro, Ring-Larsen, & Verbaan, 2010; Mangia et al., 2005).

The primary aim of this study was to evaluate the efficacy of response-guided, directly observed weekly pegylated interferon alfa-2b (PEG-IFN) and self-administered ribavirin treatment for chronic HCV genotypes 2/3 among PWID with ongoing drug use or those receiving opioid substitution therapy (OST). Secondary aims included adherence to HCV therapy, predictors of HCV treatment response, and safety following successful treatment.

Methods

Study participants

From May 11, 2012, to September 30, 2014, participants were enrolled at 17 sites in Australia (n = 5), Belgium (n = 2), Canada (n = 3), Germany (n = 1), Norway (n = 2), Switzerland (n = 3) and the United Kingdom (n = 1). The last participant visit was July 15, 2015. Study recruitment was conducted through a network of drug and alcohol clinics (n = 3), private practices (n = 2), hospital clinics (n = 9), and community clinics (n = 3). Participants attending these clinics who fulfilled the eligibility criteria were offered participation in this study.

Participants had to be >18 years of age, have chronic HCV genotype 2 or 3 infection, be HCV treatment-naïve, and have reported recent injecting drug use (defined as injecting drug use within 12 weeks of enrolment). Due to slower than anticipated recruitment, on June 26, 2013, a study protocol amendment was implemented to also include people currently receiving OST with no recent drug use and people who had injected within 24 weeks prior to enrolment. Participants with HIV infection and decompensated liver disease were excluded. Full eligibility criteria are provided in the study protocol (Supplementary material).

Study design and intervention

ACTIVATE was an international, multicentre open-label study. Participants received directly observed pegylated interferon alfa-2b (PEG-IFN weekly, 1.5 μg/kg/week) and self-administered ribavirin (RBV, 800–1400 mg daily, weight-based).

Participants with an RVR [defined as non-quantifiable HCV RNA (<15 IU/ml detected and <15 IU/ml undetected) or undetectable HCV RNA on qualitative assay at week 4] received 12 weeks of therapy (shortened duration). Participants without an RVR [defined as quantifiable HCV RNA (≥15 IU/ml) or detectable HCV RNA on qualitative assay at week 4] received 24 weeks of therapy (standard duration).

Study oversight

All participants provided written informed consent before study procedures. The study protocol was approved by St. Vincent's Hospital, Sydney Human Research Ethics Committee (primary study committee), as well as through local ethics committees at all study sites, and was conducted according to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH/GCP) guidelines. The study was registered with clinicaltrials.gov registry (NCT01364090). The sponsor (The Kirby Institute, UNSW Sydney) collected the data, managed study samples, monitored study conduct and performed the statistical analysis. An independent data and safety monitoring board reviewed the progress of the study.

Study assessments

Screening assessments included HCV RNA levels, HCV genotype, standard laboratory and clinical testing and self-reported behavioural questionnaires.

Assessments during treatment included measurement of vital signs, symptom-directed physical examinations, measurements of