Research Article

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Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users

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Background & Aims: Adherence to HCV therapy impacts sustained virological response (SVR) but there are limited data on adherence, particularly among injecting drug users (IDUs). We assessed 80/80 adherence (⩾80% of PEG-IFN doses, ⩾80% treatment), on-treatment adherence, and treatment completion in a study of treatment of recent HCV infection (ATAHC).

Methods: Participants with HCV received pegylated interferon (PEG-IFN) alfa-2a (180 μg/week, n = 74) and those with HCV/HIV received PEG-IFN alfa-2a with ribavirin (n = 35), for a planned 24 weeks. Logistic regression analyses were used to identify predictors of PEG-IFN 80/80 adherence.

Results: A total of 109 out of 163 patients received treatment (HCV, n = 74; HCV/HIV, n = 35), with 75% ever reporting IDU. The proportion with 80/80 PEG-IFN adherence was 82% (n = 89). During treatment, 14% missed ⩾1 dose (on-treatment adherence = 99%). Completion of 0–4, 5–19, 20–23, and all 24 weeks of PEG-IFN therapy occurred in 10% (n = 11), 14% (n = 15), 6% (n = 7) and 70% (n = 76) of cases, respectively. Participants with no tertiary education were less likely to have 80/80 PEG-IFN adherence (AOR 0.29, $p = 0.045$). IDU prior to or during treatment did not impact 80/80 PEG-IFN adherence. SVR was higher among those patients with ⩾80/80 PEG-IFN adherence (67% vs. 35%, $p = 0.007$), but similar among those with and without missed doses during therapy (73% vs. 60%, $p = 0.309$). SVR in those patients discontinuing therapy between 0–4, 5–19, 20–23, and 24 weeks was 9%, 33%, 43%, and 76%, respectively ($p < 0.001$).

Conclusions: High adherence to treatment for recent HCV was observed, irrespective of IDU prior to, or during, therapy. Suboptimal PEG-IFN exposure was mainly driven by early treatment discontinuation rather than missed doses during therapy.

Keywords: Injection drug users; HIV infection; Discontinuation; Pegylated interferon; Therapy.

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Abbreviations: PEG-IFN, pegylated interferon; HCV, hepatitis C virus; SVR, sustained virological response; ATAHC, Australian Trial in Acute Hepatitis C; IDU, injection drug use; IDUs, injection drug users; HIV, human immunodeficiency virus; ALT, alanine aminotransferase; PEG-IFN, pegylated interferon-α2a; ITT, intention-to-treat.

Introduction

Pegylated interferon (PEG-IFN) and ribavirin for the treatment of chronic hepatitis C virus (HCV) infection is effective in 54–56% and 27–40% of patients with HCV [1–3] and HCV/HIV, respectively [4–5]. Sustained virological response (SVR) is associated with younger age [1–2], HCV genotype [1–3], HCV RNA [1,3], HCV viral kinetics [6–7], fibrosis [1], and host genetics (e.g. *IL28B*) [8–10]. Adherence to therapy is also important and enhances SVR [11–14]. However, studies of adherence are limited by the restricted populations, small sample sizes, and varying adherence definitions [14].

Treatment response is also higher among patients with recent HCV. Response rates range from 55% to 88% among HCV patients receiving 12–24 weeks of therapy with PEG-IFN monotherapy [15–22] and from 59% to 74% among HCV/HIV patients receiving 12–24 weeks of therapy with PEG-IFN and ribavirin [22–24]. In the Australian Trial in Acute Hepatitis C (ATAHC), SVR rates of 55% for HCV (PEG-IFN) and 74% for HCV/HIV participants (PEG-IFN/ribavirin) were observed after 24 weeks of therapy [22]. Among HCV monoinfected participants, SVR was higher among those adherent to PEG-IFN (63% vs. 29%, $p = 0.025$) [22]. Among those ever having injected drugs (n = 63), SVR was similar for those participants who did and did not inject during treatment (59% vs. 53%, $p = 0.76$) and was not related to injecting frequency [22].

Among healthcare providers, there are still concerns about the suitability of HCV treatment in IDUs due to patient motivation and adherence, psychosocial issues, medical and psychiatric co-morbidities, re-infection risk, and the lack of infrastructures to ensure access to care [25]. However, response rates among IDUs are comparable to non-IDUs [26] but little is known about adherence to

HCV therapy and associated factors, particularly among IDUs and those with recently acquired HCV.

The ATAHC study was designed specifically to investigate treatment for recent HCV, predominantly in those patients with IDU-acquired infection. The study uniquely recruited both HCV and HCV/HIV participants under the same protocol. Here, we report on the adherence to PEG-IFN and predictors of adherence in the study.

Materials and methods

Study design

ATAHC was a multicenter, prospective cohort study of the natural history and treatment of recent HCV infection, as previously described [22]. HIV infected and uninfected participants were recruited from June 2004 through November 2007, through an Australian network of tertiary hospitals (n = 13) and general practice/primary care clinics (n = 3). The top five sites in Sydney (n = 2), Melbourne (n = 2), and Adelaide (n = 1) recruited 84% of participants. Recent infection with either acute or early chronic HCV was considered if the following eligibility criteria were met:

First positive anti-HCV antibody within 6 months of enrollment and *either*

a. *Acute clinical hepatitis C infection*, defined as symptomatic seroconversion illness or alanine aminotransferase (ALT) level greater than 10 times the upper limit of normal (>400 IU/L) with exclusion of other causes of acute hepatitis, at most 12 months before the initial positive anti-HCV antibody;

or

b. *Asymptomatic hepatitis C infection with seroconversion*, defined by a negative anti-HCV antibody in the two years prior to the initial positive anti-HCV antibody.

All participants with HCV RNA during the screening period (maximum 12 weeks) were assessed for HCV treatment eligibility. Heavy alcohol intake and active drug use were not exclusion criteria. From screening, participants were followed for up to 12 weeks to allow for spontaneous HCV clearance, and they were offered treatment if HCV RNA remained detectable. Participants were then seen at baseline and 12-weekly intervals for up to 144 weeks (individuals receiving HCV treatment were also seen at 4-weekly intervals up to week 12).

All study participants provided written informed consent. 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. The study was registered with clinicaltrials.gov registry (NCT00192569).

HCV treatment

Participants who began HCV treatment received pegylated interferon-α2a (PEG-IFN), 180 μg, weekly, for 24 weeks. Due to non-response at week 12 in the initial two participants with HCV/HIV co-infection, the study protocol was amended to provide PEG-IFN and ribavirin combination therapy for 24 weeks in HIV positive individuals. Ribavirin was prescribed at a dose of 1000–1200 mg for those patients with genotype 1 infection and 800 mg for those with genotype 2/3. HCV treatment was self-administered (with the exception of the first dose which was supervised by study personnel). Treatment sites were offered the option of administering or supervising injections, if this was felt necessary to optimize adherence for individual patients. Prior to treatment, medical staff informed patients on the recommended methods of medication storage, self-injection, and management and disposal of needles and syringes.

Study assessments

A questionnaire was administered at screening and every 12 weeks, to obtain information on injection of illicit drugs, social functioning (Opiate Treatment Index Social Functioning Scale) [27], and psychological parameters [Mini-International Neuropsychiatric Interview (M.I.N.I.) [28] and the Depression Anxiety Stress Scale (DASS-21) [29]].

Study visits occurred every two weeks from baseline to week 8, and every four weeks from week 8 until the end of treatment. All participants had the same number of study visits, irrespective of injecting drug use history. At each study visit, weekly adherence to PEG-IFN was recorded by the research nurse on a standardized case report form which included the method of dose administration, whether the full dose, adjusted dose, or no dose of PEG-IFN was administered, as well as reasons for dose adjustment.

Study definitions

PEG-IFN 80/80 adherence

Defined as the receipt of ⩾80% of scheduled PEG-IFN doses for ⩾80% of the scheduled treatment period. For participants in whom therapy was terminated at 12 weeks due to virological non-response, the scheduled treatment period was defined as 12 weeks.

On-treatment PEG-IFN adherence

Calculated by subtracting the number of missed PEG-IFN doses from the total duration of treatment (week that treatment was discontinued or completed) and dividing by the total therapy duration. This measures the proportion of PEG-IFN doses received from the time that treatment was initiated until treatment was discontinued or completed.

PEG-IFN dose-modification

A reduction in the dose of PEG-IFN at any time during treatment.

Early PEG-IFN treatment discontinuation

Discontinuation of PEG-IFN prior to the per-protocol planned end of treatment (24 weeks). This includes participants with clinician-directed discontinuation for virological non-response.

Study outcomes

The main study outcome was to assess PEG-IFN adherence (given that only HCV/HIV participants received ribavirin). Evaluation of HCV treatment response was based on intention-to-treat (ITT) analyses that included all participants who received at least one injection of PEG-IFN therapy. The primary endpoint for treatment was the proportion of participants with undetectable qualitative HCV RNA rates at week 48 (SVR).

Statistical analyses

We hypothesized that non-adherence to PEG-IFN therapy during recent HCV infection was due to early PEG-IFN treatment discontinuation, rather than missed doses of PEG-IFN. Weekly PEG-IFN adherence, PEG-IFN 80/80 adherence, on-treatment PEG-IFN adherence, missed PEG-IFN doses during treatment, PEG-IFN dose-modifications, and early treatment discontinuations were assessed. Bi-variate comparisons of characteristics of participants across different measures of adherence were tested using the chi-squared test. Time to treatment discontinuation was evaluated using Kaplan Meier analysis. Finally, the impact of on-treatment PEG-IFN adherence and early PEG-IFN discontinuation on SVR were also evaluated.

Logistic regression analyses were used to estimate crude and adjusted odds ratios (OR) and corresponding 95% confidence intervals (95% CI) to identify predictors of PEG-IFN 80/80 adherence and HCV treatment completion. In unadjusted analyses, potential predictors were determined *a priori* and included sex, age, education, accommodation, employment, methadone/buprenorphine treatment, social functioning, current depression, IDU at baseline (ever, past 6 months and past 30 days), alcohol, HIV infection, estimated duration of HCV, and acute presentation (acute clinical, asymptomatic). Accommodation was categorized according to rented housing, privately owned housing or unstable housing (this included hostels, drug treatment residence, prison/detention center, homeless or unknown place of residence). In addition, in unadjusted analyses, we evaluated the impact of maximum social functioning score, depression, injecting and maximum alcohol consumption during treatment on PEG-IFN 80/80 adherence and treatment completion. Social functioning was calculated using a validated scale from the Opiate Treatment Index [27] that addresses employment, residential stability, and inter-personal conflict as well as social support. A higher score reflects poorer social functioning. This scale has been validated among opiate users in Australia (range, 0–48) [27]. Current depression was evaluated using the Mini-International Neuropsychiatric Interview (M.I.N.I.) [28].