TITLE PAGE

Title: Reinfection with hepatitis C virus following sustained virological response in injection drug users

Running title: HCV reinfection following SVR in IDUs

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Abstract (242 words)

Despite that 60-90% of injection drug users (IDUs) are infected with hepatitis C virus (HCV) infection, IDUs are often denied therapy based on concerns of reinfection following treatment. However, there are little data in this regard. We evaluated HCV re-infection following sustained virologic response (SVR) among HCV-infected IDUs having received HCV treatment in a multidisciplinary program. Following treatment, participants were encouraged to return at follow-up intervals of 1 year and illicit drug use histories were obtained. In those with SVR, HCV RNA testing by PCR was performed to determine if relapse or reinfection occurred. Among 58 receiving HCV treatment between January 2002 and December 2006, 60% (35 of 58) achieved an SVR. Patients were followed for a median of 2.0 years following SVR (range, 0.4-5.0 years), with ongoing illicit and injection drug use reported in 54% (19 of 35) and 46% (16 of 35). Of the 35 with SVR, 28 remained HCV RNA negative during follow-up (80%), with four lost to follow-up and one dying of hepatocellular carcinoma and two cases of reinfection were observed (2 of 35). The rates of reinfection were 3.2 per 100 p-y (95% CI:0.4, 11.5) overall and 5.3 per 100 p-y (95% CI:0.6, 19.0) among those reporting injecting following SVR (n=16). One of two participants with HCV re-infection spontaneously cleared virus following reinfection. In conclusion, the rate of reinfection following treatment for HCV infection among current and former IDUs engaged in a multidisciplinary program is low.

Keywords: injection drug users, hepatitis C virus, treatment, reinfection, clearance

INTRODUCTION

The majority of new and existing cases of HCV infection occur among injection drug users (IDUs)[1]. However, treatment uptake in this population remains low[2, 3]. The lower uptake of treatment among IDUs when compared to other populations is likely attributed to a combination of patient, provider, organizational and structural barriers to care in this population[4-7]. However, treatment is often withheld by practitioners based on concerns of adherence, social instability, psychiatric disease and the perceived risk of HCV reinfection following successful treatment[7, 8]. However, little is known about HCV reinfection following sustained virologic response (SVR).

It is clear that reinfection with HCV can occur following treatment-induced clearance, as has been observed in IDUs[9-12] and men who have sex with men[13]. However, few prospective studies have evaluated the incidence of HCV reinfection following SVR. The rate of reinfection in these studies was less than five cases per 100 person years[9, 11]. Further data on the rate of HCV reinfection following SVR are urgently needed to guide clinical decision making in this population, particularly given the greater number of current and former IDUs receiving treatment for HCV infection.

The aim of this study was to evaluate the rate of HCV re-infection following SVR in IDUs receiving therapy within a multidisciplinary program.

METHODS

In 2002, a prospective non-randomized interventional study was initiated to investigate treatment for HCV infection among IDUs. The study design, setting and participants have been reported previously[14, 15].

In brief, participants were recruited between January 2002 and December 2006 from two community health clinics located in the inner city of Vancouver or Victoria in British Columbia, Canada. The clinics offer addiction services such as methadone maintenance therapy, needle exchange, counseling and prevention. In addition to this, other available services included primary care, nursing, addiction counseling and on-site consultation with infectious diseases specialists. Inclusion criteria included age >19 years with documented HCV RNA, along with either elevated alanine aminotransferase (ALT) enzyme levels (1.5 times the upper limit of normal on 2 occasions at least 3 months apart) *or* liver biopsy demonstrating at least Knodell stage 2 fibrosis with no evidence of decompensated cirrhosis. Patients with any cause of chronic liver disease other than HCV, pregnant or breastfeeding women, those with active suicidal ideation, psychosis or mania or those judged inappropriate for treatment by their physician, based on their medical or psychiatric condition, or their current addiction status (daily injection drug use in the setting of unstable housing) were excluded for treatment of HCV infection. The University of British Columbia Clinical Research Ethics Board approved this study.

Patients received therapy with ribavirin (RBV, 800-1200 mg/day, weight-based) along with interferon-α2b (IFN-α2b, 3 MIU thrice-weekly, n=12), pegylated interferon α-2a (180 μg once-weekly, n=14) or PEG-IFN alfa-2b (1.5 μg/kg once-weekly, n=32). Treatment duration was 48

(genotype 1) or 24 weeks (genotypes 2/3). Patients received education from nurses, physicians and counselors on HCV reinfection risks, including education about HCV transmission, emphasizing the need to avoid the sharing of injection equipment.

SVR was defined as a qualitative HCV RNA <50 IU/mL (COBAS AMPLICOR HCV Test v2.0, Roche Diagnostic Systems, Mississauga, Canada) 24 weeks post-treatment. Patients were seen at follow-up intervals of approximately one year following SVR. Patients were asked about their use of illicit and injection drug use over this period. At these visits, plasma samples were collected and tested for HCV RNA and genotype. If viremia was detected, sequencing of the hypervariable and NS5B regions was performed in cases where the pre-treatment and reinfection genotypes were similar to determine sequence identity.

The aim of the present study was to evaluate the rate of reinfection following SVR during the long-term follow-up of current and former injection drug users. Individuals with HCV reinfection were identified and the incidence calculated in cases per 100 person years, with censoring at the last negative HCV RNA assessment in cases without HCV reinfection and at the first HCV RNA positive assessment in participants with HCV reinfection following SVR.

RESULTS

Among 58 participants treated for HCV between January 2002 and December 2006, 60% (35 of 58) achieved an SVR. The demographic characteristics of these 35 patients are shown in Table 1.

Patients were followed for a mean of 2.0 years (median, 2.0 years; range, 0.4-5.0 years) following SVR, with ongoing illicit and injection drug use in 51% (18 of 35) and 46% (16 of 35) of patients respectively. Overall, 80% (28 of 35) remained HCV RNA negative during follow-up. Of the remaining seven, four were lost to follow-up, one died of hepatocellular carcinoma and two had recurrent HCV RNA. Of the four participants lost to follow-up, the durations of drug abstinence at the time of treatment initiation were 7, 12, 96 and 120 months. None of the participants reported drug use at the time of treatment initiation and only one participant reported drug use during treatment (less than weekly).

Among the 35 participants with SVR, two had potential reinfection, for an overall reinfection rate of 3.2 cases per 100 person-years, (95% Confidence Interval [CI]; 0.4-11.5). However, only considering those participants who reported injection drug use following SVR (n=16), the rate of reinfection was 5.3 cases per 100 person-years (95% CI, 0.6-19.0). None of the two individuals with reinfection were co-infected with HIV. The two cases of reinfection are described in detail below.

The first case was that of a 28 year-old male with a seven year history of injection drug use, admitting to needle sharing. He was found to carry HCV genotype 1 (unable to subtype further). The patient was initiated on methadone maintenance therapy and remained abstinent from illicit

drug use for 24 weeks. At that point, treatment with PEG-IFN alfa-2b and ribavirin was initiated. Baseline HCV RNA and ALT were 8,756 IU/mL and 100 U/L respectively. At weeks 8 and 12, HCV RNA was negative. At week 16, he relapsed to crack cocaine and injection heroin use and treatment was terminated. He then continued to use illicit drugs on an ongoing basis. Nevertheless, qualitative HCV RNA testing performed at the end of treatment and 23 weeks following therapy were negative, confirming that SVR was achieved despite the shortened course of treatment. He was lost to follow-up for 20 weeks. He then presented 43 weeks later (63 weeks following SVR), and HCV RNA testing was positive and ALT was slightly elevated (84 U/L). Viral genotyping demonstrated reinfection with genotype 1 (unable to subtype further). Sequencing to compare this isolate to the one obtained at the time of initial HCV infection was not successful, due to the low level of viremia. The patient was subsequently lost to follow-up.

The second case of reinfection was that of a 32 year-old male injection drug user with chronic genotype 3a infection (Figure 1). Treatment with IFN alfa-2b and ribavirin was initiated in 2003. At baseline, he was receiving methadone maintenance therapy, was abstinent from illicit drugs for 12 weeks and ALT was 110 U/L. He achieved an SVR following treatment, despite reporting occasional illicit drug use on an ongoing basis during the entire course of therapy. The patient remained HCV negative for 146 weeks post-SVR, despite regular poly-substance use. However, 201 weeks following SVR, HCV RNA was detected with no elevation of ALT levels. Genotyping revealed reinfection with genotype 1b. The patient was aviremic by quantitative testing 229 weeks following SVR (28 weeks following HCV reinfection) with two subsequent qualitative HCV RNA negative tests at weeks 237 and 259 following SVR, demonstrating spontaneous viral clearance of reinfection.

DISCUSSION

We have documented a low rate of HCV re-infection among IDUs successfully treated for HCV in a multidisciplinary care setting. This is despite ongoing injection drug use reported in half of patients during follow-up. To our knowledge, we have also described the first case of spontaneous clearance of HCV reinfection following treatment for chronic HCV infection.

Overall, the rate of HCV reinfection was 3.2-5.3 cases per 100 person-years. The first case of reinfection occurred with a genotype similar to that found in the initial infection, but the viral load at the time of reinfection was too low for sequencing. However, given the long duration of negativity following SVR, it is plausible that this represents a case of reinfection rather than viral recrudescence. Case 2 most likely represents a case of reinfection, given ongoing risk behaviours and the identification of a different genotype compared to the initial infection. It is noteworthy that this participant successfully cleared viremia following HCV reinfection.

There are several limitations to this report. First, the results may not be generalizable to all IDUs receiving treatment for HCV infection. Our patients received care within a multidisciplinary program providing education on the risk of reinfection following successful therapy. Second, four patients were lost to follow-up and had to be excluded from reinfection incidence calculations. However, we do not believe these participants were at considerable risk for reinfection, given the long durations of drug abstinence at treatment initiation and the fact that only one used drugs during treatment (frequency less than weekly). Third, demographic and injecting behavior information was collected retrospectively and the proportion reporting injecting behavior following SVR is likely under-reported. If this is correct, our observed rate of

reinfection among current injectors in the study may, if anything, be an over-estimate of the true rate, which is reassuring. Fourth, the first case may represent a case of viral recrudescence rather than reinfection, which would have also led to an over-estimation of the rate of reinfection observed in this study. Lastly, data are not available on injecting equipment sharing over the follow-up period.

This observed rate of reinfection following HCV treatment observed in this study overall (3.2 cases per 100 person-years) and among recent injectors (5.3 cases per 100 person-years) is lower than the rate of incident HCV infection observed in this community over the same time period. In a large community-based study of inner city residents in Vancouver the rate of HCV infection was 7.3 cases per 100 person years overall (95% CI, 5.7-8.8) and 24.5 cases per 100 person years among those with recent injecting (95% CI, 18.6-30.5)[2]. Further, the rate of reinfection observed in this study is consistent with previous reports. In Germany[11], among 18 IDUs followed for a mean of 2.8 years after successful treatment for HCV infection (50% relapsed to injection drug use following treatment), 0-2 cases of reinfection were observed (reinfection < 4.1 cases per 100 person-years). Similar results were reported from 27 IDUs followed for 5.4 years following SVR in Norway[16]. The incidence of reinfection was 0.8 cases per 100 person-years, 2.5 cases per 100 person-years among the 9 of 27 (33%) that returned to injection drug use during follow-up [16].

The low rate of HCV reinfection observed in this study may reflect our extensive program of education and counselling to reduce injection equipment sharing in the period following treatment, although we cannot confirm this based on the data from this study. We may have missed a number of cases of reinfection given the long interval between HCV RNA tests

following SVR, especially if some of the cases of reinfection were followed by spontaneous clearance, as we have now documented in at least one instance. This latter observation is consistent with data from one study in Australia in the setting of acute HCV that identified one patient initially infected with genotype 3a who spontaneously cleared HCV reinfection with genotype 1a[12]. Clearance of reinfection in this Australian study was accompanied by strong and broad HCV-specific T cell responses[12]. This may also have been the mechanism of the clearance of reinfection in our case, but we did not have samples available to determine the mechanism of clearance of reinfection in this participant.

Treatment for chronic HCV infection among IDUs is often withheld on concerns of reinfection following successful therapy[8]. The results of this study demonstrate a low rate of HCV reinfection following treatment for chronic HCV infection among current and former IDUs receiving care in a multidisciplinary program. Further, these data demonstrate that spontaneous clearance of reinfection following successful treatment for chronic HCV infection is possible. Nonetheless, education and counselling about the risk of reinfection should be continued among IDUs following successful treatment for HCV as ongoing injection drug use appears to be quite common. Taken together, these data provide a stronger rationale for expanding treatment programs for IDUs.

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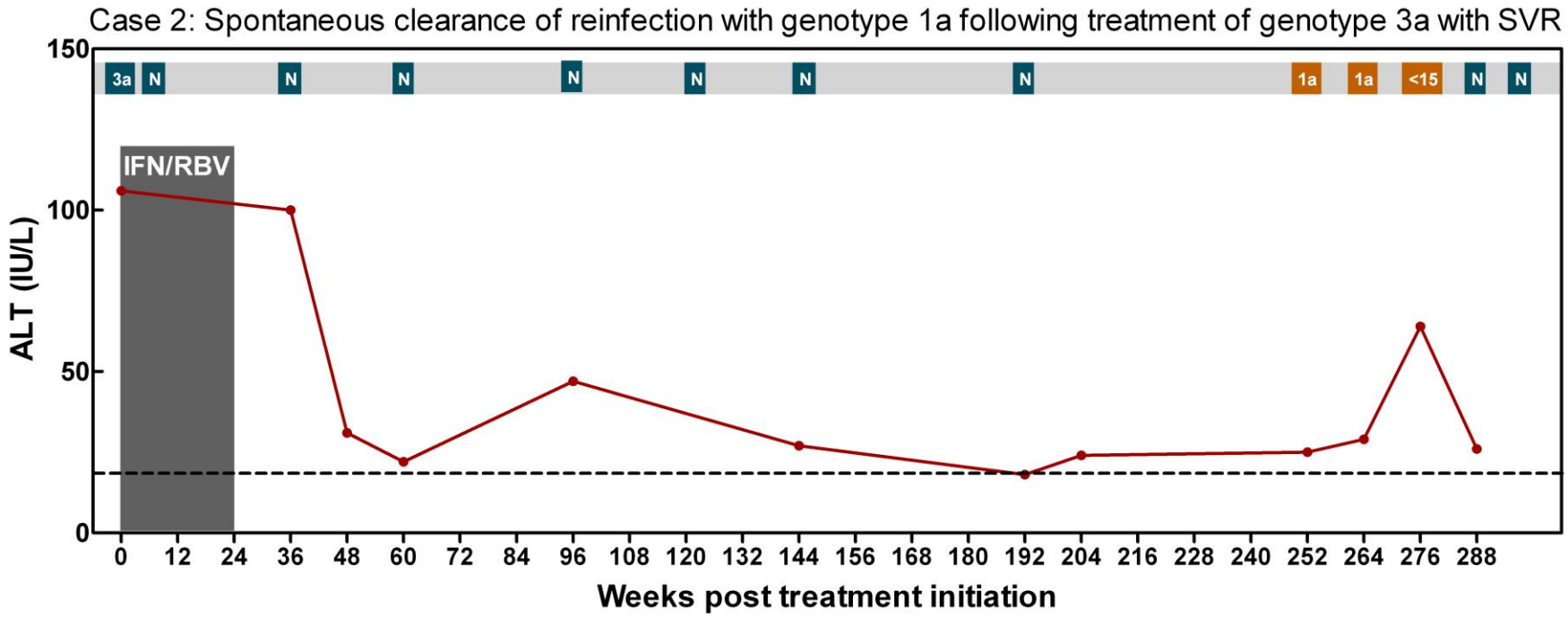
Table 1. Participant characteristics of those with sustained virological response (n=35).

Characteristics	Overall (n=35)
Mean age, (± SD)	44 (± 9.8)
Male sex, (n, %)	30 (86%)
Injection drug use ever	35 (100%)
Injection drug use in the 6 months preceding therapy	19 (54%)
Methadone maintenance therapy (current)	15 (43%)
HIV infection, (n, %)	2 (6%)
HCV genotype, (n, %)	
1	12 (34%)
2	7 (20%)
3	16 (46%)
Illicit drug use during or following treatment	23 (66%)
Illicit drug use during treatment	19 (54%)
Illicit drug use following SVR	18 (51%)
Crack cocaine	11 (31%)
Injection drug use following SVR	16 (46%)
Injection cocaine	11 (31%)
Injection heroin	11 (31%)

Figure 1. HCV RNA and alanine aminotransferase (ALT) levels in case 2, with spontaneous clearance following reinfection. Square boxes indicate HCV genotype (N=negative qualitative HCV RNA testing and <15=<15 IU/mL). Circles indicate ALT levels. Treatment with IFN/RBV is indicated by the dark grey box.


Case 2: Spontaneous clearance of reinfection with genotype 1a following treatment of genotype 3a with SVR
3a
N
N
N
N
N
N
N
1a
1a
<15
N
N
IFN/RBV
ALT (IU/L)
150
100
50
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240 252 264 276 288
Weeks post treatment initiation