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Title: Directly Observed Therapy for the Treatment of Hepatitis C Virus Infection in Current and Former Injection Drug Users

Running Head: Treatment of HCV Infection in Current and Former Injection Drug Users

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ABSTRACT (250 words)

Background and Aim: There are few studies investigating the treatment of HCV infection in current and former drug users. With this in mind, we sought to evaluate the antiviral efficacy of interferon alfa-2b (IFN α -2b) or pegylated-interferon alfa-2b (PEG-IFN α -2b) and ribavirin (RBV) in injection drug users (IDUs) enrolled in a directly observed therapy (DOT) program, as measured by sustained virologic response (SVR). **Methods:** Viremic HCV-infected IDUs, with ALT >1.5x ULN were offered 24-48 week (based on HCV genotype) therapy with RBV (800-1200 mg/day, based on weight) along with IFN α -2b (1.5 ug/kg thrice-weekly) replaced by PEG-IFN α -2b (1.5 ug/kg once weekly) as it became available. All injections were directly observed. The primary endpoint was SVR. **Results:** Overall, 40 patients (33 males) received IFN α -2b (12) or PEG-IFN α -2b (28), 55% with genotypes 2/3. Only 14 discontinued therapy, 5 due to toxicity, 6 due to illicit drug use and 3 did not achieve an early virologic response. In an intent-to-treat analysis, the overall SVR was 55% (22/40), 64% (14/22) in subjects with genotypes 2/3. There was no difference in response rates among those with >6 (50%) or $\leq$ 6 months (64%) drug abstinence ($P=0.51$) or among those with (53%) and without (57%) intercurrent drug use ($P=0.99$); however, frequent users ($n=9$) had a decreased SVR (22%) when compared to occasional users ($n=10$, 80%, $P=0.12$). **Conclusions:** Treatment of HCV in current and former IDUs within a multidisciplinary DOT program can be successfully undertaken, resulting in SVRs similar to those in randomized controlled trials.

Keywords: interferon, pegylated interferon, ribavirin, injection drug users, illicit drug users

Introduction

Hepatitis C virus (HCV) infection remains a significant global health burden, with over 170 million individuals infected worldwide (1). Only 20% or less will spontaneously clear HCV viremia, with the remainder progressing to chronic disease (2). Injection drug use (IDU) remains the primary mode of HCV acquisition, with >50% of prevalent cases and >75% of incident cases associated with this risk behavior (1). The high transmissibility of HCV via needlestick and the presence of a large reservoir of chronic HCV carriers in this population results in HCV prevalence rates ranging between 60 and 90% (1). However, despite this growing epidemic in many urban centres, very few IDUs have received treatment for HCV infection.

Response rates of 50-55% are generally observed in patients receiving pegylated interferon alfa-2a or alfa-2b in combination with twice daily ribavirin for 24-48 weeks (dependant on genotype), a figure that exceeds 80% in a subgroup of individuals carrying HCV genotype 2 or 3 infection (3-6). Current treatment guidelines advocate for treatment of HCV infection in current and former IDUs on an individual basis under specific circumstances (7-9). Despite these recommendations, very few IDUs have actually received treatment to date. This is based on concerns about patient motivation and adherence, medical and psychiatric co-morbidity, re-infection due to recurrent risk behaviors and the lack of infrastructure to ensure access to care during treatment. However, preliminary reports from some centres have confirmed that many IDUs are motivated to receive treatment (10-12), and may be more likely to do so if this is coupled with a comprehensive approach to their medical and psychiatric needs (including a systematic addiction treatment program) within existing infrastructures, perhaps with directly

observed therapy (DOT). However, to date, no study has evaluated DOT for the treatment of HCV infection. With this in mind, the present study evaluates the safety and efficacy of treatment of HCV infection in current and former IDUs enrolled in a structured DOT program.

Methods

All patients were HCV-infected IDUs attending one of two multidisciplinary health clinics located in the inner city of Vancouver (the Pender Community Health Centre) or Victoria (the Cool Aid Community Health Centre) 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.

Funding for HCV treatment in British Columbia is provided through government programs and is either partially or fully reimbursed (based on patient income level). The clinical criteria for government reimbursement are: documented viremia, 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. Men and women >19 years of age who fulfilled government criteria for subsidized treatment and in whom there was a reasonable expectation of adherence to therapy were eligible to receive it. HIV infected subjects with a CD4 count >300 cells/mm³ were also eligible for inclusion. 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 not offered treatment for HCV infection.

Physicians who are addiction specialists at the clinic completed the initial medical evaluation. At baseline, all patients underwent a complete medical history and physical examination. Nursing staff also provides risk behavior education and provides education about the treatment and potential side effects. Patients were required to see an addictions counselor to assess psychiatric status (specifically depression and suicide risk), social stability and current or former illicit drug use behaviors. Once therapy was initiated, patients attended the clinic weekly to be formally evaluated by the nurse and to receive their weekly injections. During these visits, the nurses specifically documented adherence to ribavirin, assessed medication-associated toxicity and ensured appropriate longitudinal monitoring was conducted. Illicit drug use was documented and blood tests were performed according to the standard of care. Patients maintained frequent contact with physicians for biweekly prescription of methadone and medications needed to address treatment-associated toxicities. Addiction counselors were available on site to provide additional individual support, as required, with particular attention to exacerbation of depression.

For the majority of subjects attending our clinics, HCV medication is provided free of charge through government programs. Patients received combination therapy with ribavirin (RBV, 800-1200 mg/day, based on weight) along with interferon- α 2b (IFN- α 2b, 3 million international units thrice-weekly) replaced by pegylated interferon- α 2b (PEG-IFN- α 2b, 1.5 μ g/kg once weekly), as it became available. Patients initiating therapy prior to July 2003 received interferon and ribavirin, while those who received therapy after July 2003 received pegylated interferon and ribavirin. Treatment duration was 48 weeks in subjects infected with HCV genotype 1 and 24 weeks in those infected with HCV genotypes 2/3. Staff administered all IFN (thrice-weekly) and PEG-IFN (weekly) injections under direct observation and ribavirin was self-administered.

Subjects experiencing moderate anemia (<10 g/dL) received a ribavirin dose reduction of 200 mg/day, while subjects experiencing more severe anemia (<8.5 g/dL) were discontinued from therapy. Subjects experiencing moderate hematologic toxicity associated with reductions in white blood cells ($<1.5 \times 10^9$ /L), neutrophils (0.75×10^9 /L) or platelets (80×10^9 /L) received a 50% reduction in interferon dose, while those with more significant reductions in white blood cells ($<1.0 \times 10^9$ /L), neutrophils (0.50×10^9 /L) or platelets (50×10^9 /L) were discontinued from therapy.

The primary end point for this prospective, observational trial was sustained virologic response (SVR) to interferon-based therapy, defined as an HCV RNA <50 IU/mL at 24 weeks post-treatment (COBAS AMPLICOR HCV Test v2.0, Roche Diagnostic Systems, Mississauga, Canada). Chi-Squared or Fisher's Exact test were used, as appropriate, for all statistical comparisons, which were completed on an intention-to-treat basis. Statistically significant differences were assessed at a significance level of 0.05 and all reported p-values are two-sided. All experimental procedures were followed in accordance with the Helsinki Declaration of 1975. The University of British Columbia Clinical Research Ethics Board approved this study.

Results

A total of 40 HCV-infected participants were enrolled in the study (of whom 33 were male and 7 were female). Of these, 12 began treatment before July 2003 and received interferon injections thrice weekly, while the remaining 28 were given pegylated interferon once weekly. The demographics and clinical characteristics of subjects enrolled in this study are shown in Table 1. All patients had injection drug use as a risk factor for HCV infection. Fifty three percent of patients were enrolled in a methadone maintenance program, receiving a median dose of 67 mg/day. Overall, 23 patients (58%) self-reported a previous history of depression and 14 (35%) were receiving antidepressants prior to initiating therapy for HCV infection. Eighteen patients (45%) had HCV genotype 1, 6 (15%) had genotype 2 and 16 (40%) had genotype 3. Three patients were co-infected with HIV.

The disposition of the 40 study subjects is shown in Figure 1. In total, 26 subjects completed the full course of therapy. Of the 14 subjects who did not, 5 subjects experienced treatment-limiting adverse events (1 - nausea/vomiting, 1 - tinnitus, 1 - neutropenia, 1 - depression and 1 - anemia). Three subjects infected with genotype 1 were discontinued from therapy due to lack of an early virologic response (EVR), defined as an undetectable viremia or a 2 log₁₀ decrease in HCV RNA by week 12. Six subjects were discontinued from treatment due to non-adherence associated with ongoing illicit drug use, four of these reporting concomitant depression. In total, 12/14 (86%) discontinuations occurred within the first four months of therapy (Figure 2).

At the beginning of HCV treatment, 14/40 subjects were on antidepressants, with 4/14 (28%) not completing therapy, 2/3 due to depression and/or illicit drug use and non-adherence. Of the

remainder of the population (9/26 reporting a previous history of depression), 4 started on antidepressants during HCV therapy, and 10/26 (38%) did not complete therapy, 4/10 due to depression and/or illicit drug use and non-adherence. In this population, prior use of antidepressants was not predictive of successful treatment completion ($p = 0.75$).

As shown in Figure 3, at the end of treatment, the proportion of patients responding to HCV therapy was 28 of 40 (70%). However, due to viral relapse in 6 subjects receiving IFN- α 2b (3 subjects) and PEG-IFN- α 2b (3 subjects), SVR was observed in only 22 of 40 subjects (55%). In total, 8/18 (44%) and 14/22 individuals (64%) infected with HCV genotype 1 and HCV genotypes 2/3 had an SVR (Figure 4, $P=0.34$). Five of twelve individuals (42%) receiving interferon-based therapy achieved an SVR as compared to 17 of 28 (61%) individuals receiving pegylated interferon-based therapy (Figure 4, $P=0.31$). Among subjects weighing <75 kg achieved, an SVR was achieved in 60% (9/15) as compared to 52% (13/25) in subjects weighing ≥ 75 ($P=0.75$). Among patients enrolled in a methadone maintenance program, the SVR rate was 52% (11/21) as compared to 58% (11/19) among subjects not receiving methadone ($P=0.76$). In total, 37% (7/19) and 57% (12/21) of subjects receiving and not receiving methadone used illicit drugs during treatment.

The median duration of drug abstinence among all patients was 11.5 months. As shown in Figure 5, there was no difference in SVR among patients that had admitted to drug use in the 6 months preceding therapy (9/14, 64%) and individuals that had not used drugs in the 6 months prior to initiating therapy for HCV infection (13/26, 50%, $P=0.51$). Overall, 19/40 patients (48%) used illicit drugs at least once during treatment for HCV infection, with 18 subjects (45%) admitting

the use of cocaine or heroin. Of these, 9 used cocaine only, 4 used heroin only and 5 used multiple substances. Of the 19 subjects that used drugs, 10 used them occasionally (monthly/two or fewer times) and 9 used them frequently (everyday/every other day). Four of the nine regular users used injection cocaine, one used injection heroin, one used both injection heroin and cocaine and two used crack cocaine. The association between drug use during treatment and sustained virologic response is shown in Figure 5. Overall, there was no difference in response rates between subjects that did (12/21, 57%) and did not (10/19, 53%) use illicit drugs during treatment ($P=0.99$). However, the sustained virologic response was 57% in individuals without drug use during treatment, 80% among occasional users and 22% among frequent users. However, these differences did not achieve statistical significance ($P=0.12$). Discontinuations were observed in 5/9 (56%) of frequent users as compared to 9/31 (29%) subjects that did not use illicit drugs or were occasional users.

Discussion

This prospective, observational trial is among the first studies evaluating the antiviral efficacy of IFN α -2b or PEG-IFN α -2b in combination with ribavirin among current and former injection drug users enrolled in a directly observed therapy (DOT) program. Overall, we have demonstrated that 55% of subjects achieved an SVR, despite the fact that many individuals continued to use illicit drugs throughout their course of treatment. These results are comparable to response rates (54-56%) observed to date in large, randomized controlled trials using PEG-IFN α -2b in combination with ribavirin for the treatment of HCV infection (3, 5). Our results were achieved despite the fact that 35% of subjects had used illicit drugs in the 6 months preceding therapy and that 48% of patients used illicit drugs at least once during their course of treatment.

Pretreatment drug abstinence ≤ 6 months was not associated with poorer outcomes. This is consistent with data from one study of 76 current and former IDUs receiving self-administered IFN α -2b plus ribavirin in a community-based setting (13, 14). They observed that a shorter duration of pre-treatment drug abstinence was not associated with a significant reduction in virologic outcomes (22% vs. 30%, $P=0.18$). With this in mind, the decision to initiate treatment for HCV infection in current and former injection drug users should not be arbitrarily based on a pre-defined period of drug abstinence and must be an individualized decision based on the willingness of the patient to initiate treatment, social conditions which may impact the stability of the patient and other medical co-morbidities which may preclude treatment. There are data available to suggest that adherence to pre-treatment appointments may provide a good proxy of adherence to treatment for HCV infection in illicit drug users (15).

Illicit drug use of any kind during treatment for HCV infection was not associated with reduced response rates, unless it exceeds a specific frequency threshold, largely confirming data generated in other evaluations of similar subjects (13, 15-22). In one study of 50 patients offered self-administered treatment with IFN α -2a (n=34) and IFN α -2a plus weight-based ribavirin (n=16), 36% of patients achieved an SVR, despite the fact that 80% of patients relapsed to illicit drug use during treatment (15). Of the 76 subjects receiving IFN α -2b plus ribavirin in a study by Sylvestre et al., 28% of subjects achieved a sustained virologic response, despite the fact that 59% used illicit drugs during treatment (13). Intercurrent drug use was not associated with poorer outcomes ($P=0.09$). However, 0/8 individuals with drug use every 1-2 days responded to treatment. Data from 12 active IDUs receiving treatment with either IFN or PEG-IFN with or without RBV in a hospital-based setting in Australia demonstrated SVR rates of 50% (16). In most cases (11/12), drug use occurred at least every week. This is consistent with data from our study demonstrating that regular illicit drug use (every 1-2 days) was associated with reduced SVR rates (22% vs. 57%), while occasional use was not (80% vs. 57%). This is likely due to higher discontinuation rates that were observed among regular illicit drug users (56%) as compared to those that did not use illicit drugs or were occasional users (29%). Collectively, these data suggest that individuals with daily illicit drug use may respond less favorably to HCV treatment as a result of higher rates of therapy discontinuation. This may provide some insight into appropriate patient selection for HCV treatment among current and former IDUs. However, also based on these data, historical or ongoing occasional illicit drug use should not necessarily be considered a contraindication for HCV therapy. Further prospective studies appropriately

powered to address the impact of various illicit drugs (i.e. cocaine vs. heroin) and the frequency of illicit drug use prior to and during treatment on response to HCV treatment are needed.

The impact of HCV genotype on response to HCV treatment also warrants further discussion. Overall, subjects with genotypes 2/3 achieved higher SVR rates (64%) as compared those infected with genotype 1 (44%), which is consistent with large clinical trials demonstrating higher response rates in those infected with genotypes 2/3 (3-6). Overall, 55% of the individuals in this study were infected with genotypes 2/3 (genotype 2 – 15%, genotype 3 – 40%), which is consistent with epidemiologic data in Vancouver demonstrating a higher prevalence of genotype 3 infection among injection drug users (23). This is also consistent with other reports from Canada, Australia and Europe demonstrating a higher prevalence of HCV genotype 3 infection among IDUs (24-26). Given the higher response rates in genotype 2/3 subjects, this has important implications for strategies specifically targeting HCV therapy in this subgroup of patients.

There were several limitations to this study. First, this study is a prospective, observational trial. Although a randomized trial comparing DOT to self-administered therapy would be ideal, this was not possible in this setting given that DOT is the standard of care at these sites. Second, it would have been useful to have a comparison group of subjects that did not initiate treatment to understand the factors that are associated with the uptake of HCV treatment in this population. Such a study is currently ongoing in our centre. Lastly, the sample size was relatively small with only 40 patients having initiated treatment. However, these results provide important data supporting the proof-of-concept of DOT HCV treatment, providing the foundation for future prospective trials with the appropriate comparison groups. At our centres, a study is underway

comparing response rates, costs and patient quality of life after treatment for HCV infection among current and former IDUs receiving care within either a high or low multidisciplinary program.

Given the paucity of data evaluating the treatment of HCV infection in current and former injection drug users, the results from this study provide further evidence to suggest that the treatment of HCV infection in this group can be successful, even despite ongoing substance use during therapy. Our model utilizes the pre-existing infrastructure for the treatment of primary care and addiction within an inner city community health clinic to provide treatment for HCV. Important components of this model include a comprehensive multidisciplinary team and directly observed therapy (DOT). This includes the integration of administrative staff, nurses, counselors, physicians and researchers (providing the necessary expertise to evaluate the program in an objective manner). Nursing support is an absolutely essential component of the program. Nurses provide patient education prior to and during treatment, assess medication-associated toxicity, and ensure appropriate longitudinal monitoring is conducted as they administer weekly interferon injections. Directly observed monitoring of interferon injections may provide an important means of engaging subjects and maintaining a continuity of care during treatment. This also allows the multidisciplinary team to immediately address any side effects, ongoing illicit drug use, psychiatric issues and adherence issues which may arise.

Importantly, of those that discontinued therapy due to non-adherence, 4/6 subjects also developed concomitant depression. Given that many IDUs have a history of depression, monitoring and management of depression prior to and during treatment for HCV should be an important

component of HCV treatment programs among IDUs. Some have suggested that the use of antidepressants as a prophylactic measure at the time of initiation of HCV treatment may help reduce the occurrence of drug-associated depression and reduce the rate of premature treatment discontinuation. In our observational cohort, the patients that started therapy on antidepressants were no more likely to complete it. A number of small studies suggest that prophylactic treatment with antidepressants may be effective in reducing discontinuations associated with IFN-mediated depression (27, 28). However, this issue may be best resolved in a single prospective, randomized controlled study of adequate power. Such a study is already underway in Canada, CTN 194.

Given that the future burden of HCV infection will be largely among IDUs, programs for the treatment of HCV in this population must be expanded. Successful pilot programs have been described in a number of centres in North America (13, 21, 29, 30), Europe (15, 17, 19, 20, 22) and Australia (16). Our data add to this body of knowledge, in an era where more convenient formulations of interferon are available, allowing for more cost-effective DOT programs (requiring a single injection every week) to be set up. However, there still exists a considerable knowledge gap in this area. There are no data to recommend the best treatment program for IDUs, including the type and cost of infrastructure that must be put in place. Strategies for managing the neuropsychiatric side effects of interferon are also needed. Data evaluating HCV re-infection is also sparse. Although there are some data suggesting that prior spontaneous clearance of HCV infection is protective with respect to HCV re-infection (31, 32), it is not clear whether protection against HCV infection extends to those who have cleared their viremia following antiviral therapy. Preliminary data suggests that lower rates of re-infection are

observed after the treatment-induced clearance of HCV infection in IDUs when compared to the incidence of HCV infection in uninfected individuals (17, 33), however, this must be confirmed in prospective cohorts. Moreover, given that re-infection will still occur (although perhaps at a lower rate), it is critical to educate patients about the potential risks for HCV re-infection associated with needle and equipment sharing.

As IDUs continue to drive the HCV epidemic throughout the world, it is obvious that any attempt at its control must include systematic programs for the treatment of HCV infection in this population. Ultimately, the components of an effective program may be best evaluated in prospective trials, to allow for the identification of the essential elements of a successful program. Information derived from such trials will lead to the design of guidelines for the approach to HCV-infected IDUs in any situation in which they may be encountered.

Acknowledgements: We thank the staff of the Pender and Cool Aid Community Health Centres, and their clients, who agreed to participate in the study. This research was partially supported by the Vancouver Coastal Health Research Institute, Vancouver Coastal Health (Pender Community Health Centre), the Cool Aid Society (Cool Aid Community Health Centre), the British Columbia Medical Services Foundation, Schering Canada and Hoffmann-La Roche. Training support was provided by the Natural Sciences and Engineering Research Council of Canada (J.D.R.) and the National Canadian Research Training Program in Hepatitis C (J.G.). BC has received grants for clinical research from Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Agouron, and Abbott. BC has also received grants for educational activities from Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Agouron, and Abbott. BC has served as an advisor or consultant to Boehringer Ingelheim, Bristol-Myers Squibb, and Agouron. SD has served as a consultant for Bristol-Myers Squibb and Pfizer.

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Table 1. Baseline Characteristics

Characteristic	N=40
Mean Age – years (SD)	42.7 (8.6)
Male sex – n (%)	33 (82.5)
Body weight – kg	
Mean (SD)	82.8 (16.8)
≥75 kg – n (%)	25 (62.5)
Mean Estimated Duration of Infection – years (SD)**	13.2 (10.0)
Drug Abstinence	
< 6 months – n (%)	14 (35.0)
Median Time – months (IQR)	11.5 (4.8-30.0)
On Methadone Maintenance Therapy – n (%)	21 (52.5)
Median Methadone Dose – milligrams/day (SD)	67 (36)
History of Depression – n (%)	23 (58.0)
Pre-treatment with antidepressants – n (%)	14 (35.0)
HCV Genotype – n (%)	
1	18 (45.0)
2	6 (15.0)
3	16 (40.0)
Alanine aminotransferase – U/liter	
Median (IQR)	139 (87-216)
Median Alanine aminotransferase Quotient (IQR)	2.53 (1.58-3.93)

Median AST – U/liter (IQR)	93 (60-144)
HIV infection – n (%)	3 (7.5)

*SD, Standard Deviation; IQR, Interquartile range; U/liter, Units/liter.

**Duration of infection was calculated by the number of years injecting minus one year.

Figure 1. Subject Disposition. AEs, Adverse Events; EVR, early virologic response

Figure 2. Number of patients discontinuing interferon-based therapy early.

Figure 3. Virological response to treatment in all patients as measured by HCV RNA. EOT, End of treatment; SVR, sustained virologic response.

Figure 4. Virological response to treatment according to genotype and regimen received as measured by SVR, sustained virologic response.

Figure 5. Virological response to treatment according to duration of drug abstinence and intercurrent drug use as measured by SVR, sustained virologic response.