Hepatitis C Virus Eradication in Intravenous Drug Users Maintained with Subcutaneous Naltrexone Implants

Gary P. Jeffrey,[1,2] Gerry MacQuillan,[1,2] Fern Chua,[3] Sam Galhenage,[2] Judith Bull,[2] Emma Young,[2] Gary Hulse,[4] and George O'Neil [3]

The effectiveness of HCV antiviral therapy in patients who have undergone recent drug dependency treatment and continue to inject drugs sporadically is presently not clear. Patients attending a community-based drug rehabilitation and naltrexone implant clinic from October 2002 until March 2005 were screened for HCV infection and if positive offered further assessment and treatment with interferon and ribavirin therapy. The first 50 patients to commence HCV therapy and complete at least 6 months follow-up were prospectively studied. ETR response (HCV PCR negative) was 34/50 (68%) and SVR 6 months post-treatment was 31/50 (62%). Viral eradication was maintained in those 22 patients that have had 12 months or more post-treatment follow-up. Eleven (22%) patients stopped therapy early due to side effects or poor compliance. Only two patients with an ETR likely reinfected due to unsafe injection practices. One was re-treated and achieved an SVR. Of the patients achieving a 6-month SVR, 17 of 31 patients reported no further IDU and 13 of 31 patients occasional IDU during treatment and this was maintained after HCV treatment cessation. 46% of patients received antidepressant and/or antipsychotic medication during treatment. *Conclusion:* This study of HCV treatment in a community-based subcutaneous naltrexone implant clinic found antiviral therapy resulted in a 62% SVR. This result is comparable to that reported in hospital-based clinics in non-IDU patients. The side effect profile and compliance was also similar. HCV antiviral therapy should be offered to this large and currently under treated group. (HEPATOLOGY 2007;45:111-117.)

See Editorial on Page 3

Hepatitis C infection is a leading cause of disease worldwide and a significant proportion of chronically infected individuals develop progressive disease and in many centers hepatitis C virus (HCV) infection is the leading indication for liver transplantation.[1,2] Recent studies indicate that complications of hepatitis C–related cirrhosis, such as hepatocellular carcinoma and liver failure, will increase over the next 20 years.[3] Injecting drug users constitute the largest group of people infected with HCV. Users who continue to share needles have a high risk of infecting themselves and their injecting partners.[4] The prevalence of injecting drug use (IDU) continues to increase both worldwide and within Australia.[5]

The availability of interferon (IFN)-based treatment for chronic HCV infection has produced excellent rates of viral clearance, in particular the combination of pegylated IFN and ribavirin has produced rates of sustained virological response (SVR) ranging from 40% to 80% depending on viral genotype.[6,7] However, for patients who are currently injecting drugs, HCV treatment with IFN-based therapy has not been routinely recommended by many physicians caring for such patients. The reasons for this include the belief that injecting drug users are unlikely to adhere to the monitoring visits required to detect and

Abbreviations: ALT, alanine aminotransferase; AMPRF, Australian Medical Procedures Research Foundation; BMI, body mass index; ETR, end-of-treatment response; HCV, hepatitis C virus; IDU, injecting drug use; IFN, interferon; PCR, polymerase chain reaction; SVR, sustained virological response.

From the [1]School of Medicine and Pharmacology, the University of Western Australia; [2]Department of Gastroenterology/Hepatology, Sir Charles Gairdner Hospital; [3]Australian Medical Procedures Research Foundation (AMPRF); and [4]School of Psychiatry, the University of Western Australia, Perth, Western Australia.

Received July 17, 2006; accepted August 23, 2006.

Shering Corp (Kenilworth, NJ) provided funding for the nurse practitioner.

Address reprint requests to: Dr. Gary P. Jeffrey, Department of Gastroenterology/Hepatology, Sir Charles Gairdner Hospital, Verdun St., Nedlands, Perth, Western Australia 6009. E-mail: gjeffrey@cyllene.uwa.edu.au; fax: (61) 08 93 46 3098.

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.21470

Potential conflict of interest: Dr. Jeffrey advises for Roche.

avoid severe adverse events secondary to IFN and ribavirin therapy, that illicit drug use poses a greater short-term threat to health than hepatitis C infection, that side effects of treatment are increased, and that active drug users are more likely to reinfect themselves. Collectively, these factors may reduce the benefit whilst increasing the risk of treatment. In 2002, in a consensus statement on the management of hepatitis C, the National Institutes of Health recommended that people who use illicit drugs should be offered HCV treatment on an individual, case-by-case basis.[8] Other international guidelines have reiterated the policy of drug detoxification and abstinence prior to consideration of HCV treatment. However, the more recent 2004 AASLD Practice Guidelines have suggested that treatment of HCV infection should not be withheld from people who currently use intravenous drugs.[9] This view is supported by a recent meta-analysis of clinical studies that reported outcomes of HCV treatment for IDU.[10]

There are a limited number of studies reporting outcomes of treatment for HCV infection in active IDU.[11-14] Although these early results are encouraging, the SVR rates achieved using IFN-based treatment were not always equivalent to those achieved in the large registration trials and other hospital-based clinic studies.[6,7,15] Some IDU included in these trials received methadone maintenance therapy and others received none. Only one study delivered community-based care and there was not always coordinated management of the HCV treatment and the methadone maintenance therapy. A shared care model of HCV treatment has been reported to enhance the delivery HCV treatment to non-IDU HCV-infected individuals.[15] This model involved the coordination of care between hepatologist, family doctor, nurse specialist, and liaison psychiatrist and resulted in excellent adherence to therapy with only 2% of patients being non-compliant and 7% being withdrawn from treatment due to side effects. Applying a similar model to the treatment of HCV in active IDU may result in improved outcomes of treatment.

The most commonly used long term therapy for opiate addiction has been methadone maintenance treatment. While numerous studies have supported the efficacy of methadone in treating opioid dependence and subsequently decreasing individual and societal harm from illicit drug use, it does not prevent illicit opioid use in all.[16,17] Depending on the dose of methadone used varying proportions of those who enter treatment are still likely to be using illicit drugs several years after commencement, potentially compromising the efficacy of HCV treatment. As an alternative to methadone, naltrexone was introduced with the promise that it might overcome some of these deficiencies. Naltrexone is a long-acting opioid antagonist that can be taken orally as a single daily dose and is non-addictive and produces no euphoria.[18] Unfortunately, poor compliance rates have significantly limited its clinical effectiveness and it has not been widely accepted in drug rehabilitation programs.[19] Depot formulations of naltrexone have therefore been developed in an attempt to improve its effectiveness by improving compliance. One novel and effective naltrexone formulation is an implantable subcutaneous sustained release preparation that delivers therapeutic blood levels of naltrexone for 4 to 6 months.[20] These naltrexone implants have been used for opiate detoxification and subsequent maintenance therapy with excellent compliance rates and outcomes.[21,22]

A shared care program of HCV treatment was commenced in 2002 at the AMPRF drug detoxification and rehabilitation clinic. Since 2001, this community-based outpatient naltrexone implantation clinic has treated more than 850 patients with naltrexone implants. The shared care HCV clinic was staffed by a nurse practitioner, psychologist, addiction specialist, and hepatologist. The aim of this project was to determine if current injecting drug users who had undergone opiate detoxification and maintenance therapy with naltrexone implantation could be successfully and safely treated for HCV infection using the shared care model of HCV management.

Patients and Methods

Patients included were those with HCV infection who attended the Australian Medical Procedures Research Foundation community outpatient clinic in Perth, Western Australia from October 2002 until March 2005 for opiate detoxification and maintenance therapy. After opiate detoxification, the majority was administered a naltrexone implant subcutaneously. The GoMedical Implant is produced under International Patent Application Number: PCT/AUO11/01107, by GoMedical Industries Pty Ltd, Australia. In these implants, naltrexone is encapsulated in poly-DL-lactide micro spheres compressed into tablets and 10 tablets are grouped together to form one implant. Each implant contains either 1.7g or 3.4g of naltrexone and has an *in vitro* release rate of 0.3-0.4% of its residual mass per day. The implants are placed under the skin in the lower abdominal wall using local anaesthesia. Implants are replaced after 3-6 months as required.

A shared care model for HCV management was developed with an AMPRF medical officer with expertise in addiction medicine, a nurse specialist in HCV management, clinical psychologist, and a hepatologist reviewing patients at the AMPRF community clinic. Emergency medical and psychiatric back-up facilities were available at

Sir Charles Gairdner Hospital as required. Patients were initially assessed by the addiction specialist and nurse specialist and provided with educational literature regarding HCV infection and treatment and also advised regarding safe injecting practices and other harm minimization principles. If the patient requested further HCV information or HCV treatment they were seen by the hepatologist prior to any liver biopsy being performed. Treatment was commenced by the medical officer and nurse specialist and patients were reviewed monthly in the clinic or more frequently as required. Any change in medication was a combined decision between the medical officer and hepatologist

The first 50 patients that commenced HCV treatment are reported here. Patients were included if they had active HCV infection and were aged between 18 years and 65 years. Active HCV infection was determined by a positive qualitative in-house real-time HCV RNA PCR assay on at least two occasions. Quantitative HCV PCR analysis was performed using the COBAS Amplicor HCV monitor test V2 (Roche Molecular Systems, Branchburg, NJ). Patients were initially screened with a HCV antibody test. Patients with infection duration of 6 months or more (chronic HCV, n = 49) and infection duration less than 6 months (acute HCV, n = 1) were included. Patients with normal serum levels of alanine aminotransferase (ALT) levels, well-compensated cirrhosis and those with a previous history of additional drug use including alcohol, benzodiazepines, amphetamines, cocaine and marijuana could also be included in the study. Exclusion criteria included pregnancy, no reliable contraception methods, severe uncontrolled depression/psychosis, severe renal failure, severe uncontrolled diabetes, severe cardiovascular disease, and HIV infection.

HCV treatment was started and monitored by the medical officer and nurse practitioner and consisted of combination therapy with alpha-IFN plus ribavirin. The IFN preparation, administered subcutaneously, was either IFNα-2b at a dose of 3 million units, 3 times a week (n = 15) or pegylated INFα-2b at a dose of 1.5 mcg/kg once weekly (n = 35). Pegylated INFα-2b was used in patients after the Australian Federal Government started full reimbursement for this medication. Ribavirin was administered orally twice daily at a daily dose of 1000 mg in patients less than 75 kg or 1200mg in patients over 75kg. Therapy was for 24 weeks for HCV genotypes 2 and 3 and for 48 weeks for genotypes 1 and 4. Pharmacotherapy was dispensed through a community pharmacy. The nurse specialist or medical officer reviewed subjects every 4 weeks for symptom assessment and results review. Blood tests were performed at week 1, week 2, week 4 and then monthly for the duration of treatment. After 12 weeks of treatment, a repeat HCV RNA RT- PCR assay was performed to assess response to therapy. If the HCV RNA remained positive and the serum ALT remained elevated, therapy was terminated. If the ALT normalized but the HCV RNA was detected, therapy was continued for a further 12 weeks, but was subsequently terminated if the HCV RNA remained positive at 24 weeks. Patients were followed for at least 6 months following completion of HCV treatment. Data collection was prospective and was facilitated by the nurse specialist.

The doses of IFN and ribavirin were reduced during therapy due to significant cytopaenias. Dose reduction of IFN and ribavirin was to 50% of the original dose. The dose of IFNα-2b was halved if the total white cell count was $<1.5 \times 10^9$/l, neutrophil count was $<0.75 \times 10^9$/l and platelet count was $<50 \times 10^9$/l. The dose of ribavirin was halved if the haemoglobin was <100 g/l or unconjugated bilirubin was >68 μmol/l. Therapy was permanently ceased if the haemoglobin fell below 85g/l, total white cell count fell below 1.0×10^9/l, neutrophil count fell below 0.5×10^9/l or platelet count fell below 25×10^9/l.

Compliance with and completion of the course of HCV treatment was assessed by monitoring patient collection of drugs from pharmacy. Attendance to all clinic appointments was recorded. Monitoring whether medication was taken was by self-report. A specifically designed questionnaire was used to monitor HCV risk behaviors in the 3 months prior to, during, and 3 months following treatment. The questionnaire included data on the frequency of illicit drug use, alcohol intake, sharing of needles, syringes, and other injecting paraphernalia before or after another person, and needle stick injury. Injecting drug use was quantified as none, minimal (any use), or heavy (daily use). Alcohol use was quantified as none, minimal (any use), moderate (40g-100g daily) or heavy (>100g daily).

The primary endpoint of treatment was a SVR defined as the absence of serum HCV RNA 24 weeks after treatment was completed. Results were analyzed on an intention-to-treat basis. Secondary endpoints included end-of-treatment response (ETR) which was defined as negative serum HCV RNA at the completion of treatment, assessment of patient side effects and compliance with HCV treatment and assessment of changes in self-reported HCV risk behaviors before, during, and after treatment. Data were analyzed using *t* tests for continuous variables and χ^2 tests for discrete variables. Univariate and multivariate logistic regression analysis was used to predict markers of a sustained virological response to combination therapy. Significance was determined at the level of $P < 0.05$. Logistic Regression was performed using SPSS version 14. Informed consent was obtained from patients

Table 1. Patient Characteristics and Response to Treatment

	Total	SVR	Non-SVR
Number	50	31	19
Male:Female	34:16	21:10	13:6
Mean age in years (range)	35 (19-54)	32 (21-48)	38 (19-54)
Mean BMI (range)	24 (18-46)	24 (18-34)	26 (18-46)
Genotype 1	17	9	8
Genotype 2	3	1	2
Genotype 3	30	21	9
Viral load (IU/ml) - $\geq 5 \times 10^5$	21	11	10
5×10^4 - 4.9×10^5	21	14	7
5×10^3 - 4.9×10^4	5	3	2
5×10^2 - 4.9×10^3	3	3	0
Metavir F0,1,2	43	29	14
Metavir F3,4	6	1	5†
Previous antiviral therapy	6	2	4
Subcutaneous naltrexone implant	41	24	17
Antidepressant with HCV treatment	16	10	6
Antipsychotic with HCV treatment	12	7	5
Alcohol >100g/day‡	14	4	10†

NOTE. Data expressed as n unless otherwise indicated.
†Significantly different from the SVR group, univariate anaylsis $P < 0.05$.
‡More than 100g of alcohol/day for more than 5 years.

prior to commencing HCV treatment and the study was approved by the Sir Charles Gairdner Hospital ethics committee.

Results

The characteristics of the 50 patients that had HCV treatment and completed at least 6 months follow-up are shown in Table 1. Most were male (male:female 2:1) and the mean age was 35 years (range 19-54). The mean BMI was 24 (range 18-46) and only 4 had a BMI of ≥30. 66% had genotype 2 or 3 and 58% had a viral load $<5 \times 10^6$ IU/ml. Liver biopsy was performed before HCV treatment was started in 49 patients with chronic HCV. Metavir fibrosis stage was six patients with F0, 27 patients with F1, ten patients with F2, five patients with F3, and one patient with F4. The one patient who did not undergo liver biopsy had acute HCV infection. Six patients had had previous HCV treatment, three of these receiving IFN monotherapy. Forty-one subjects received naltrexone implants for opiate avoidance maintenance therapy, three others received oral naltrexone, four oral buprenorphine, and two refused any therapy. Antidepressant medication and/or antipsychotic medication was used in 64% of patients before HCV therapy commenced and in 46% of patients during HCV therapy.

Intention-to-treat analysis was used to determine the primary end point of SVR 6 months post–HCV therapy and this was achieved in 31 patients (62%). This result was maintained in those 22 patients that have now had 12 months or more post-treatment follow-up. Five patients that had an ETR failed to achieve a SVR and this was due to recurrence of HCV infection in three (all genotype 2/3) and failed follow-up in two (one genotype 3). Three patients that were not documented to have achieved an ETR eventually had a SVR and this was due to no HCV PCR assay being performed at the end of HCV treatment in two and early cessation of HCV treatment in the other. Analysis of the data including only those subjects that completed more than 80% of the dose of medication for more than 80% of the time found that a SVR was obtained in 30 of 43 patients (70%).[23] Analysis of the factors that predicted a SVR found that the presence of severe fibrosis ($P = 0.027$) and heavy alcohol usage ($P = 0.003$) was significantly associated with a reduced likelihood of an SVR (Table 1). Genotype ($P = 0.3$), age ($P = 0.14$), BMI ($P = 0.26$), viral load ($P = 0.2$), heavy IDU prior to treatment ($P = 0.3$) and during treatment ($P = 0.5$) were not predictive of a SVR. Using multivariate logistic regression severe fibrosis ($P = 0.06$) was trending toward significance as a marker of non-response. Heavy alcohol use was associated with a non-response ($P = 0.01$).

Eleven (22%) patients stopped therapy early due to side effects or poor compliance. Four patients that achieved a SVR stopped due to non-compliance in one, somatic side effects in two, and imprisonment in another. Of the seven patients without a SVR, three stopped therapy due to non-compliance, two stopped due to somatic side effects, one stopped for pregnancy, and another for depression. The frequency of side effects was significant with 54% of the patients experiencing flu-like symptoms, 32% developing anorexia/nausea, 30% having mood swings, and 28% complaining of depression. Headache and hair thinning each occurred in 20%, diarrhea in 8%, infection in 6%, and rash in 2%. Dose reduction of IFN or ribavirin due to hematological abnormalities occurred infrequently. Only three subjects had IFN dose reductions due to neutropenia.

The majority (88%) of subjects prior to undergoing detoxification and maintenance therapy with naltrexone implants had a history of heavy (daily) IDU (Fig. 1). In those 41 patients with naltrexone implants, the median time from implant placement to HCV treatment was 6 months (range 0-36). During HCV treatment IDU frequency had decreased significantly with only one of 48 having heavy use and 17 of 48 having minimal IDU. This pattern was maintained after the completion of HCV treatment. Two of the three patients that had a recurrence of HCV following an ETR gave a history of unsafe injection practices. One was re-treated and achieved an SVR. Importantly, of those 31 patients that achieved a 6 month SVR, 17 reported no further IDU, and 13 only occasional IDU during treatment and this was maintained after HCV treatment cessation. Before HCV treatment began,

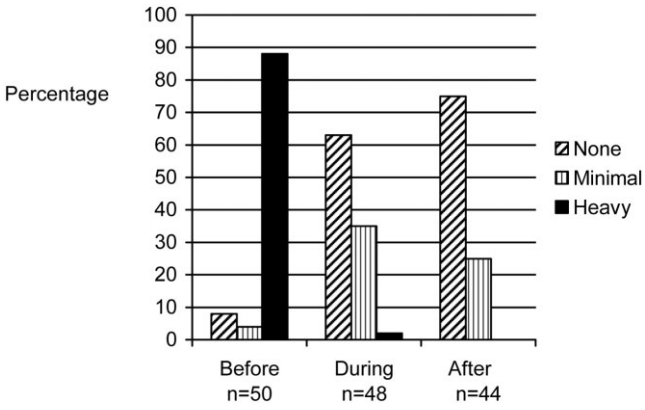

Fig. 1. Injecting drug use in subjects before naltrexone implant treatment (Before), during HCV treatment (During) and after HCV treatment (After). n = number of patients analyzed. Frequency of injecting drug use defined as none, minimal (any use), or heavy (daily use).

heavy daily alcohol intake was present in 28% patients and heavy daily marijuana use was present in 34% of patients. All patients decreased the alcohol intake to less that 70g/week during and after therapy, while heavy marijuana use decreased to 12% for the same period. Any or heavy marijuana use during therapy was not associated with improved SVR ($P = 0.76$, $P = 0.15$).

Discussion

It is now established that HCV treatment requires a coordinated, multidisciplinary health professional team and an informed and committed patient to achieve the best rates of HCV eradication with IFN-based treatments, irrespective of whether a patient is an active injecting drug user. The 62% SVR achieved in this study for all genotypes is similar to those reported by the large controlled clinical registration trials of pegylated IFN and ribavirin where the SVR was 54% and 63%.[6,7] The 70% SVR for genotype 3 patients and 53% SVR for genotype 1 patients is consistent with the known resistance to IFN-based therapy of HCV genotype 1. The high viral eradication rates obtained after treatment of acute HCV did not contribute to the excellent SVR in this study, as the SVR remained 61% after exclusion of the single acute HCV patient included in the analysis.[24] Previous studies of HCV treatment in active IDU did not report equivalent SVR rates and the improved outcome in this study may have been partly due to the use of pegylated IFN and ribavirin in two thirds of our cases, although the SVR for those 15 patients receiving IFN and ribavirin was 80% and for those 35 who received pegylated IFN and ribavirin it was 49%. Twelve of the 15 patients that received IFN and ribavirin were genotype 3 and pegylated IFN and ribavirin added little benefit to SVR rates for this genotype.[6]

Other factors that may have also contributed to the excellent SVR in this study was the early stage of liver fibrosis present in most patients and the high proportion (66%) of patients with HCV genotype 3. Although, neither stage of fibrosis or HCV genotype 1 was associated with non-response using multivariate logistic regression analysis, this lack of association may have been due to the relatively small number of subjects in the study. A history of previous heavy alcohol intake was associated with non-response ($P < 0.05$) in this group of IDU subjects with naltrexone implants. Others have recently reported that previous moderate alcohol intake (>30g/day) was associated with a decreased SVR to pegylated IFN and ribavirin[25] and this is in agreement with other published data in HCV subjects treated with IFN monotherapy.[26] The exact mechanism whereby previous moderate or heavy alcohol intake results in poorer HCV response rates to IFN-based therapy is unknown. Alcohol use within 12 months of IFN and ribavirin treatment for HCV was associated with decreased retention in therapy but probably had no effect on the efficacy of the antiviral effect of treatment.[27]

Theoretically, there appears to be some advantages to the use of naltrexone rather than methadone maintenance therapy with regards to effects on immune response and on viral clearance. *In vitro* studies have suggested that opiates can reduce endogenous IFN production and enhance HCV replicon expression, which could potentially compromise the anti-HCV effect of exogenous IFN.[28,29] It is interesting that this effect can be blocked by naltrexone, suggesting that the use of subcutaneous naltrexone implants may augment the effect of IFN therapy. There is also a considerable body of evidence that has demonstrated that opiates impair the adaptive and innate immune response to infectious agents.[30] The excellent SVR found in this present study using subcutaneous naltrexone implants that provide constant serum levels of naltrexone may in part be related to this immune modulating effect of naltrexone and this warrants further study.

The side effect profile of IFN/pegylated IFN and ribavirin in this group of active IDU patients was no worse than that reported for non-IDU patients in the highly selected HCV population treated in the pegylated IFN/ribavirin registration trials and also in hospital-based clinics.[6,7,15] Flu-like symptoms were present in half and altered mood and anorexia/nausea were present in one third. Depressive symptoms were reported in 28% and at the end of treatment half of all patients were receiving antidepressant medication and/or antipsychotic medication. Others have previously reported the high prevalence of depression in IDU with HCV, with 50% having evidence of moderately severe depression.[31] This study found that active IDU patients tolerated side effects as

well as non-IDU patients reported in the literature and drug discontinuation in 14% due to side effects was also similar to reported rates. One benefit of the "shared care" approach to treatment is that collaborative involvement of addiction specialists and psychiatric services with patient care allows a planned approach to preexisting or IFN-induced psychiatric disorders. In those with a history of depression often prophylactic antidepressant therapy or early preemptive therapy for minor exacerbations of depression allows patients to complete HCV treatment and achieve a SVR.

One major concern regarding HCV treatment for active IDU patients is that any benefit of treatment would be lost if patients reinfected themselves due to continued unsafe injection techniques. Long-term follow-up studies of active IDU that have had more than 6-month post-treatment SVR would provide some reassuring evidence that this was not the case. This current study has follow-up data on 22 patients that have now had 12 months or more post-treatment follow-up and all have remained HCV RNA negative. One other study of rehabilitated IDU patients has provided follow-up data a median of 5 years following end of treatment and only one of 27 reinfected.[32] Combined, these data suggest that reinfection due to continued risky IDU is not a significant problem, however, further data are clearly required. Nevertheless, reinfection due to continued intravenous drug use probably occurred in two patients in this present study after an ETR, but fortunately retreatment in one resulted in a SVR. Reinfection with HCV after spontaneous recovery has been reported in HCV patients but interestingly the risk of developing chronic HCV infection from reinfection is less than that in those who are infected for the first time.[33] It is not known whether this benefit also occurs with reinfection after previous IFN-induced viral clearance.[34]

Contrary to some opinions regarding likely poor compliance with HCV treatment requirements, the active IDU patients in this study were highly motivated to access HCV treatment and attend the required follow-up visits in the community shared care clinic. The excellent compliance rate attested to this with only 8% of patients dropping out of the study due to compliance issues. Many of the patients linked the eradication of HCV infection with opiate detoxification and rehabilitation as a single package that provided a means of commencing a new period in their lives away from the environment of narcotic use. The provision of a shared care clinic where the hepatologist and nurse practitioner visited the drug rehabilitation and naltrexone implant clinic and not vice versa was central in developing the trust and confidence between IDU patients and health care workers that was required to successfully engage patients in HCV treatment.

This prospective uncontrolled observational study has provided further data to the existing evidence that HCV treatment should be offered to active IDU individuals only after they understand the requirements of treatment and its risks and benefits. The use of subcutaneous naltrexone implants and a community-based shared care facility as the provider of HCV treatment results in viral clearance rates equivalent to outcomes achieved in the large controlled clinical trials.

References

1. Thomas DL. Hepatitis C epidemiology. Curr Top Microbiol Immunol 2000;242:25-41.
2. Zekry A, Whiting P, Crawford DH, Angus PW, Jeffrey GP, Padbury RT, et al. Liver transplantation for HCV associated liver cirrhosis: Recipient predictors of outcomes in a population with significant genotype 3 and 4 distribution. Liver Transplant 2003;9:339-347.
3. Buti M, San Miguel R, Brosa M, Cabases JM, Medina M, Angel Casado M, et al. Estimating the impact of hepatitis C virus therapy on future liver-related morbidity, mortality and costs related to chronic hepatitis C. J Hepatol 2005;42:639-645.
4. Hahn JA, Page-Shafer K, Lum PJ, Bourgois P, Stein E, Evans JL, et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis 2002;186:1558-1564.
5. Wodak A. Injecting nation: achieving control of hepatitis C in Australia. Drug Alcohol Rev 1997;16:275-284.
6. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958-965.
7. Fried MW, Shiffman ML, Reddy KJ, Smith C, Marinos G, Gonçales FL, et al. Peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus infection. N Eng J Med 2002;347:975-982.
8. National Institutes of Health Consensus Statement on Management of Hepatitis C: 2002. NIH Consensus and State-of-the-Science Statements 2002;19.
9. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. HEPATOLOGY 2004;39:1147-1171.
10. Schaefer M, Heinz A, Backmund M. Treatment of chronic hepatitis C in patients with drug dependence: time to change the rules? Addiction 2004; 99:1167-1175.
11. Backmund M, Meyer K, Von Zielonka M, Eichenlaub D. Treatment of hepatitis C infection in injection drug users. HEPATOLOGY 2001;34:188-193.
12. Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, Schindlbeck N, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. HEPATOLOGY 2003;37:443-451.
13. Van Thiel DH, Anantharaju A, Creech MS. Response ot treatment of hepatitis C in individuals with a recent history of intravenous drug abuse. Am J Gastroenterol 2003;98:2281-2288.
14. Sylvestre DL, Litwin AH, Clements BJ, Gourevitch MN. The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone. J Subst Abuse Treat 2005;29:159-165.
15. Kontorinis N, Young J, Garas G, Speers D, Chester BP, MacQuillan G,et al. Outcome, tolerability and compliance of compassionate use interferon and ribavirin for hepatitis C infection in a shared care hospital clinic. Intern Med J 2003;33:500-504.
16. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. The

Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD002209. DOI:10.1002/14651858.CD002209.
17. Caplehorn JRM, Ross MW. Methadone maintenance and the likelihood of risky needle-sharing. Int J Addict 1995;30:685-698.
18. Rawson RA, McCann MJ, Hasson AJ, Ling W. Addiction pharmacotherapy 2000: new options, new challenges. J of Pscychoactive Drugs 2003; 32:371-377.
19. Ward J, Hall W, Mattick RP. Role of maintenance treatment in opioid dependence. Lancet;1999;353:221-226.
20. Hulse GK, Arnold-Reed DE, O'Neil G, Chan CT, Hansson R, O'Neil P. Blood naltrexone and 6-β-naltrexol levels following naltrexone implant: comparing rwo naltrexone imlplants. Addict Biol 2004;9:59-65.
21. Hulse GK, O'Neil G, Hatton M, Paech MJ. Use of oral and implantable naltrexone in the management of the opioid impaired physician. Anaesth Intensive Care 2003;31:196-201.
22. Hulse GK, O'Neil G, Arnold-Reed DE. Methadone maintenance vs. implantable naltrexone treatment in the pregnant heroin user. International J of Gyn Obst 2004;85:170-171.
23. McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 2002;123:1061-1069.
24. Kamal AM, Fouly AE, Kamel RR, Hockenjos B, Tawil AA, Khalifa KE, et al. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. Gastroenterology 2006;130:632-638.
25. Chang A, Skole K, Gautam M, Schmutz J, Black M, Thomas R, et al. The impact of past alcohol use on treatment response rates in patients with chronic hepatitis C. Aliment Pharmacol Ther 2005;22:701-706.
26. Tabone M, Sidoli L, Laudi C, Pellegrino S, Rocca G, Della Monica P, et al. Alcohol abstinence does not offset the strong negative effect of lifetime alcohol consumption on the outcome of interferon therapy. J Viral Hepat 2002;9:288-294.
27. Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, et al. Alcohol use and treatment of hepatitis C virus: results of a national multicentre study. Gastroenterology 2006;130:1607-1616.
28. Geber WF, Lefkowitz SS, Hung CY. Effect of morphine, hydromorphone, methadone, mescaline, trypan blue, vitamin A, sodium salicylate, and caffeine on the serum interferon level in response to viral infection. Arch Int Pharmacodyn Ther 1975;214:322-327.
29. Li Y, Zhang T, Douglas SD, Lai JP, Xiao WD, Pleasure DE, et al. Morphine enhances hepatitis C virus (HCV) replicon expression. Am J Pathol 2003;163:1167-1175.
30. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosupression: a review. Am J Ther 2004;11:354-365.
31. Golub ET, Latka M, Hagan H, Havens JR, Hudson SM, Kapadia F, et al. Screening for depressive symptoms among HCV-infected injection drug users: examination of the utility of the CES-D and the Beck Depression Inventory. J Urban Health 2004;81:278-290.
32. Dalgard O, Bjoro K, Hellum K, Myrvang B, Skaug K, Gutigard B, et al. Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up. Eur Addict Res 2002;8:45-49.
33. Mehta SH, Cox A, Hoover DR, Wang XH, Mao Q, Ray S, et al. Protection against persistence of hepatitis C. Lancet 2002;359:1478-83.
34. Asselah T, Vidaud D, Doloy A, Boyer N, Martinot M, Vidaud M, et al. Second infection with a different hepatitis C virus genotype in a intravenous drug user during interferon therapy. Gut 2003;52:900-902.