Predictors of deferral of treatment for hepatitis C infection in Australian clinics

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ABSTRACT

Objective: To determine uptake of treatment for hepatitis C virus (HCV) infection and predictors of deferral of treatment for HCV by using prospectively collected data from the Australian Chronic Hepatitis C Observational Study (ACHOS).

Design, patients and setting: Cohort study involving interview and medical record review at enrolment and routine follow-up clinic visits of patients with chronic HCV and compensated liver disease attending a national network of 24 HCV clinics between April 2008 and December 2009. Eligible patients were those who had not been previously treated, were enrolled within 6 months of their first clinic visit, were eligible for treatment and had been enrolled for at least 6 months.

Main outcome measure: Predictors of patients undergoing HCV treatment within the first 6 months of assessment.

Results: 1239 patients were enrolled in ACHOS, of whom 406 met the criteria for inclusion in the subcohort for this study. Among this subcohort, 171 (42%) received treatment within 6 months of their first clinic visit. Current injecting drug use (odds ratio [OR], 0.26; 95% CI, 0.08–0.77), past and current treatment for drug dependency (OR, 0.34; 95% CI, 0.18–0.67, and OR, 0.42; 95% CI, 0.22–0.81, respectively) and alcohol use above 20 g/day (OR, 0.20; 95% CI, 0.08–0.46) were independent predictors of deferral of treatment. At least one of these factors applied to 41% of the subcohort. Clinical factors, including HCV genotype, HCV RNA level, and stage of liver disease were not associated with deferral of treatment for HCV.

Conclusion: Factors related to drug and alcohol use, rather than clinical factors, influenced uptake of treatment for HCV. Further support for patients with drug and alcohol dependency is required to optimise treatment uptake.

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The burden of disease associated with hepatitis C virus (HCV) infection is increasing even though effective treatment is available. HCV infection is now the most frequent indication for liver transplantation in Australia.[1] In addition, hospitalisation rates for HCV-related liver disease and liver cancer have increased significantly in recent years.[2] Treatment with combination therapy of pegylated interferon and ribavirin has the potential to reduce this burden, with virological "cure" rates of more than 50%,[3,4] and a consequent reduction in the risk of progression of liver disease.[5] However, only a minority of people in Australia who are infected with HCV have been treated.[6] Identifying the factors associated with low levels of treatment uptake may be an important step towards reducing HCV-related morbidity.

Several studies have previously investigated barriers to treatment uptake in the clinic setting. However, most were conducted in only one or two clinics[7-9] or in a specific subpopulation, such as United States veterans,[10,11] and these studies were generally cross-sectional or involved a retrospective review of existing, sometimes incomplete, patient records.

In Australia, HCV treatment is provided through the government-subsidised Highly Specialised Drugs (HSD) program under section 100 (S100) of the *National Health Act 1953* (Cwlth). All patients with chronic HCV infection aged 18 years or older are eligible, provided they are using effective forms of contraception and have compensated liver disease.[12] The aim of our study was to determine the level of uptake of antiviral treatment, and to identify predictors of deferral of such treatment by using prospectively collected data from a network of HCV clinical services across Australia.

METHODS

The Australian Chronic Hepatitis C Observational Study (ACHOS) is a prospective cohort study of patients attending 24 clinics in a variety of settings (Box 1) in four Australian states and the Australian Capital Territory. Between April 2008 and December 2009, eligible patients were recruited at each clinic. In most clinics, consecutive patients were recruited; however, in larger clinics where the work volume did not permit consecutive sampling, a random sampling strategy was used. Criteria for enrolment in ACHOS were based on eligibility for current HCV treatment under the HSD program (as described above).[12] To examine predictors of treatment uptake among recently assessed HCV-treatment-naive patients, we selected an ACHOS subcohort which only included patients enrolled within 6 months of their first clinic visit, who had been enrolled for at least 6 months, and who had not previously been treated with antiviral therapy for HCV. If a patient's reason for deferring treatment indicated they were ineligible for treatment under the HSD program,[12] they were excluded.

At the time of enrolment into ACHOS, patients were interviewed by the site coordinator and/or clinician and their medical and pathology records were reviewed to obtain demographic, lifestyle and clinical information. Patients were considered current injecting drug users (IDUs) if they reported injecting in the previous 6 months. Alcohol consumption was assessed by questions about frequency (number of days per week, less than weekly, not in the past year, never) and average number of standard drinks (10 g of alcohol) on a day that alcohol is consumed.[13] Year of infection, if unknown, was estimated as the year of first injecting drug use among patients who acquired HCV infection through injecting drug use. Clinical data that we collected included whether the patient had cirrhosis (clinical diagnosis or confirmed by biopsy), any history of a treated psychiatric illness, and past and current types of treatment for drug dependency and HCV infection. Pathology test results included serological tests for HIV and hepatitis B, liver histology, HCV genotype, HCV RNA levels, and haematological and biochemical

1 Numbers of clinics and patients enrolled in the Australian Chronic Hepatitis C Observational Study (ACHOS) and patients in the predictor analysis subcohort by clinic type

Clinic type	Number of clinics	Number of patients	
		ACHOS	Analysis subcohort
Major metropolitan hospital	13	704 (56.8%)	250 (61.6%)
Primary care	1	67 (5.4%)	2 (0.5%)
Drug dependency	2	116 (9.4%)	10 (2.5%)
Regional	6	299 (24.1%)	126 (31.0%)
Correctional centre	2	53 (4.3%)	18 (4.4%)
Total clinics	24	1239 (100%)	406 (100%)

parameters. All data were recorded by the site coordinator in a secure web-based data entry system.

The timing of follow-up visits to the clinic after the enrolment visit were determined by the patient's clinician according to routine clinical care requirements. At follow-up visits, data about changes in treatment or health, reasons for treatment deferral and new pathology test results were recorded.

Ethics approval for the study was granted by the University of New South Wales and ethics committees representing each of the clinic sites. All patients provided written informed consent.

Statistical analysis

Treatment uptake was defined as patients commencing treatment (with standard interferon or pegylated interferon with or without ribavirin, and/or a clinical trial drug) for their HCV infection in the 6 months after their first clinic visit. Factors significantly associated with treatment uptake ($P \leq 0.1$) in a univariate analysis were included in a multivariate logistic regression model. Modelling was performed using a stepwise backward elimination procedure, retaining only factors that were significant at $P \leq 0.05$ in the final model. A logistic regression model conditional on clinic site was performed as a sensitivity analysis to ensure that results were robust to possible differences in patterns of treatment uptake between sites.

RESULTS

There were 1239 patients enrolled in ACHOS between April 2008 and December 2009; 17% had received treatment previously and 49% received treatment at or after enrolment. Of the total cohort, 436 (35%) were enrolled within 6 months of their first clinic visit and had follow-up for at least 6 months. Twenty-two of these patients (5%) were excluded because they had previously been treated (21) or their treatment status was unknown (one), and eight were excluded because they were ineligible for treatment under the HSD program[12] (pregnancy or family planning as the reason for deferral of treatment). This left a subcohort of 406 patients for our analysis of predictors of HCV treatment uptake. All 24 clinic sites and five clinic types were represented in the subcohort (Box 1). However, proportionally fewer patients of primary care and drug dependency clinics were eligible for the analysis subcohort because many of these patients were longstanding clients who were attending the clinics for reasons other than their HCV infection.

Patient characteristics

Characteristics of the patients selected for the analysis subcohort were generally similar to the rest of the ACHOS cohort (data not shown; see http://www.nchecr.unsw. edu.au/NCHECRweb.nsf/page/ACHOS for the ACHOS cohort profile) except for the subcohort having a smaller proportion of patients who: (i) had had a liver biopsy (removed as a criterion for treatment in April 2006; 19% v 44%; $P < 0.001$); (ii) were infected with HCV genotype 1, 4 or 6 (46% v 56%; $P = 0.004$); and (iii) reported current treatment for drug dependency (18% v 27%; $P < 0.001$). Data on HCV RNA levels, biochemical parameters, and cirrhosis status were also more complete in the analysis subcohort. In both cohorts, about two-thirds were past IDUs, more than a third had a history of psychiatric illness, over a fifth were born overseas, but few had HIV or chronic hepatitis B co-infection.

Treatment uptake

Of the 406 patients selected for the analysis subcohort, 171 (42%) commenced treatment within 6 months of their first clinic visit, while 235 deferred treatment. Of those who were treated, 163 (95%) received pegylated interferon plus ribavirin, four received pegylated interferon monotherapy and four received standard interferon plus ribavirin. By far the most frequently recorded reason for deferring treatment for HCV was that patients were still in their initial stages of assessment (Box 2). However, 54 of the 235 patients recorded as deferring treatment (23%) did not return for follow-up visits after their initial assessment at enrolment and, of these, 27 (50%) were recorded as being in their initial stages of assessment.

Predictors of treatment deferral

Factors that were not associated with treatment deferral in the univariate analysis

2 Reasons recorded by the clinic for treatment deferral in the analysis subcohort

Deferral reason	Patients
Patient still in initial stage of assessment process	120 (51.1%)
Patient declined or unwilling	19 (8.1%)
Patient on waiting list to commence treatment	15 (6.4%)
Alcohol dependency	13 (5.5%)
Chronic medical comorbid condition	13 (5.5%)
Lifestyle-related*	10 (4.3%)
Psychiatric comorbid condition	10 (4.3%)
Awaiting new treatment	8 (3.4%)
Drug dependency	8 (3.4%)
Early liver disease	6 (2.6%)
Other comorbid condition	5 (2.1%)
Less responsive hepatitis C virus genotype (1 or 4)	4 (1.7%)
Other	4 (1.7%)
Total patients who deferred treatment	235 (100%)

* Includes social, accommodation, study, travel and legal reasons. ◆

3 Factors associated with deferral of hepatitis C virus treatment among patients in the analysis subcohort

	Treatment		Univariate analysis			Multivariate analysis		
Predictor	No	Yes	OR (95% CI)	*P*	*P* (overall)	OR (95% CI)	*P*	*P* (overall)
Total patients	235	171 (42.1%)						
Country of birth								
Australia	194	127 (39.6%)	1			1		
Other	41	44 (51.8%)	1.64 (1.01–2.65)	0.044		1.29 (0.79–2.10)	0.302	
Injecting drug use								
Never	45	53 (54.1%)	1			1		
Past	159	113 (41.5%)	0.60 (0.38–0.96)	0.033	< 0.001*	1.05 (0.61–1.80)	0.858	0.023*
Current	31	5 (13.9%)	0.14 (0.05–0.38)	< 0.001		0.26 (0.08–0.77)	0.015	
Treatment for drug dependency								
Never	117	125 (51.7%)	1			1		
Past	45	18 (28.6%)	0.37 (0.21–0.68)	0.001	< 0.001*	0.34 (0.18–0.67)	0.002	0.001*
Current	49	22 (31.0%)	0.42 (0.24–0.74)	0.003		0.42 (0.22–0.81)	0.009	
Unknown	24	6 (20.0%)						
Alcohol use								
Never or past	99	88 (47.1%)	1			1		
Current ⩽ 20 g/day	89	67 (42.9%)	0.85 (0.55–1.30)	0.446	< 0.001*	0.88 (0.56–1.38)	0.574	< 0.001*
Current > 20 g/day	38	8 (17.4%)	0.24 (0.10–0.53)	0.001		0.20 (0.08–0.46)	< 0.001	
Unknown	9	8 (47.1%)						
Duration of infection								
< 10 years	65	33 (33.7%)	1			1		
10–19 years	62	39 (38.6%)	1.24 (0.69–2.21)	0.469	0.021†	1.12 (0.60–2.08)	0.717	0.254†
⩾ 20 years	100	90 (47.4%)	1.77 (1.07–2.94)	0.027		1.38 (0.79–2.41)	0.265	
Missing data	8	9 (52.9%)						
Cirrhosis at enrolment								
No	203	158 (43.8%)	1			1		
Yes	28	11 (28.2%)	0.50 (0.24–1.05)	0.066		0.59 (0.31–1.09)	0.059	
Unknown	4	2 (33.3%)						

* *P* value for heterogeneity. † *P* value for linear trend.
A table of the complete results can be found in the online version of this article at http://www.mja.com.au/public/issues/194_08_180411/gid11090_fm_add.html ◆

included: sex, age, Indigenous status, language spoken at home, APRI Score (AST [aspartate aminotransferase] to platelet ratio index score),[14] alanine aminotransferase level,[15] HCV genotype or HCV RNA level, liver biopsy (yes/no), HIV or HBV co-infection (past or current), diabetes, or history of treated psychiatric illness (see http://www.mja.com.au/public/issues/194_08_180411/gid11090_fm_add.html). Of the factors that were associated with treatment deferral in the univariate analysis (Box 3), only current injecting drug use, past or current treatment for drug dependency, and alcohol use above 20 g per day remained statistically significant independent predictors of treatment deferral in the multivariate analysis (Box 3).

Despite remaining an independent predictor of deferral of HCV treatment, past or current treatment for drug dependency (compared with never being treated for drug dependency) was associated with current drug use (19% v 4%; $P < 0.001$), younger age at first visit (39 years v 48 years; $P < 0.001$), and a history of treated psychiatric illness (47% v 25%; $P < 0.001$).

Patients with cirrhosis (Child–Pugh class A) were less likely to have commenced treatment, but the significance of this association was borderline ($P = 0.059$). Among patients who did defer their treatment, those with cirrhosis were more likely to have deferred because of a chronic medical comorbid condition than those without cirrhosis (25% v 3%; $P < 0.001$). Patients born overseas were more likely to have commenced treatment, but this association was not significant in the multivariate analysis because some of the association with treatment was explained by the fact that patients born overseas had a lower rate of current injecting drug use than Australian-born patients (5% v 10%; $P < 0.001$).

The sensitivity analysis using a conditional logistic regression model stratified by clinic showed similar results to the multivariate analysis described above (data not shown), which indicated that there were no significant differences in the patterns of treatment uptake between clinics.

Distribution of risk factors for deferral

Of the 406 patients in the analysis subcohort, 165 (41%) had at least one of the factors related to drug and alcohol use that were found to be independently associated with treatment deferral (current injecting drug use, past or current treatment for

drug dependency, alcohol use above 20 g per day).

DISCUSSION

Within an Australian network of HCV clinics, most treatment-naive patients had either commenced treatment (42%) or had not yet completed their treatment assessment (30%) within 6 months of their first clinic visit. Few patients (5%) were unwilling to receive treatment and only eight were ineligible for treatment under the Australian Government-subsidised HCV treatment program. Factors related to drug and alcohol use (current injecting drug use, alcohol consumption of over 20 g/day and past or current treatment for drug dependency) rather than those related to HCV (virological or liver disease factors) were the major influences on the uptake of HCV treatment.

The level of uptake of and eligibility for treatment in our cohort was generally higher than has been reported in other clinic-based studies. Treatment uptake in community-based specialist clinics has been reported at between 27% and 38%,[8,9] with up to 71% considered ineligible.[8] The low uptake of HCV treatment within the broad Australian population with chronic HCV (< 2% treated yearly)[6] compared with the relatively high uptake within the ACHOS subpopulation of newly assessed treatment-naive patients suggests that the major impediments to a higher level of uptake in the HCV-affected population are low referral rates for HCV treatment assessment and suboptimal infrastructure for treatment delivery. Once assessment is undertaken, even within a population with high levels of comorbidity, the broad eligibility criteria and government-subsidised treatment program in Australia enable relatively high treatment levels.

The widespread availability of direct-acting antiviral agents that is anticipated in the near future has the potential to improve referral rates and further increase treatment uptake in the Australian clinic setting. In clinical trials, the direct-acting antiviral agents boceprevir and telaprevir almost doubled the efficacy and significantly shortened the required duration of treatment for patients infected with HCV genotype 1, the most common genotype.[16] It is therefore likely that these new treatment regimens will be considered more acceptable, and treatment uptake will increase. However, it will be important to monitor the impact of the new regimens, and we plan to do so using an expanded ACHOS cohort.

Factors related to drug and alcohol use were the only factors significantly associated with deferral of treatment in our study. Current drug and alcohol use have previously been identified as strong predictors of treatment deferral,[8,17] even in the current era, when treatment guidelines no longer list these factors as contraindications.[12] However, the association between deferral of treatment and past and current treatment for drug dependency has not been examined in many studies, and when it has, the results have been inconsistent.[7-9,18] In a Canadian liver clinic, patients on methadone maintenance treatment, after adjusting for other factors, were eight times more likely to be treated for HCV.[8] In contrast, an Australian community-based study found that individuals currently receiving treatment for drug dependency were five times less likely to be treated.[18] Such discrepant findings may be the result of variations in unmeasured patient factors that are associated with both the uptake of HCV treatment and treatment for drug dependency.

There are many barriers to treatment uptake that can explain the association between treatment deferral and factors related to drug and alcohol use. The health care provider may wish to stabilise the patient's drug, alcohol, psychiatric and medical comorbid conditions before commencing HCV treatment.[19] Other barriers include a reluctance to treat former IDUs, especially those on treatment for drug dependency (because of a perceived risk of drug use relapse),[20] and considerations relating to HCV reinfection.[21] Despite these concerns and our findings, there is limited evidence to suggest that treatment outcomes are worse for patients being treated for drug dependency and currently using injecting drugs.[22]

Strategies to enhance assessment for and uptake of HCV treatment among patients with drug and alcohol dependency include integrating care for drug and alcohol dependency and associated psychiatric and medical comorbid conditions with assessment for HCV treatment. Such models have been shown to be effective in current IDUs,[23] patients receiving methadone maintenance treatment[24] and the US veteran population.[25] Peer support groups have also been shown to increase assessment for and uptake of treatment when combined with multidisciplinary care.[26]

Patients with HCV-related cirrhosis are at considerable risk of complications including hepatocellular carcinoma and liver failure.[27] Thus, the lower treatment uptake among patients with cirrhosis (all with compensated disease) is a major concern, even though it was of borderline statistical significance. Our findings contrast with those from a review of the US Department of Veterans Affairs database, which found that patients with cirrhosis were 1.6 times (95% CI, 1.5–1.7 times) more likely to receive a prescription for HCV treatment.[10] Our contrasting results may be the result of us examining uptake within the first 6 months of assessment, as patients with cirrhosis are likely to take longer to assess because they have more complex medical histories, as evidenced by the greater proportion with a chronic medical comorbid condition.

Our study has several limitations. First, although we measured a range of lifestyle and patient-related characteristics, we were unable to include some socioeconomic factors. Both level of education and social support have previously been reported as predictors of increased treatment uptake.[8,9,11] However, a more recent Australian study that included comprehensive measures of social support did not find these factors to be important.[18] Second, although we recorded patients' reasons for deferral, it is unclear whether the decision was made by the patient or health care provider. However, we do know that 27 of the 120 patients in their initial stages of assessment did not return for follow-up visits. Third, our study examined predictors of treatment uptake during the first 6-month assessment period. A priori, this was considered to be sufficient time to reach a decision about therapy in uncomplicated cases. With longer follow-up, we would have the power to perform a survival analysis to examine predictors of delayed treatment uptake. Finally, it should be noted that patients who attend clinics are probably more interested in receiving treatment than the broader community of people living with HCV.

In summary, we found a relatively high rate of uptake of HCV treatment within our network of HCV clinics, with only factors relating to drug and alcohol use being associated with deferral of treatment. Improved comanagement of drug and alcohol dependency together with enhanced infrastructure for the delivery of HCV treatment should enable increased uptake of treatment for HCV at the population level and reduce the morbidity associated with this disease.

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COMPETING INTERESTS

None identified.

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