ORIGINAL RESEARCH ARTICLE

COACTION PUBLISHING

Treatment eligibility in Alaska Native and American Indian persons with hepatitis C virus infection

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Objectives. Treatment with pegylated interferon and ribavirin may prevent progression of liver disease among patients with chronic hepatitis C virus infection (HCV). Treatment initiation is based on published clinical eligibility criteria, patients' willingness to undergo treatment and likelihood of success. We examined treatment eligibility in a cohort of Alaska Native and American Indian persons with chronic HCV infection.
Study design. Retrospective cohort study.
Methods. Medical records of all treatment naïve HCV RNA positive patients given an appointment by hepatology specialty clinic staff in 2003 and 2007 were evaluated by a hepatology provider to investigate documented reasons for treatment deferral.
Results. Treatment was initiated in 4 of 94 patients (4%) in 2003 and 14 of 146 patients (10%) in 2007. Major reasons for treatment deferral in 2003 versus 2007 included inconsistent appointment attendance (36% of deferrals vs. 18%), active substance abuse (17% vs. 22%), patient decision (17% vs. 27%), liver biopsy without fibrosis or normal ALT (8% vs. 3%), uncontrolled psychiatric condition (7% vs. 7%) and concurrent medical condition (6% vs. 9%). There was significant improvement in proportion of appointments attended in 2007 versus 2003 (76% vs. 67%, $p = 0.04$) and the percentage of patients attending at least 1 appointment (84% vs. 66%, $p = 0.002$).
Conclusions. Multiple reasons for treatment deferral were documented. Despite a significant improvement in hepatology clinic attendance and an increase in the number of patients started on treatment in 2007 compared to 2003, the overall percentage of those treated remained low.

Keywords: *hepatitis C treatment*; *hepatology clinics*; *treatment eligibility*

Received: 1 December 2011; Revised: 17 January 2012; Accepted: 8 February 2012; Published: 24 April 2012

An estimated 4.1 million people in the United States are chronically infected with hepatitis C virus (HCV), primarily via intravenous drug use or blood transfusion prior to screening of the blood supply in 1992 (1). These persons are at risk for development of cirrhosis, liver failure and hepatocellular carcinoma. Treatment for HCV is effective in only approximately 50% of patients. The currently approved treatment is a combination of pegylated interferon and ribavirin for 24–48 weeks, depending on genotype. Recent licensing of 2 oral protease inhibitors, telaprevir and boceprevir, is expected to improve treatment response significantly in persons with genotype 1 when combined with pegylated interferon and ribavirin, as well as decrease duration of treatment in many patients. Antiviral treatment is initiated in hopes of achieving a

Citation: Int J Circumpolar Health 2012, **71**: 18445 - http://dx.doi.org/10.3402/ijch.v71i0.18445

sustained virologic response, defined as undetectable HCV RNA 6 months post-treatment, and preventing further progression of liver disease (2).

Not all patients infected with HCV are good candidates for current antiviral treatment. In those patients willing to undergo treatment, initiation of therapy is based on the likelihood of treatment success. Current and previous practice guidelines published by the American Association for the Study of Liver Diseases list characteristics of persons for whom therapy "is widely accepted," "is currently contraindicated" or "should be individualized (2,3)." Guidelines published prior to 2004 proposed eligibility criteria based on similar concepts (4). These "eligibility" criteria are used by medical providers to ensure that those individuals most likely to benefit receive treatment.

In a population-based longitudinal cohort study of Alaska Native and American Indian persons infected with HCV, a relatively small number of patients have received HCV treatment despite increased identification and available institutional resources (5). Utility and applicability of published eligibility criteria for HCV treatment have not been studied in Alaska Native and American Indian persons. The goal of this retrospective cohort study was to assess treatment acceptance in patients based on documented behaviours and determine which of the published treatment eligibility criteria most influenced the provider's decision to start treatment.

Materials and methods

Patients

Alaska Native and American Indian persons living in Alaska are eligible for health care in a prepaid managed healthcare system through the Alaska Native Tribal Health Consortium and Alaska Native Medical Center (ANMC), a tertiary referral hospital in Anchorage. Since 1995, the Alaska Native Tribal Health Consortium Liver Disease and Hepatitis Program has enrolled 1,234 people into a longitudinal outcomes cohort study of chronic HCV infection. All participants had a positive anti-HCV test confirmed either by recombinant immunoblot assay or HCV RNA by polymerase chain reaction. Of 986 persons in this study population living on June 1, 2010, most resided in urban areas, including 60% in Anchorage, 15% in Fairbanks and 11% in Juneau and Sitka. Details of this patient cohort have been previously described, including clinical outcomes through 2005 (6).

Approval for this study was obtained from the Institutional Review Boards of the Alaska Area Indian Health Service, the University of Washington Medical Center and the Centers for Disease Control and Prevention and appropriate Alaska Native Health Corporation boards. All patients provided written informed consent that included permission for chart review of previous records.

Study design

Medical records of all treatment naïve HCV RNA positive patients given appointments in the hepatology specialty clinic at ANMC over 2 specific 1-year periods (January 1–December 31, 2003, and January 1–December 31, 2007) were evaluated by a hepatology provider (physician or nurse practitioner) to examine treatment eligibility based on clinical guidelines, patient preference and patient attendance at appointments. These 1-year periods were selected 4 years apart in order to investigate differences in treatment eligibility over time. In addition to pertinent history, physical examination and laboratory testing, hepatology clinic providers routinely discussed the nature of HCV infection, including long-term prognosis, routine follow-up recommendations, the role of liver biopsy, indications for treatment and detailed discussions of the treatment regimen and potential side effects. Documented patient behaviours and responses were also used to establish patient acceptance of treatment.

The hepatology clinic was staffed by 2 physicians and 1 nurse practitioner for 5 half-day clinics weekly in 2003 and by 2 physicians and 2 nurse practitioners for 7 half-day clinics weekly in 2007. One of the 2 nurse practitioners was hired in 2006 and dedicated to hepatitis C management, including treatment. Beginning in 2002, all patients with chronic HCV infection living in the Anchorage area were sent a letter biannually recommending that they make a follow-up clinic appointment and have their liver function tests performed. Most follow-up appointments were made by clinic staff at the request of patients who contacted the clinic. Some patients who did not make clinic appointments or have liver function tests performed after receiving a reminder letter were contacted by clinic staff and offered an appointment, which was made with patient agreement. Likewise, patients referred by other providers for a new clinic appointment were contacted by clinic staff and offered an appointment, which was made with their agreement. Most patients seen in the ANMC hepatology clinic in Anchorage resided in the Anchorage area. Those referred from other areas of the state generally had travel to Anchorage provided free of charge to the patient.

Laboratory testing and histologic evaluation

Alanine aminotransferase (ALT) testing was performed at the ANMC laboratory (Anchorage, AK) on an Aeroset Chemistry analyzer (Abbott Laboratories, USA). An ALT level of lower than 40 U/L was defined as normal. Testing for HCV RNA and genotype was performed at the University of Washington as previously described (7). Liver biopsy was performed only for clinical reasons, primarily to evaluate for possible treatment. Liver biopsy slides were evaluated by at least 1 of the 2 physicians

Citation: Int J Circumpolar Health 2012, **71**: 18445 - http://dx.doi.org/10.3402/ijch.v71i0.18445

(SL or BM), both practicing hepatologists, for clinical purposes. In addition, biopsy slides were evaluated by a study pathologist (HD) who was blinded to patient identity and demographic, clinical and biological data. Fibrosis was evaluated using the Knodell system (8).

Statistical analysis

Patient data were analysed for characteristics that included gender, age, years since diagnosis, genotype, ALT level, Knodell fibrosis score, risk factors (injection drug use, blood transfusion and other) and alcohol consumption at the time of entry into the study (consumption of any alcohol and consumption of >50 g/day). Statistical analysis was performed to compare characteristics of persons with consistent hepatology clinic appointment attendance to those with inconsistent attendance for given appointments. Additionally, documented reasons for treatment eligibility were compared in 2003 and 2007 using the likelihood ratio chi-square statistic. We used the Cochran-Armitage test for trend to examine if the percentage of persons who attended their appointments varied with age, ALT level and time since diagnosis. All p-values were 2-sided and values <0.05 were considered statistically significant. The p-values were exact when sample size necessitated. All analyses were conducted by the use of SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Treatment initiation

Treatment with pegylated interferon and ribavirin was initiated in 4 of 94 patients (4%) in 2003 and 14 of 146 patients (10%) in 2007. Of the 4 patients started on treatment in 2003, 1 achieved a sustained virologic response; 1 discontinued treatment due to side effects; treatment failed in another, and the fourth relapsed after achieving an end of treatment response. Of the 14 patients started on treatment in 2007, 4 achieved a sustained virologic response; 8 discontinued treatment due to side effects; treatment failed in 1 and 1 relapsed.

Treatment eligibility 2003

In 2003, we identified 94 treatment naïve patients who were scheduled for 175 appointments in the ANMC hepatology clinic. Of 19 patients who were scheduled for multiple appointments, 14 did not attend any of the appointments and 5 attended at least one of the scheduled appointments; attendance at this appointment was used by the provider to evaluate for treatment eligibility. Thirty-two of the 94 patients (34%) did not attend any of the appointments and, thus, were considered not eligible for treatment during the study period by the provider. Of the 90 patients not treated, reasons for providers deferring treatment were inability to attend scheduled appointments, 32 (36%); documented alcohol or drug abuse within 6 months of evaluation, 16 (17%); patient decision to defer treatment despite being considered an eligible candidate, 16 (17%); liver biopsy without fibrosis or normal ALT, 8 (8%); documented uncontrolled psychiatric condition, 7 (7%); concurrent medical condition precluding treatment, 6 (6%); decompensated cirrhosis, 3 (3%), and age >65 years, 2 (2%) (Table I).

Treatment eligibility 2007

In 2007, we identified 146 treatment naïve patients who were scheduled for 278 appointments in the ANMC hepatology clinic. Of 45 patients who had multiple scheduled appointments, 2 attended none of them and 43 attended at least 1. Overall, 24 of the 146 patients (16%) did not attend any scheduled appointments. Of the 132 patients not treated, reasons for providers deferring treatment were patient decision to defer, 36 (27%); alcohol or drug abuse within 6 months of evaluation, 29 (22%); inability to attend scheduled appointments, 24 (18%); concurrent medical condition precluding treatment, 12 (9%); uncontrolled psychiatric condition, 9 (6%); decompensated cirrhosis, 7 (5%); patients considering or planning treatment but not yet started, 7 (5%); liver biopsy without fibrosis or normal ALT, 4 (3%); age >65 years, 2 (1%), and other, 2 (1%) (Table I).

Characteristics of patients who attended scheduled clinic appointments (2003 and 2007)

The proportion of appointments attended increased significantly in 2007 versus 2003 (73% vs. 67%, respectively, $p = 0.04$). Likewise, the percentage of patients who attended at least 1 scheduled appointment increased in 2007 versus 2003 (84% vs. 66%, $p = 0.002$) (Table II). In 2003, persons with a history of intravenous drug use were significantly less likely to attend clinic appointments than those with other risk factors ($p = 0.04$). In 2007, there was a significant difference in time since diagnosis among those who attended clinic appointments. Among persons diagnosed with HCV infection <3 years prior to the appointment, 93% attended at least 1 appointment compared to 86% and 73% for diagnosis 3–7 and ≥ 8 years prior, respectively ($p = 0.009$). There was no significant difference in other characteristics in either year among those who attended scheduled appointments (Table III).

Discussion

Between 2003 and 2007, the number of chronic HCV-infected persons who made appointments in the ANMC hepatology clinic increased by over 50% and the number of appointments attended nearly doubled. Likewise, the number of patients started on HCV treatment more than tripled between 2003 and 2007, increasing from 4 (4%) to 14 (10%).

Table I. Reasons for non-treatment of Alaska Native and American Indian persons with chronic hepatitis C seen in a hepatology clinic in 2003 and 2007

Reason	2003 (%)	2007 (%)
Inability to attend scheduled clinic appointments	32 (36%)	24 (16%)
Alcohol or drug abuse within 6 months	16 (17%)	29 (22%)
Patient decision to defer treatment	16 (17%)	36 (25%)
Liver biopsy without fibrosis or normal ALT	8 (8%)	4 (3%)
Uncontrolled psychiatric condition	7 (7%)[a]	9 (6%)[b]
Concurrent medical condition precluding treatment	6 (6%)[c]	12 (8%)[d]
Decompensated cirrhosis	3 (3%)	7 (5%)
Age >65 years	2 (2%)	2 (1%)
Considering or planning treatment	0	7 (5%)
Other	0	2 (1%)
Total	90	132

[a]Includes bipolar disorder (2), depression, dementia and mental retardation.
[b]Includes bipolar disorder (2), schizophrenia, depression and personality disorder (2).
[c]Includes rheumatoid arthritis, seizure disorder, severe diabetes mellitus, systemic lupus erythematosis, chronic renal failure and severe chronic back pain.
[d]Includes cancer (2), myopathy, malabsorption syndrome, pregnancy, severe diabetes mellitus, chronic obstructive lung disease, severe chronic back pain and autoimmune hepatitis.

Of those who attended clinic appointments but were not treated, we found little difference in the reasons patients were not started on HCV treatment between 2003 and 2007. Substance abuse and individual patient decision to defer treatment remained the 2 most common reasons (16–36%), whereas smaller percentages had concurrent medical or psychiatric conditions, liver biopsies without fibrosis or normal ALT and decompensated cirrhosis.

Previous studies of HCV treatment eligibility have reported similar findings, including low rates of treatment. A large US Veterans Administration study examined a nationwide database of over 100,000 HCV-infected patients and found that treatment was initiated in only 11.9% and completed in only 22.5% of those, which was less than 2% of the whole cohort (9). A smaller Veterans Administration study looked at the reasons for non-treatment in 354 patients referred to a hepatology clinic, 70% of whom were not treated. The most common reasons for non-treatment were non-adherence to follow-up visit (24%), normal liver enzymes (14%), concurrent medical problems (11%), alcohol and drug abuse (9%), psychiatric problems (7%) and advanced liver disease (7%) (10). A study of 293 patients at a teaching county hospital in Cleveland, Ohio, found that 72% of patients were not treated. Reasons included non-adherence (37%), medical or psychiatric contraindications (34%), ongoing substance abuse (13%), personal preference (11%) and normal liver enzymes (5%) (11).

As we have identified more patients with HCV, the number of appointments made in our hepatology clinic has increased. Hepatology clinic appointments for HCV at ANMC are made by referral for initial evaluation, often by primary care providers, and directly by patients for follow-up. We did not attempt to differentiate between these reasons for making appointments in our study.

Table II. Comparison of appointment attendance in a hepatology clinic by Alaska Native and American Indian persons between 2003 and 2007

Study year	Number of appointments	Proportion of appointments attended (%)	Number of patients	Number of patients attending ≥1 scheduled appointment (%)
2003	175	118 (67%)	94	62 (66%)[a]
2007	278	212 (76%)	146	122 (84%)[a]
p-value[b]		0.04		0.002
Combined	453	73% (330)	240	77% (184)

[a]If persons who were seen in both years are removed, those attending ≥1 appointment were 64% (42/66) in 2003 vs. 86% (101/118) in 2007, $p = 0.002$.
[b]p-value compares 2003 percentage vs. 2007 percentage.

Citation: Int J Circumpolar Health 2012, **71**: 18445 - http://dx.doi.org/10.3402/ijch.v71i0.18445

Table III. The percentage of Alaska Native and American Indian persons with chronic hepatitis C virus (HCV) infection attending hepatology clinic scheduled appointments in 2003 and 2007, according to demographic and HCV infection characteristics

		2003		2007	
Characteristic	Level	Attendance rate[a]	p-value	Attendance rate	p-value
Sex	Female	67% (34/51)	0.87	82% (61/74)	0.71
	Male	65% (28/43)		85% (61/72)	
Age	<40 years	63% (19/30)	0.10	83% (25/30)	0.48
	40–49 years	56% (23/41)		88% (46/52)	
	≥50 years	87% (20/23)		80% (51/64)	
Time since diagnosis	<3 years	80% (20/25)	0.26	93% (40/43)	0.009
	3–7 years	59% (27/46)		86% (43/50)	
	≥8 years	65% (15/23)		73% (38/52)	
HCV genotype	1	61% (36/59)	0.41	81% (79/98)	0.15
	2	74% (14/19)		81% (17/21)	
	3	75% (12/16)		99% (24/25)	
ALT level[b]	<40	62% (16/26)	0.34	85% (33/39)	0.79
	40 to <80	62% (21/34)		85% (50/59)	
	≥80	73% (22/30)		87% (39/45)	
Knodell fibrosis score	0–1	69% (22/32)	0.39	80% (41/51)	0.78
	3–4	82% (9/11)		83% (15/18)	
HCV risk factor for infection	IVDU[c]	58% (35/60)	0.04[e]	80% (74/92)	0.17[e]
	BT[d]	80% (12/15)		86% (12/14)	
	Other	78% (14/18)		90% (36/40)	
Consume any alcohol	Yes	64% (28/44)	0.71	82% (55/67)	0.66
	No	67% (33/49)		85% (67/79)	
History of >50 g/day of alcohol	Yes	67% (23/34)	0.79	88% (34/41)	0.38
	No	65% (39/60)		82% (86/105)	

[a]Percent of patients attending ≥1 appointment.
[b]ALT, alanine aminotransferase, in units/liter.
[c]IVDU, intravenous drug use.
[d]BT, blood transfusion.
[e]p-value for IVDU vs. all others.

Several factors may explain why a significantly larger percentage of patients attended appointments in 2007 compared to 2003. They include the hiring of an additional nurse practitioner in 2006 who was dedicated to HCV, resulting in a more aggressive approach on our part to HCV management and treatment. Information was not available regarding whether the patient was initially seen by a physician or a nurse practitioner but all patients were seen by a physician before treatment was started. By 2007, many patients had been receiving regular reminder letters to get laboratory and clinic follow-up for several years.

The role of Native healers in appointment attendance was not evaluated. Native healers were available in the Primary Care Clinic at ANMC and their care was coordinated with primary care providers. However, records of visits with Native healers were not available on patient charts, and we do not know if any of the patients seen in the hepatology clinic sought advice from them.

Despite the increase in clinic appointments, the percentage of those who made appointments and were subsequently started on treatment remained very small. A more comprehensive team approach utilising primary care providers, mental health providers, social workers and pharmacists, available in our primary care center, as well as hepatology providers might increase treatment numbers in a setting like Anchorage. A model for increasing treatment numbers around the state could be based on the rural University of New Mexico Project ECHO program, which has provided care for hepatitis C patients via audio and visual conferencing (12). With the Food and Drug Administration approval of telaprevir (13) and boceprevir (14), treatment for genotype 1 will be significantly more effective. This likely will increase the number of patients seeking treatment.

Patients attending appointments in 2007 were significantly more likely to have been diagnosed with HCV infection <3 years prior to the appointment, compared

to those with a longer time since diagnosis ($p = 0.009$). This also occurred in 2003 but was not statistically significant. The reason for this is uncertain, but it is possible that persons more recently diagnosed could be more motivated to obtain information about their disease than persons who have known about their diagnosis for a longer period and may have already been seen in the clinic.

We do not have an obvious explanation why persons with the risk factor of intravenous drug use were significantly less likely to attend appointments in 2003 compared to those with other risk factors. We found no difference in risk factors among those who attended appointments in 2007. We previously documented that a history of intravenous drug use is the major risk factor for HCV infection in this cohort; 60% gave this history (3). However, we do not think this was a major factor since, by 2007, 80% of persons with an intravenous drug use history attended clinic appointments. Knowledge of treatment side effects and other factors could have influenced appointment attendance. We determined that persons not attending clinic appointments were not eligible for hepatitis C treatment during the study period, as other investigators have done. It is conceivable, however, that a significant number of these patients were actually eligible for treatment but were unable to attend appointments for temporary personal reasons, such as child care or other family issues, transportation difficulties or work responsibilities. Investigation of reasons for not attending appointments was not part of this study, however.

This study was unique because it was population based and evaluated a group whose health care needs have been underserved. It was limited somewhat by the relatively small study size. We also did not attempt to determine if cultural factors influenced patient decisions to seek treatment. Hepatitis C is primarily an urban disease in Alaska due to a low rate of intravenous drug use in rural villages; so, our results may not be applicable to rural areas where specialty care and treatment are not always available.

In conclusion, we found multiple reasons why treatment was deferred in a cohort of Alaska Native and American Indian persons with chronic HCV infection. Despite a significant improvement in hepatology clinic appointment attendance between 2003 and 2007 and an increase in the number of patients started on treatment, the overall percentage of those treated remained low.

Acknowledgements

This study was supported by the University of Washington (Seattle, WA) National Institutes of Health Grant Nos. A48214 and A1066209, the Liver Disease and Hepatitis Program of the Alaska Native Tribal Health Consortium, Anchorage, and the Arctic Investigations Program of the Centers for Disease Control and Prevention, Anchorage, AK. We thank Brenna Simons, Ph.D., for helpful suggestions and careful review of this manuscript.

Conflict of interest and funding

None of the authors have any conflict of interest to declare, including no financial or personal relationships with other people or organizations that could potentially influence the results or interpretation of this work.

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Citation: Int J Circumpolar Health 2012, **71**: 18445 - http://dx.doi.org/10.3402/ijch.v71i0.18445

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