Rate, delay and predictors of hepatitis C treatment in British Columbia

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AHL Yau, T Lee, A Ramji, HH Ko. Rate, delay and predictors of hepatitis C treatment in British Columbia. Can J Gastroenterol Hepatol 2015;29(6):315-320.

BACKGROUND: The current treatment rate for chronic hepatitis C virus (HCV) infection is suboptimal despite the availability of efficacious antiviral therapy.
OBJECTIVE: To determine the rate, delay and predictors of treatment in patients with chronic HCV infection.
METHODS: A retrospective chart review of chronic HCV patients who were being evaluated at a tertiary hepatology centre in Vancouver, British Columbia, was performed.
RESULTS: One hundred sixty-four patients with chronic HCV infection who were assessed for treatment between February 2008 and January 2013 were reviewed. Treatment was initiated in 25.6% (42 of 164). In multivariate analyses, male sex (OR 7.90 [95% CI 1.35 to 46.15]) and elevated alanine aminotransferase (ALT) level (>1.5 times the upper limit of normal) (OR 3.10 [95% CI 1.32 to 7.27]) were positive predictors of treatment, whereas active smoking (OR 0.09 [95% CI 0.02 to 0.53]) and Charlson comorbidity index (per point increase) (OR 0.47 [95% CI 0.27 to 0.83]) were negative predictors of treatment. The most common reasons for treatment deferral were no or minimal liver fibrosis in 57.7% (n=30), persistently normal ALT levels in 57.7% (n=30) and patient unreadiness in 28.8% (n=15). The most common reasons for treatment noninitiation were patient refusal in 59.1% (n=26), medical comorbidities in 36.4% (n=16), psychiatric comorbidities in 9.1% (n=4) and decompensated cirrhosis in 9.1% (n=4). There was a statistically significant difference in the median time delay from HCV diagnosis to general practitioner referral between the treated and untreated patients (66.3 versus 119.5 months, respectively [P=0.033]). The median wait time from general practitioner referral to hepatologist consult was similar between the treated and untreated patients (1.7 months versus 1.5 months, respectively [P=0.768]). Among the treated patients, the median time delay was 6.8 months from hepatologist consult to treatment initiation.
CONCLUSIONS: The current treatment rate for chronic HCV infection remains suboptimal. Medical and psychiatric comorbidities represent a major obstacle to HCV treatment. Minimal hepatic fibrosis may no longer be a major reason for treatment deferral as more efficacious and tolerable antiviral therapies become available in the future. Greater educational initiatives for primary care physicians would promote early referral of patients. More nursing support would alleviate the backlog of patients awaiting treatment.

Key Words: *Boceprevir; Direct-acting antiviral agent; Hepatitis C; Telaprevir; Treatment*

Les taux, les retards et les prédicteurs de traitement de l'hépatite C en Colombie-Britannique

HISTORIQUE : Le taux de traitement actuel de l'infection par le virus de l'hépatite C (VHC) est sous-optimal, malgré l'existence d'une antivirothérapie efficace.
OBJECTIF : Déterminer le taux, les retards et les prédicteurs de traitement chez les patients atteints d'une infection chronique par le VHC.
MÉTHODOLOGIE : Les chercheurs ont effectué une analyse rétrospective des dossiers des patients atteints d'un VHC chronique évalués dans un centre tertiaire d'hépatologie de Vancouver, en Colombie-Britannique.
RÉSULTATS : Les chercheurs ont analysé 164 patients atteints d'une infection chronique par le VHC qui avaient été évalués en vue d'un traitement entre février 2008 et janvier 2013. Le traitement a été amorcé chez 25,6 % d'entre eux (42 sur 164). Aux analyses multivariées, le sexe masculin (RC 7,90 [95 % IC 1,35 à 46,15]) et un taux d'alanine aminotransférase (ALT) élevé (plus de 1,5 fois la limite supérieure de la normale (RC 3,10 [95 % IC 1,32 à 7,27]) étaient des prédicteurs positifs du traitement, tandis qu'un tabagisme actif (RC 0,09 [95 % IC 0,02 à 0,53]) et un index de comorbidité de Charlson (par point d'augmentation; RC 0,47 [95 % IC 0,27 à 0,83]) étaient des prédicteurs négatifs du traitement. Les principales raisons de reporter le traitement étaient l'absence ou le peu de fibrose hépatique chez 57,7 % des patients (n=30), des taux d'ALT toujours normaux chez 57,7 % des patients (n=30) et la réticence chez 28,8 % des patients (n=15). Les principales raisons de ne pas amorcer le traitement étaient le refus du patient dans 59,1 % des cas (n=26), des comorbidités médicales dans 36,4 % des cas (n=16), des comorbidités psychiatriques chez 9,1 % des patients (n=4) et une cirrhose décompensée chez 9,1 % d'entre eux (n=4). Il y avait une différence statistiquement significative entre les patients traités et non traités pour ce qui est de l'attente médiane entre le diagnostic de VHC et l'aiguillage par un omnipraticien (66,3 mois au lieu de 119,5 mois, [P=0,033]). Les patients traités et non traités présentaient un temps d'attente médian similaire entre l'aiguillage de l'omnipraticien et la consultation chez l'hépatologue (1,7 mois au lieu de 1,5 mois, [P=0,768]). Chez les patients traités, l'attente médiane était de 6,8 mois entre la consultation chez l'hépatologue et le début du traitement.
CONCLUSIONS : Le taux de traitement actuel de l'infection chronique par le VHC demeure sous-optimal. Les comorbidités médicales et psychiatriques constituent un obstacle majeur au traitement du VHC. Une fibrose hépatique minimale ne sera peut-être plus une raison importante pour reporter le traitement lorsque des antiviraux plus efficaces et plus faciles à tolérer seront mis en marché. Plus de projets de formation des médecins de première ligne favoriseraient l'aiguillage précoce du patient. Un plus grand soutien infirmier réduirait le nombre de patients en attente d'un traitement.

Chronic hepatitis C virus (HCV) infection has been estimated to affect 2% to 3% of the population worldwide (170 million individuals) (1) and 0.8% of Canadians (275,000 individuals) (2). In Canada, HCV-related morbidity and mortality increased 15% to 18% annually between 1994 and 2004 (3). The increasing medical and economic burden of HCV on the health care system has prompted the development of more efficacious treatment regimens. Two direct-acting antiviral agents – telaprevir and boceprevir – were approved in Canada in May 2011, in combination with pegylated interferon and ribavirin for the treatment of HCV genotype 1, with a sustained virological response (SVR) rate of 60% to 75% in treatment-naive patients (4).

Before the advent of protease inhibitors, when pegylated interferon and ribavirin were standard of care for chronic HCV, low rates of treatment uptake had been reported, ranging from 8.2% to 31.8% among United Startes (US) Veterans (5-11), 9.1% to 50.4% among US non-veterans (12-16), 16.0% to 37.8% in Canada (17-19), 21.3%

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Received for publication October 28, 2014. Accepted February 3, 2015

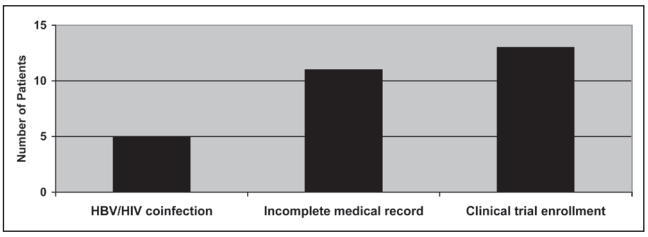

Figure 1) *Patients excluded from study participation. HBV Hepatitis B virus*

in Denmark (20), 16% in France (21), and <1% in Greece, Poland, Romania and Russia (21).

Despite the recent advances in chronic HCV treatment and the availability of efficacious antiviral agents, the current treatment rate is suboptimal. It is, therefore, important to better understand the barriers that result in low treatment rates. We performed a retrospective analysis of chronic HCV patients being referred to a tertiary hepatology centre affiliated with the University of British Columbia (Vancouver, British Columbia). Our aims were to determine the treatment rate; identify the predictors of treatment and the reasons for nontreatment; and determine the mean wait time from diagnosis to treatment initiation.

METHODS

Study population

A total of 164 patients with chronic HCV infection, who were evaluated for antiviral therapy between February 2008 and January 2013 by one of two hepatologists (HHK, AR) at a referral-based tertiary hepatology centre in downtown Vancouver, British Columbia, were reviewed. Most patients were from the greater Vancouver metropolitan area and were referred by their primary care providers. Patients who were eligible for treatment were offered pegylated interferon and ribavirin with or without telaprevir or boceprevir for 24 or 48 weeks, depending on the HCV genotype. All patients received comprehensive education and counselling about HCV by a specially trained nurse during their first office visit, and had regular follow-up appointments with both the nurses and physicians throughout treatment. Patients were excluded from the study if they were coinfected with hepatitis B virus (HBV) or HIV, enrolled in a clinical trial or if there was incomplete documentation in their medical record. The present study was approved by the University of British Columbia Institutional Review Board.

Data collection

A retrospective chart review was performed to collect information regarding patient demographics, medical history, details of HCV infection (route of transmission, genotype and previous treatment), psychiatric history (as reported by patients or referring physicians), social history and laboratory results (blood work, abdominal ultrasound, transient hepatic elastography [Fibroscan, Echosens, France] and liver biopsy). Patients with chronic HCV infection were identified from the electronic medical records using the *International Classification of Diseases, Ninth Revision* (ICD-9) ICD-9 diagnostic code 5731. Specific demographic information collected include age, sex, ethnicity and distance from home to hepatology centre. The distance from home to hepatology centre was defined as 'near' or 'far' based on a cut-off distance of 30 km. Medical comorbidity was quantified using the Charlson comorbidity index, in which 1 to 6 points were assigned for each of the 17 major medical conditions (22). Age was also taken into account in calculating the Charlson comorbidity index. Whether diagnostic tests (liver enzymes, HCV antibody, HCV RNA, HCV genotype and abdominal ultrasound) were ordered by the referring physicians within six to 12 months of referral were documented. Treatment initiation was the primary outcome of the study, and was defined as having received pegylated interferon and ribavirin with or without telaprevir or boceprevir for any duration of time. For patients in whom treatment was not started, the charts were reviewed to determine the reasons for treatment deferral or noninitiation. Finally, the time delay from HCV diagnosis to referral, from referral to hepatologist consult and from initial assessment by hepatologist to treatment initiation was determined.

Statistical analysis

Baseline characteristics of all patients were described using means and SDs for continuous data, and counts and percentages for categorical data. Demographic and clinical variables of treated and untreated patients were compared using *t* tests or Wilcoxon rank-sum tests for continuous data, and χ^2 or Fisher's exact tests for categorical data as appropriate. Factors that were statistically significant (P<0.20) from the univariate analyses and those found to be clinically important based on a literature review were selected as candidates to enter multivariate logistic regression models. Backward stepwise selection was performed such that variables with the largest P value were sequentially removed at each step from the model ending when all remaining variables had a two-sided P<0.05. Independent predictors of antiviral therapy initiation were identified with calculation of their respective OR and 95% CI. Data were analyzed using SAS version 9.3 (SAS Institute, USA).

RESULTS

Patient characteristics (Table 1)

A total of 164 patients with chronic HCV infection were assessed for treatment between February 2008 and January 2013. The mean age was 54.7 years, 69.5% (n=114) were men, 82.4% (n=131) were Caucasian and 66.5% (n=107) resided within 30 km of the tertiary hepatology centre. Twenty-nine patients were excluded due to HBV or HIV coinfection (n=5), incomplete medical record (n=11) or clinical trial enrollment (n=13) (Figure 1).

The most common risk factor for HCV infection was illicit drug use (43.9% [n=72]), followed by blood transfusion (21.3% [n=35]), tattooing (20.1% [n=33]) and sexual contact (4.9% [n=8]). Other risk factors were acupuncture, dental work, ear piercing, hemodialysis and needle stick injury (11.0% [n=18]). HBV and HIV coinfections were found in 0.6% (n=1) and 2.4% (n=4), respectively. Liver cirrhosis was present in 26.5% (n=40). The mean Charlson comorbidity index was 2.3.

Psychiatric conditions were present in 26.2% (n=43), with mood disorders 22.6% (n=37) being the most common, followed by anxiety disorders 7.9% (n=13) and psychiatric disorders 1.2% (n=2). Active use of tobacco, alcohol and illicit drugs were found in 40.3% (n=56), 35.7% (n=56) and 19.6% (n=19), respectively.

Liver enzyme levels were analyzed before treatment in 98.8% (n=162), with a mean alanine aminotransferase (ALT) level of 109.2 IU/L. HCV RNA was quantified before treatment in 84.1% (n=138), with a mean viral load of 5.7 $\log_{10}$ IU/mL. HCV genotype 1 was most commonly found in 70.6% (n=108), followed by genotype 3 in 15.7% (n=24) and genotype 2 in 10.5% (n=16).

Fibroscan was performed before treatment in 84.1% (n=138), whereas liver biopsy was performed before treatment in 27.4% (n=45). In patients with liver biopsy showing F0 (n=5), F1 (n=8), F2 (n=10), F3 (n=9) and F4 (n=3), the mean Fibroscan score was 6.1 kPA (range 3.6 to 9.4 kPA), 5.3 kPA (range 3.3 to 11.6 kPA), 9.5 kPA (range 5.3 to 13.4 kPA), 15.1 kPA (range 10.0 to 26.6 kPA [excluded an outlier of 75.0 kPA that was falsely elevated due to transaminitis], and 52.6 kPA (range 48.0 to 57.2 kPA), respectively. Higher Fibroscan scores appeared to predict the presence of portal hypertension.

Previous HCV treatment was documented in 27.4% (n=45), in which 35.6% (n=16) were relapsers, 11.1% (n=5) partial responders, 27.9% (n=12) were null responders and 22.2% (n=10) did not complete or tolerate the treatment.

Antiviral therapies initiated by hepatologists (Figure 2)

Treatment was initiated in 25.6% (42 of 164) of patients. Antiviral regimens consisted of pegylated interferon (n=42), ribavirin (n=42), boceprevir (n=10) and telaprevir (n=11). A total of 27 patients with

TABLE 1
Univariate logistic regression for treatment initiation

Characteristics	All (n=164)	Treated (n=42)	Deferred (n=52)	Not recommended (n=18)	P*	P†
Demographic						
Age‡, years, mean ± SD	54.7±9.6	54.6±8.6	52.4±9.7	57.6±7.5	0.420	0.125
Male sex‡	114 (69.5)	33 (78.6)	36 (69.2)	10 (55.6)	0.308	0.070
Ethnicity‡						
Caucasian	131 (82.4)	32 (80.0)	41 (82.0)	15 (88.2)	0.629	0.794
Asian	23 (14.5)	7 (17.5)	6 (12.0)	2 (11.8)		
Other§	5 (3.1)	1 (2.5)	3 (6.0)	0 (0.0)		
Distance to specialist						
Near (<30 km)	107 (66.5)	31 (75.6)	32 (61.5)	11 (64.7)	0.150	0.398
Far (>30 km)	54 (33.5)	10 (24.4)	20 (38.5)	6 (35.3)		
Medical						
Risk factors for HCV infection						
Illicit drug use	72 (43.9)	17 (40.5)	24 (46.2)	7 (38.9)	0.581	0.908
Blood transfusion (before 1992)	35 (21.3)	10 (23.8)	9 (17.3)	5 (27.8)	0.435	0.745
Sexual contact	8 (4.9)	1 (2.4)	3 (5.8)	1 (5.6)	0.626	0.514
Tattooing	33 (20.1)	14 (33.3)	9 (17.3)	3 (16.7)	0.072	0.189
Other¶	18 (11.0)	4 (9.5)	7 (13.5)	3 (16.7)	0.555	0.419
Cirrhosis‡	40 (26.5)	13 (33.3)	6 (11.8)	7 (43.8)	0.013	0.466
Charlson comorbidity index‡, mean ± SD	2.3±1.6	2.4±1.4	1.9±1.4	3.7±2.2	0.097	0.031
Psychiatric						
Any psychiatric disorders‡	43 (26.2)	9 (21.4)	12 (23.1)	7 (38.9)	0.849	0.161
Anxiety disorders	13 (7.9)	4 (9.5)	5 (9.6)	3 (16.7)	1.000	0.419
Mood disorders	37 (22.6)	8 (19.0)	8 (15.4)	6 (33.3)	0.638	0.231
Psychotic disorders	2 (1.2)	1 (2.4)	0 (0.0)	1 (5.6)	0.447	0.514
Social						
Smoking	56 (40.3)	11 (30.6)	17 (37.8)	11 (64.7)	0.497	0.019
Alcohol‡	56 (35.7)	14 (35.0)	16 (31.4)	6 (33.3)	0.715	0.902
Drugs‡	19 (19.6)	5 (20.8)	6 (20.0)	3 (27.3)	0.940	0.674
Disability	35 (21.3)	12 (28.6)	11 (21.2)	4 (22.2)	0.406	0.610
Diagnostic						
Liver enzyme measurement (before treatment)‡	162 (98.8)	42 (100.0)	51 (98.1)	17 (94.4)	–	–
Alanine aminotransferase, IU/L, mean ± SD	109.2±92.7	133.8±12.7	78.5±61.8	117.2±118.9	0.001	0.269
HCV RNA (before treatment), n (%)	138 (84.1)	42 (100.0)	42 (80.8)	13 (72.2)	–	–
Viral load, $\log_{10}$ IU/mL, mean ± SD	5.7±1.0	5.7±0.8	5.7±1.2	5.6±0.9	0.540	0.704
HCV genotype‡						
1	108 (70.6)	27 (65.9)	36 (72.0)	10 (76.9)	0.957	0.722
2	16 (10.5)	4 (9.8)	4 (8.0)	1 (7.7)		
3	24 (15.7)	8 (19.5)	8 (16.0)	1 (7.7)		
4	3 (2.0)	1 (2.4)	1 (2.0)	1 (7.7)		
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
6	2 (1.3)	1 (2.4)	1 (2.0)	0 (0.0)		
Fibroscan** (before treatment)	138 (84.1)	31 (73.8)	49 (94.2)	15 (83.3)	–	–
Hepatic stiffness, kPA, mean ± SD	13.3±13.8	14.3±11.7	10.0±12.9	16.0±12.0	0.001	0.527
Liver biopsy stage (before treatment)	45 (27.4)	14 (33.3)	14 (26.9)	7 (38.9)	–	–
0	5 (12.5)	1 (8.3)	3 (23.1)	0 (0.0)	0.265	0.713
1	9 (22.5)	2 (16.7)	6 (46.2)	0 (0.0)		
2	10 (25.0)	4 (33.3)	2 (15.4)	2 (33.3)		
3	9 (22.5)	2 (16.7)	0 (0.0)	3 (50.0)		
4	7 (17.5)	3 (25.0)	2 (15.4)	1 (16.7)		
Therapeutic						
Previous treatment	45 (27.4)	15 (35.7)	9 (17.3)	4 (22.2)	–	–
Relapse	16 (35.6)	7 (46.7)	4 (44.4)	0 (0.0)	0.624	0.382
Partial response	5 (11.1)	2 (13.3)	0 (0.0)	0 (0.0)		
Null response	12 (27.9)	4 (26.7)	2 (22.2)	2 (66.7)		
Incomplete/intolerable	10 (22.2)	2 (13.3)	3 (33.3)	1 (33.3)		

*Data presented as n (%) unless otherwise indicated. Data not shown for untreated patients who refused treatment (n=26) or who were lost to follow up (n=26). *Comparison between treated and deferred; †Comparison between treated and not recommended; ‡Clinically important variable based on literature review; §Other ethnicity (Chinese, Indian, Native, Pakistanian, Vietnamese); ¶Other risk factors (acupuncture, dental work, ear piercing, hemodialysis, needle stick injury); **Echosens, France*

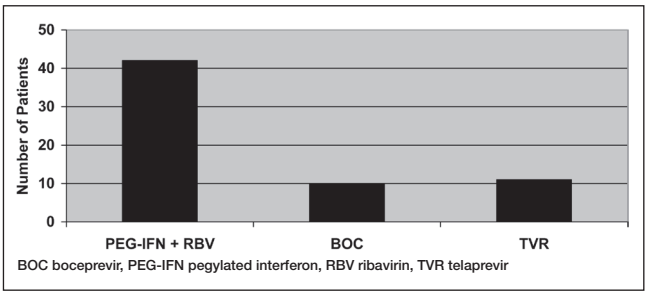

Figure 2) *Antiviral therapies initiated by hepatologists*

TABLE 2
Multivariate logistic regression for treatment initiation

Subgroup and predictor	OR (95% CI)*	P
Treated versus deferred		
ALT >1.5 times the upper limit of normal	3.10 (1.32–7.27)	0.009
Treated versus not recommended		
Male sex	7.90 (1.35–46.15)	0.022
Charlson comorbidity index (per point increase)	0.47 (0.27–0.83)	0.009
Smoking	0.09 (0.02–0.53)	0.008

**OR >1 indicates a higher probability of receiving treatment. ALT Alanine aminotransferase*

HCV genotype 1 were treated, six of whom did not receive triple therapy with a first-generation protease inhibitor. Among these six patients, five were assessed for treatment before the approval of boceprevir and telaprevir in May 2011, and one could not tolerate boceprevir or telaprevir due to anemia. Among untreated patients (122 of 164), 11.0% (18 of 164) were not suitable treatment candidates. The remaining 31.7% (52 of 164) patients had their treatment deferred, 15.9% (26 of 164) refused treatment and 15.9% (26 of 164) were lost to follow-up.

Univariate analyses for treatment initiation (Table 1)
In univariate analyses, patients who had their treatment deferred were more likely to have no liver cirrhosis (P=0.013), normal ALT levels (P=0.001), and a minimal or mild degree of liver fibrosis assessed by Fibroscan (P=0.001). In contrast, patients in whom treatment was not recommended were more likely to be active smokers (P=0.019) and had a higher Charlson comorbidity index (P=0.031).

Multivariate analyses for treatment initiation (Table 2)
In multivariate analyses, male sex (OR 7.90 [95% CI 1.35 to 46.15]) and elevated ALT level (>1.5 times the upper limit of normal) (OR 3.10 [95% CI 1.32 to 7.27]) were positive predictors of treatment initiation, whereas active smoking (OR 0.09 [95% CI 0.02 to 0.53]) and Charlson comorbidity index (per point increase) (OR 0.47 [95% CI 0.27 to 0.83]) were negative predictors of treatment initiation. An ALT threshold of 1.5 times the upper limit of normal was chosen because it was the minimum level required to obtain provincial coverage for HCV treatment.

Reasons for treatment deferral (Table 3)
Reasons for treatment deferral included no or minimal liver fibrosis in 57.7% (n=30), persistently normal ALT level in 57.7% (n=30), patient unreadiness in 28.8% (n=15), pending HCV investigations in 7.7% (n=4), breastfeeding in 3.8% (n=2), previous null responder in 1.9% (n=1) and hepatocellular carcinoma in 1.9% (n=2).

Reasons for treatment noninitiation (Table 4)
Reasons for treatment noninitiation included patient refusal in 59.1% (n=26), medical comorbidities in 36.4% (n=16), psychiatric comorbidities in 9.1% (n=4), decompensated cirrhosis in 9.1% (n=4), active substance use in 4.5% (n=2), lack of social supports in 4.5% (n=2), excessive active alcohol use in 4.5% (n=2) and previous nonadherence or noncompliance in 2.3% (n=1).

TABLE 3
Reasons for treatment deferral

	n (%)
No or minimal liver fibrosis	30 (57.7)
Persistently normal alanine aminotransferase level	30 (57.7)
Patient unreadiness	15 (28.8)
Pending hepatitis C investigations	4 (7.7)
Breastfeeding	2 (3.8)
Previous null responder	1 (1.9)
Hepatocellular carcinoma	1 (1.9)

TABLE 4
Reasons for treatment noninitiation*

	n (%)
Patient refusal	26 (59.1)
Medical comorbidities	16 (36.4)
Psychiatric comorbidities	4 (9.1)
Decompensated cirrhosis	4 (9.1)
Active substance use	2 (4.5)
Lack of social supports	2 (4.5)
Excessive active alcohol use	2 (4.5)
Previous nonadherence/noncompliance	1 (2.3)

**No reasons provided (n=26)*

Time delay from diagnosis to treatment initiation (Table 5)
There was a statistically significant difference in the median time lag from HCV diagnosis to general practitioner (GP) referral between the treated and untreated patients (66.3 versus 119.5 months, respectively [P=0.033]). The median wait time from GP referral to hepatologist consult was similar between the treated and untreated patients (1.7 months versus 1.5 months, respectively [P=0.768]). Among the treated patients, the median time delay was 66.1 months from diagnosis to treatment initiation, 7.9 months from GP referral to treatment initiation, and 6.8 months from hepatologist consult to treatment initiation.

Among the treated patients, the time delay from HCV diagnosis to GP referral and the wait time from hepatologist consult to HCV treatment both appear to shorten progressively over the years from February 2008 to January 2013. Unfortunately, when patients were stratified according to year of assessment, the number in each group was too small for statistical comparison (data not shown). Among the untreated patients, no meaningful trend in wait times was observed over the years.

Diagnostic tests ordered by primary care physicians (Figure 3)
Primary care physicians had ordered ALT tests within six months of referral in 75.6% (n=124), HCV antibody in 39.0% (n=64), HCV RNA in 51.8% (n=85), HCV genotype in 57.9% (n=95) and abdominal ultrasound within one year in 52.4% (n=86).

DISCUSSION

In the present study, the initiation rate of HCV treatment was 25.6%, which is comparable with previously reported rates of 16.0% to 37.8% in Canada (17-19). However, several potential confounders need to be considered. It should be noted that the actual treatment rate at our centre is higher than that reported in our study that excluded patients who enrolled in clinical trials. The treatment rate observed in our study could be higher than that of smaller centres due to the focus on viral hepatitis at our tertiary referral centre. Furthermore, our centre is staffed with two full-time nurses who are indispensable in facilitating treatment uptake with the currently approved triple therapy. In contrast, the treatment rate could be lower at our tertiary referral centre, which encounters a high proportion of difficult-to-treat patients with advanced age, multiple medical and psychiatric comorbidities, decompensated cirrhosis and hepatocellular carcinoma.

TABLE 5
Time interval from hepatitis C virus (HCV) diagnosis to treatment initiation

Interval, months	n	Treated, median (IQR)	n	Untreated, median (IQR)	P
HCV diagnosis to general practitioner referral	36	66.3 (2.8–123.1)	79	119.5 (20.5–203.5)	0.033
HCV diagnosis to HCV treatment	37	66.1 (17.1–123.5)		–	–
General practitioner referral to hepatologist consult	38	1.7 (0.6–2.7)	117	1.5 (0.8–2.5)	0.768
General practitioner referral to HCV treatment	38	7.9 (5.1–15.4)		–	–
Hepatologist consult to HCV treatment	42	6.8 (3.5–14.2)		–	–

IQR Interquartile range

Following the approval of boceprevir and telaprevir in May 2011, the treatment rate remained suboptimal (31.8% [21 of 66]) among HCV genotype 1 patients in our study. Similarly, Chen EY et al (23) reported a disappointingly low rate of treatment initiation of 18.7% in chronic HCV patients who were offered triple therapy. Although boceprevir and telaprevir have significantly improved SVR, they must be used in combination with pegylated interferon and ribavirin, and are associated with additional side effects (24-26). Furthermore, there is increasing recognition and anticipation among patients and physicians of the improved efficacy and tolerability of the newer antiviral regimens that will become available in the near future (23). These newer antiviral agents are desperately needed because HCV treatment will have minimal effects in reducing liver-related morbidity and mortality if the treatment rate remains low.

Elevated ALT level (>1.5 times the upper limit of normal) was found to be a positive predictor of treatment initiation in our study. This finding is expected because an ALT level >1.5 times the upper limit of normal is required for obtaining provincial drug coverage in British Columbia, in accordance with consensus guidelines that recommend antiviral therapy in chronic HCV patients with persistently high levels of ALT (18,20). In contrast with previous studies, age (18,20), ethnicity (11), presence of liver cirrhosis (6,18), viral load (11), genotype (20) and patient motivation (18) did not have a positive impact on treatment decision.

Active smoking was identified as a negative predictor of treatment initiation in the present study. It may represent a surrogate marker for other potential barriers to treatment such as lack of social support or low socioeconomic status. Charlson comorbidity index (per point increase) was also found to be a negative predictor of treatment initiation. This finding is not surprising because patients with advanced age and comorbid illnesses are less likely to tolerate the side effects of antiviral therapy. In contrast with previous studies, age (6,8,17,27), sex (12), ethnicity (6,8,13), advanced liver disease (8,27), psychiatric comorbidities (6,11,17,27), active alcohol use (5,6,12,17) and active substance use (6,11,17,19,20,27) did not have a negative impact on treatment decision.

The most common reasons for treatment deferral in our study were no or minimal liver fibrosis, persistently normal ALT level and patient unreadiness. Patients with normal ALT level and minimal liver fibrosis do not meet public reimbursement criteria and, thus, would have no choice but to defer therapy. The most common reasons for treatment noninitiation were patient refusal, medical comorbidities, psychiatric comorbidities and decompensated cirrhosis. As interferon-free antiviral regimens with improved safety and tolerability become available, the concern for side effects in patients with medical and psychiatric comorbidities will diminish and the treatment rate will increase accordingly. Our findings were in accordance with previous studies, which also reported other reasons for nontreatment including patient nonadherence to follow-up (5,10,12,14,17), patient concern about efficacy and side effects of medications (18,19,28), active alcohol and substance use (5,9,10,12,14,15,17-19,29), and lack of social supports (10,12,28).

The long delay from HCV diagnosis to GP referral may be due to several reasons. First, there may be gaps in primary care physicians' knowledge of HCV management (30). Second, significant barriers to specialist referral were reported by 50% of primary care physicians, including long wait times, long travel distances and substance dependence (30).

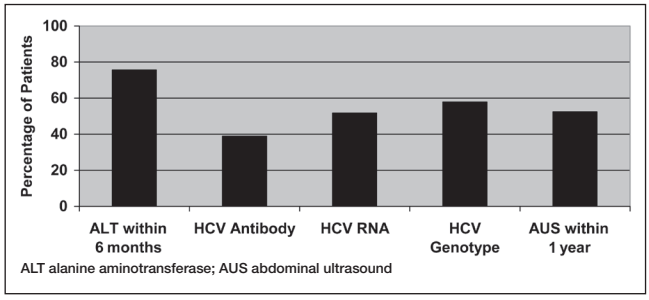

Figure 3) *Diagnostic tests ordered by primary care physicians. HCV Hepatitis C virus*

However, our study found that the wait time from GP referral to hepatologist consult was <2 months and that 66.5% of patients resided within 30 km of the tertiary hepatology centre. The short wait time from GP referral to hepatologist consult is perhaps a unique feature of our centre because both hepatologists make efforts to prioritize and assess patients with chronic HCV as soon as possible.

Furthermore, HCV treatment in patients with substance abuse has been shown to be feasible with ongoing support and monitoring through rehabilitation programs (10,17). Finally, some patients with HCV may not be interested in evaluation for treatment for some time after diagnosis. This would also explain the longer time delay from diagnosis to referral in untreated patients.

The prolonged wait time from hepatologist consult to HCV treatment may be due to several reasons. First, a significant proportion of our patients did not have all of the relevant investigations (eg, HCV viral load and genotype) ordered by the referring physicians before seeing the specialist. Second, many patients have medical and psychiatric comorbidities that require assessment and clearance by other consultants before initiation of antiviral therapy. Third, inadequate nursing support may be a contributing factor to the delay in treatment initiation following assessment by the hepatologist; however, the data points in our study were insufficient to detect any statistical significance. Our centre is staffed with only two full-time and nongovernment-funded nurses, each of whom is able to follow a limited number of patients at a certain time. This undoubtedly limits treatment uptake with pegylated interferon, ribavirin and the first-generation protease inhibitors, which are associated with complex dosing schedules and frequent adverse events.

Limitations of our study include its single-centre retrospective design and referral bias to a tertiary centre with a special interest in viral hepatitis. It is likely that the burden of mental health and socioeconomic obstacles varies among different centres. In addition, it should be noted that a significant number of patients were excluded due to incomplete data in the chart and enrollment in clinical trials. In fact, we estimated that only 11% of all patients being evaluated at our centre had complete retrospective data for study inclusion. Furthermore, case identification from our electronic medical records using the ICD-9 diagnostic code 5731 for viral hepatitis may have inadvertently missed some chronic HCV patients who were being evaluated for gastrointestinal concerns other than HCV. Nonetheless, we believe that the patient sample included in our study remains an accurate representation of the patient population seen at our tertiary

referral centre. Finally, it is worth mentioning that the mean hepatic stiffness (based on Fibroscan) did not fully correlate with the fibrotic stage (based on liver biopsy), presumably due to such factors as the small number of patients with available test results, falsely elevated hepatic stiffness in the presence of transaminitis and sampling error of liver biopsy.

The landscape of HCV treatment is rapidly changing. As newer direct-acting antiviral agents with improved efficacy and tolerability are being approved, additional studies will be needed to re-examine the rate and predictors of antiviral therapy initiation. Finally, with the advent of all-oral interferon-free antiviral regimens with potentially fewer side effects, it is anticipated that more physicians will treat HCV and refer only the more complicated cases to hepatologists. Meanwhile, the role of nurses will gradually evolve into one of health promotion and disease prevention.

CONCLUSION

The current treatment rate for chronic HCV infection remains sub-optimal. Medical and psychiatric comorbidities represent a major obstacle to HCV treatment. The long delay from HCV diagnosis to GP referral should prompt greater educational efforts to enhance the knowledge of primary care physicians. More nursing support from the provincial health authorities would help alleviate the backlog of patients awaiting treatment. With the availability of all-oral, interferon-free antiviral regimens in the near future, it is hoped that patients who do not tolerate interferon-based therapy would benefit from these future treatment options and that primary care physicians would take on a greater role in providing HCV treatment to patients.

DISCLOSURES: The authors have no financial disclosures or conflicts of interest to declare.

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