Predictors of antiviral therapy in a post-transfusion cohort of hepatitis C patients

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INTRODUCTION: In the past, antiviral therapy has been given to 15% to 30% of patients infected with hepatitis C virus (HCV). The efficacy of therapy has recently improved with the addition of ribavirin and pegylated interferon. The aim of the present study was to identify the clinical, socioeconomic and health-system predictors of antiviral treatment for HCV.

METHODS: A retrospective analysis of compensation claims data of patients who acquired HCV through blood transfusions between 1986 and 1990 was performed. The patients consisted of 2456 Canadian HCV-positive individuals. The authors reviewed narrative comments from physicians, and constructed univariate and multivariate logistic regression models, using receipt of antiviral therapy with interferon or interferon/ribavirin as the primary outcome.

RESULTS: Of the 2456 patients, approximately 30% appeared to be eligible, but only 16% received treatment. Univariate analyses suggested that the disease severity, age, HIV status and province of residence were associated with the likelihood of receiving treatment (P<0.01). The final, multivariable model indicated that in patients with HCV: intermediate disease severity (eg, fibrosis, P<0.0001); middle age (P<0.0001); HIV-negative status (P<0.0001); and province of residence (Quebec, P<0.0001; and Saskatchewan, P<0.0001) were independent predictors of treatment. Narrative comments of physicians emphasized the importance of age, HIV status and patient preferences in clinical decision-making.

DISCUSSION: Given the efficacy and cost-effectiveness of current antiviral therapy, treatment rates of HCV patients may be suboptimal. Further work is required to understand barriers to treatment related to geography, organization of medical care, age, medical provider and patient preferences.

Key Words: *Antiviral therapy; Comorbidity; Hepatitis C*

Les prédicteurs d'une thérapie antivirale au sein d'une cohorte postransfusionnelle de patients atteints d'hépatite C

HISTORIQUE : Par le passé, la thérapie antivirale était administrée à 15 % à 30 % des patients infectés par le virus de l'hépatite C (VHC). L'efficacité de la thérapie s'est récemment améliorée grâce à l'ajout de ribavirine et d'interféron pégylé. La présente étude visait à repérer les prédicteurs cliniques, socioéconomiques et du système de santé favorisant une thérapie antivirale en cas d'hépatite C.

MÉTHODOLOGIE : Une analyse rétrospective des demandes de réclamation de patients ayant contracté le VHC par transfusion sanguine entre 1986 et 1990 a été exécutée. Les patients se composaient de 2 456 Canadiens positifs au VHC. Les commentaires narratifs des médecins et des modèles de régression logistiques univariés et multivariés reconstitués, faisant appel à l'administration d'une thérapie antivirale à l'interféron ou à l'interféron associé à la ribavirine comme résultat primaire, ont été examinés.

RÉSULTATS : Des 2 456 patients à l'étude, environ 30 % semblaient admissibles, mais seulement 16 % avaient été traités. Selon les analyses univariées, la gravité de la maladie, l'âge, le statut du VIH et la province de résidence s'associaient à la possibilité de recevoir un traitement (P<0,01). D'après le modèle multivarié final, chez les patients atteints du VHC, la gravité moyenne de la maladie (p. ex., fibrose, P<0,0001), l'âge mur (P<0,0001), la séronégativité au VIH (P<0,0001) et la province de résidence (Québec, P<0,0001, et Saskatchewan, P<0,0001) étaient des prédicteurs indépendants de traitement. Les commentaires narratifs des médecins soulignaient l'importance de l'âge, du statut du VIH et des préférences des patients dans la prise de décision clinique.

DISCUSSION : Étant donné l'efficacité et la rentabilité de la thérapie antivirale courante, les taux de traitement des patients atteints du VHC peuvent être suboptimaux. D'autres travaux s'imposent pour comprendre les obstacles au traitement au plan de la géographie, de l'organisation des soins médicaux, de l'âge, du dispensateur de soins et des préférences des patients.

There are an estimated 275,000 individuals infected with the hepatitis C virus (HCV) in Canada (1). Although the risk may be lower for nontransfusion patients (2), Canadian estimates suggest that one in four Canadians with transfusion-acquired HCV will develop cirrhosis, and one in eight will die from liver disease (3). HCV-related deaths are projected to double in Canada over the next decade (4) and surpass those due to HIV infection.

Interferon in combination with ribavirin therapy is highly effective in eliminating viral replication (5,6), and when successful, decreases the risk of progression to late-stage liver disease. However, antiviral therapy may not be optimally used. Published estimates suggest that the rate of antiviral treatment among unselected HCV patients in the community ranges from 14% (7) to 28% (8), with the reported number of eligible patients around 30% (9,10).

Consensus guidelines stipulate that the indications for antiviral treatment of HCV patients are HCV-RNA-positive status, elevated alanine aminotransferase levels or a liver biopsy showing portal or bridging fibrosis (11-14). Suggested

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contraindications to therapy include decompensated cirrhosis, hepatocellular carcinoma (7,11-13,15,16), advanced age (7,16), active alcohol abuse, psychological/psychiatric problems and ongoing illicit drug use, among others (7,8,13,15-19).

In addition, the likelihood of receiving treatment may be affected by behavioural, socioeconomic and health system factors. The type of physician evaluating the patient can be important because it has been reported that twice as many patients are treated by gastrointestinal specialists than by generalists (20). In addition, patients' preferences play a role because some patients refuse antiviral therapy after being identified as being HCV-positive (7,8,16-18,21).

The socioeconomic status of the patient and the distance to health care facilities and specialists may all play a role in determining whether patients receive treatment.

The purpose of the present study was to systematically explore the clinical, socioeconomic and health-system factors associated with antiviral treatment in a population of HCV-positive individuals infected through blood transfusion.

METHODS

Study population

In Canada, an estimated 10,000 to 16,000 individuals were infected with HCV through blood product transfusions between January 1, 1986 and July 1, 1990. The provincial, territorial and federal governments of Canada agreed to compensate these individuals in the 1986 to 1990 Hepatitis C Compensation Agreement (22). Claimants are assigned to one of six disease levels based on the severity of their HCV-related illness. As part of the claims process, clinical and demographic data were collected from all claimants and their physicians, and then entered into a database (22). By 2002, the database contained information from 2456 claimants. Individual disease level data, purged of unique identifiers, were made available to the investigators for the present study.

Additional data sources

Four additional sources of data were used: the 1996 Canadian Census to impute claimants' incomes (23); the Canadian Healthcare Association's *Guide to Canadian Healthcare Facilities* to identify all Canadian hospitals (24); a database of previously identified Canadian hepatitis C specialists (15); and the Statistics Canada postal code conversion files to derive latitude and longitude of all the postal codes (25).

The distance of each patient to the nearest hospital and the nearest HCV specialist within each province was calculated using the following equation (26):

$$D = 6{,}370{,}997 \times \arccos(\sin[LAT1] \times \sin[LAT2] + \cos[LAT1] \times \cos[LAT2] \times \cos[LONG1 - LONG2])$$

D Distance; LAT Latitude; LONG Longitude.

Eligible subset

The available data did not contain sufficient clinical information to definitively determine which patients were eligible for treatment. The compensation agreement forms provided space for the physician to comment about the compensation claimant including reasons why the patient was not treated. These free text reasons were counted according to theme. Seven hundred thirty-two patients were categorized as being potentially eligible for treatment if their physician did not indicate a reason why they were not being treated, and they were concurrently classified with disease level 3, 4 or 5. The univariate results of this subset were very similar and the multivariate model for the eligible subset contained the same variables as the entire study population. However, the clinical information available was insufficient to definitively classify patients as eligible; hence, only the results of the entire study population are reported.

Statistical analysis

For both the entire study population and the subset of eligible patients the following statistics were used. Descriptive statistics to characterize the distribution of potential predictors of antiviral therapy were used. The outcome variable was any antiviral drug treatment for HCV, any interferon product or combination interferon/ribavirin product. The relationships between the outcome variable and clinical variables (disease level, HIV status, liver biopsy, HCV antibody test, HCV RNA and hemophilia), and demographic variables (age, marital status, income, sex, province, urban or rural residence, and distance to the specialist and the hospital) were also explored.

Univariate analyses with the χ^2 test were performed. A logistic regression model of the predictors of antiviral treatment was constructed, using the backwards selection approach. The variables that were either potentially significant ($P<0.25$) or believed to be clinically important were selected as candidates for the model. Clinically important variables were selected by consensus judgement of local HCV specialists in combination with a literature review. Following the fit of the model with these variables, the Wald statistic test was performed for all of the variables. The variables with the largest P value were sequentially removed from the model. This process was continued until a final parsimonious model, including only variables that were significant ($P<0.01$) and/or clinically important, was reached. In the final model, disease level 6, the most severe disease level, and Ontario, with the largest number of individuals, were used as reference values. To verify the model, a forward selection was used to construct the model.

All statistical analyses were performed using SAS version 8.1 (SAS Institute Inc, USA).

Study approval and disclaimer

The study was approved by the Ontario Superior Court, the University of Toronto Research Ethics Board and the Joint Committee, representing post-transfusion HCV compensation claimants and federal, provincial and territorial governments (22). The present study did not receive funding from academic, government, commercial or private sources.

RESULTS

Overall, 392 of 2456 (16%) HCV-infected compensation claimants received antiviral therapy. The number of patients starting treatment increased over time (Figure 1). Increases in the number treated occurred after 1989, when the first interferon trials were published (27,28), after 1993, when the first Canadian guidelines on HCV treatment were published (11), and after 1998, when the combination interferon and ribavirin trials were published (29,30).

Clinical variables

Claimants were assigned to one of six compensation levels, defined mainly by the severity of their hepatic disease. Disease level 1 individuals had only been identified as HCV-antibody positive; disease level 2 individuals had been tested for HCV RNA and found to be positive; disease level 3 claimants had a liver biopsy indicating nonbridging fibrosis or had met the criteria

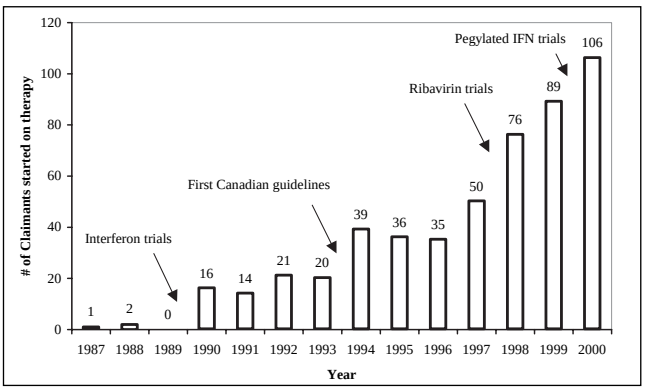

Figure 1) *Claimants started on antiviral therapy from 1987 to 2000, including repeaters. IFN Interferon*

for HCV drug therapy (alanine aminotransferase greater than 1.5 times normal); disease level 4 claimants had bridging fibrosis on liver biopsy; disease level 5 claimants had biopsy-proven cirrhosis or noninvasive markers of cirrhosis (eg, thrombocytopenia or splenomegaly); and disease level 6 claimants had evidence of liver failure and/or hepatocellular carcinoma. More patients were treated in levels 3, 4 and 5 relative to those in levels 1, 2 and 6 (P<0.0001) (Table 1).

The univariate analyses showed other significant differences between treated and nontreated patients (Table 1). Patients who had a polymerase chain reaction test or a biopsy were more likely to have treatment than those who did not have these investigations (P<0.0001). HIV-positive patients were less likely to have been treated than HIV-negative patients (P<0.0001).

The univariate analyses showed that the treatment rate was not affected by residence (urban versus rural) (P=0.96), sex (P=0.49), hemophilia (P=0.80), income quintile (P=0.71) or distance to the hospital (P=0.58). However, the likelihood of treatment was affected by age and the province of residence (P<0.0001). Marital status and the distance to an HCV specialist were borderline significant (P<0.05) (Table 1). The median distance to an HCV specialist (32.06 km) was selected as a marker for designating patients living close to or far from a specialist. More patients in the 'close' group (n=206, 17.40%) were treated compared with those in the 'far' group (n=169, 14.27%; P=0.037). The treatment rate varied significantly by province (P<0.0001). For example, only 14.6% of Ontario patients (n=898) were treated. In contrast, 32% of Manitoba patients were treated, and 26% and 27% of patients in Prince Edward Island and Saskatchewan were treated, respectively (Table 1). A statistically greater proportion of patients with a partner (married, common law or same sex) were treated versus those without (single, divorced, separated or widowed) (P=0.0027). The treatment rate was highest (24.8%) in patients between 40 and 49 years of age, and lower in both younger and older patients (Table 1).

The univariate analysis results of the presumably eligible patient subset (n=732) were not notably different from those of the entire study population, except that the distance to the specialist was no longer significant (P=0.96).

Multivariate model

In the final model, the following variables were statistically significant determinants of treatment: disease level; HIV status; age; and province of residence (Table 2).

TABLE 1
Baseline clinical and demographic characteristics

Variable	Total (n=2456)	Treated, n (%)	P
Disease severity (level)*			
HCV antibody-positive (1)	546	1 (0.18)	
HCV RNA-positive (2)	657	3 (0.46)	
Nonbridging fibrosis/ abnormal ALT (3)	651	226 (34.72)	
Bridging fibrosis (4)	119	62 (52.10)	
Cirrhosis, etc (5)	224	70 (31.25)	
HCC/liver decompensation (6)	222	30 (13.51)	<0.0001
HCV antibody test			
Present	2027	316 (15.59)	
Absent	429	91 (21.21)	<0.0011
HCV-PCR			
Present	1640	316 (19.27)	
Absent	816	76 (9.31)	<0.0001
Biopsy			
Present	498	207 (41.57)	
Absent	1958	185 (9.45)	<0.0001
HIV			
Positive	327	26 (7.95)	
Negative	1959	350 (17.87)	<0.0001
Distance to nearest specialist			
<32.06 km	1184	206 (17.40)	
≥32.06 km	1184	169 (14.27)	0.037
Province			
Alberta	220	39 (17.73)	
British Columbia	543	58 (10.68)	
Manitoba	75	24 (32.00)	
New Brunswick	76	5 (6.58)	
Newfoundland	28	4 (14.29)	
Nova Scotia	87	14 (16.09)	
Ontario	898	131 (14.59)	
Prince Edward Island	19	5 (26.32)	
Quebec	409	88 (21.50)	
Saskatchewan	63	17 (26.98)	
Territories	4	0 (0.00)	<0.0001
Marital status			
Single	731	109 (14.91)	
Partner	1260	256 (20.32)	0.0027
Age group (years)			
0–9	2	0 (0.00)	
10–17†	79	10 (12.66)	
18–29	244	30 (12.30)	
30–39	425	74 (17.41)	
40–49	464	115 (24.78)	
50–59	341	70 (20.53)	
60–69	361	67 (18.56)	
70–79	373	22 (5.90)	
80–89	151	4 (2.65)	
≥90	11	0 (0.00)	<0.0001

**Disease level explained in text; †18 is legal adult. ALT Alanine aminotransferase; HCC Hepatocellular carcinoma; HCV Hepatitis C virus; PCR Polymerase chain reaction*

The results indicate that patients who had been categorized as disease level 1 or 2 had, respectively, one in 100 or one in 50 odds of being treated relative to an individual with disease level 6. Patients with disease level 3, 4 and 5 had 2.29-, 3.75- and 2.51-times greater odds, respectively, of being treated as patients with disease level 6 (Table 2).

TABLE 2
Predictors of treatment

Variable	Estimate	P	OR	95% CI
Intercept	−5.4287	<0.0001	N/A	N/A
Disease severity (level)*				
HCV antibody-positive (1)	−3.6775	<0.0001	0.010	0.001 to 0.077
HCV RNA-positive (2)	−2.9929	<0.0001	0.020	0.006 to 0.069
Nonbridging fibrosis/ abnormal ALT (3)	1.7285	<0.0001	2.291	1.446 to 3.628
Bridging fibrosis (4)	2.2204	<0.0001	3.746	2.111 to 6.647
Cirrhosis, etc (5)	1.8218	<0.0001	2.514	1.507 to 4.196
HIV-negative versus -positive	0.7127	<0.0001	4.160	2.584 to 6.698
Age	0.1208	<0.0001	N/A	N/A
Age × age	−0.00139	<0.0001	N/A	N/A
Other provinces†	0.1287	0.4241	1.137	0.830 to 1.559
Quebec	0.6822	0.0003	1.978	1.372 to 2.852
Manitoba	0.6503	0.0355	1.916	1.045 to 3.513
Saskatchewan	1.7656	<0.0001	5.845	2.532 to 13.491

**All disease levels compared with disease level 6 (reference Table 1); †All provinces compared with Ontario (reference Table 1). ALT Alanine aminotransferase; HCV Hepatitis C virus; N/A Not applicable*

TABLE 3
Clinical and sociodemographic reasons reported by physicians for not recommending therapy

Clinical reasons	Patients (n)*	Sociodemographic reasons†	Patients (n)*
Total	206	Total	73
Normal ALT	43	Age (old)	27
HIV-positive	42	Age (young)	8
Hepatologist opinion	22	Patient choice	12
Other clinical reason (unspecified)	18	Alcohol consumption	5
		Prescription undecided	3
Cardiac disease	15	Waiting for research protocol	3
Side effects	13	Not available at this time	2
Psychiatric disease	12	Previous lack of good therapy	1
Asymptomatic	12	Unaware of prescription	1
Biopsy results	7	Other reasons	11
Cancer	6		
Cytopenias	5		
Autoimmune	4		
Relapser/nonresponder	4		
PCR-negative	3		

**Some patients had several reasons indicated for not being treated (n=263); †Includes patient preferences. ALT Alanine aminotransferase; PCR Polymerase chain reaction*

Individuals who were HIV-negative had a fourfold greater odds of receiving treatment than those who were HIV-positive (Table 2).

The age coefficients indicate that probability of treatment increased with age up to middle age, specifically 44 years, and then decreased.

Patients living in the provinces of Quebec, Manitoba and Saskatchewan had 1.98, 1.92 and 5.85 times greater odds of being treated than patients in Ontario. All of the other provinces combined had an OR point estimate of 1.14, relative to patients in Ontario (Table 2).

The multivariate model of the eligible patients subset contained the same overall variables except that residing in Manitoba was no longer a significant variable (P=0.56). As expected, there was no statistical difference among disease levels 3, 4 and 5 (results not shown).

Reasons indicated by physicians for not treating a patient

The physicians' reasons for not treating a patient, as indicated freetext on the compensation agreement forms, are described in Table 3. The most frequently cited reasons for not treating patients were normal alanine aminotransferase levels (n=43 responses) and HIV infection (n=42 responses) (Table 3).

DISCUSSION

Our study found that the overall treatment rate in all transfusion-infected HCV-positive compensation claimants evaluated is 15.96%, which is comparable with other treatment rates reported (7). However, because approximately 30% of our study cohort had no physician-specified contraindication and exhibited hepatitis C manifestations such as nonbridging fibrosis, bridging fibrosis, cirrhosis and/or met a protocol for HCV drug therapy, this rate may be suboptimal. The importance of the province of residence, disease level, HIV status and age as predictors of treatment in this cohort of HCV-positive individuals raises several issues.

As we expected, a significantly greater proportion of our study's patients who had nonbridging fibrosis, bridging fibrosis, cirrhosis and/or met a protocol for HCV drug therapy was treated. However, it is unknown how many patients categorized with disease level 1 or 2 actually had significant liver disease but were underdiagnosed. Treating patients with histologically mild disease should be considered because it is cost-effective, reduces the risk of future liver disease (31,32) and reduces the infectious pool.

Not surprisingly, age was also found to be a predictor of treatment (13-15). While guidelines for HCV treatment (11-13) call for consideration of age in the treatment decision, these recommendations are not directly supported by the evidence. Indeed, recent studies (31-33) suggest that antiviral therapy may be cost effective for patients up to 71 years of age. Further work is required to understand the role of age in clinical treatment decisions and to place age-related treatment recommendations on an evidence-based foundation.

The importance of HIV in the final model is also somewhat concerning. HIV therapy, specifically the development of highly active antiretroviral therapy in the 1990s, has improved survival of HIV-positive individuals. This has led to suggestions that HIV and HCV coinfected patients receive HCV therapy (34,35). However, there are often practical barriers to treatment such as frequent drug interactions and side effects, lack of guidelines and limited data on efficacy and tolerance of antiviral treatment in HIV and HCV coinfected patients.

An unanticipated result was that the province of residence was found to be a predictor of treatment. The reasons for this variation are not clear. One hypothesis is that some smaller provinces with higher treatment rates (eg, Saskatchewan and Manitoba) include patients who are mostly cared for by a small number of specialists with a high propensity to treat. If true, the centralization of HCV services and the implementation of standardized, evidence-based treatment guidelines may offer promise as methods of increasing the overall treatment rates.

The present study contained several limitations. The study sample only included those who qualified for and received compensation in the 1986 to 1990 Hepatitis C Compensation

Agreement. This group is most likely to include individuals who are active, relatively healthy consumers, and less likely to include inmates and injection drug users. Also, our study population receives compensation to cope with and treat their infection. Our data were derived from an administrative database which contained limited clinical information. These limitations notwithstanding, we believe that our study can be generalized to community-living HCV-infected patients who have acquired their infection through the blood supply.

In summary, the results indicate that the current treatment rate even in a well-described patient population with financial incentives for clinical care and antiviral treatment may be suboptimal. The results indicate that the major predictor of treatment is a patient's hepatic disease state, with age, HIV status and geographic location also having some influence. Given that antiviral therapy will produce a sustained viral response in greater than 50% of patients (6), that treatment is highly cost-effective, even in older patients, and that the current HCV-related burden of illness is projected to grow in the coming decade, there is likely room for improvement in bringing more patients in for treatment. To better understand the barriers to treatment related to geography, organization of medical care, age, medical provider and patient preferences further research is needed. Insights derived from this type of research need to be translated into changes in practice style and the organization of care in the interests of making a major impact on the clinical and economic burden posed by HCV in the coming decade.

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